Logan University Symposium 2026

The 2021 Nobel Prize And Chiropractic Care

Two Hours

Dan Murphy, DC

118 pages 236 references

SUBLUXATION:

AN

ELECTRICAL

PHENOMENON

BY

DEANNE L. JOHNSON-HARRISON, B.S., M.S.

illustrated by

RANDY R. COLLINS, D.C.

ENERGY MEDICINE

THE SCIENTIFIC BASIS

James L. Oschman

FOREWORD BY
Candace Pert

11 Gravity, structure, emotions

Introduction

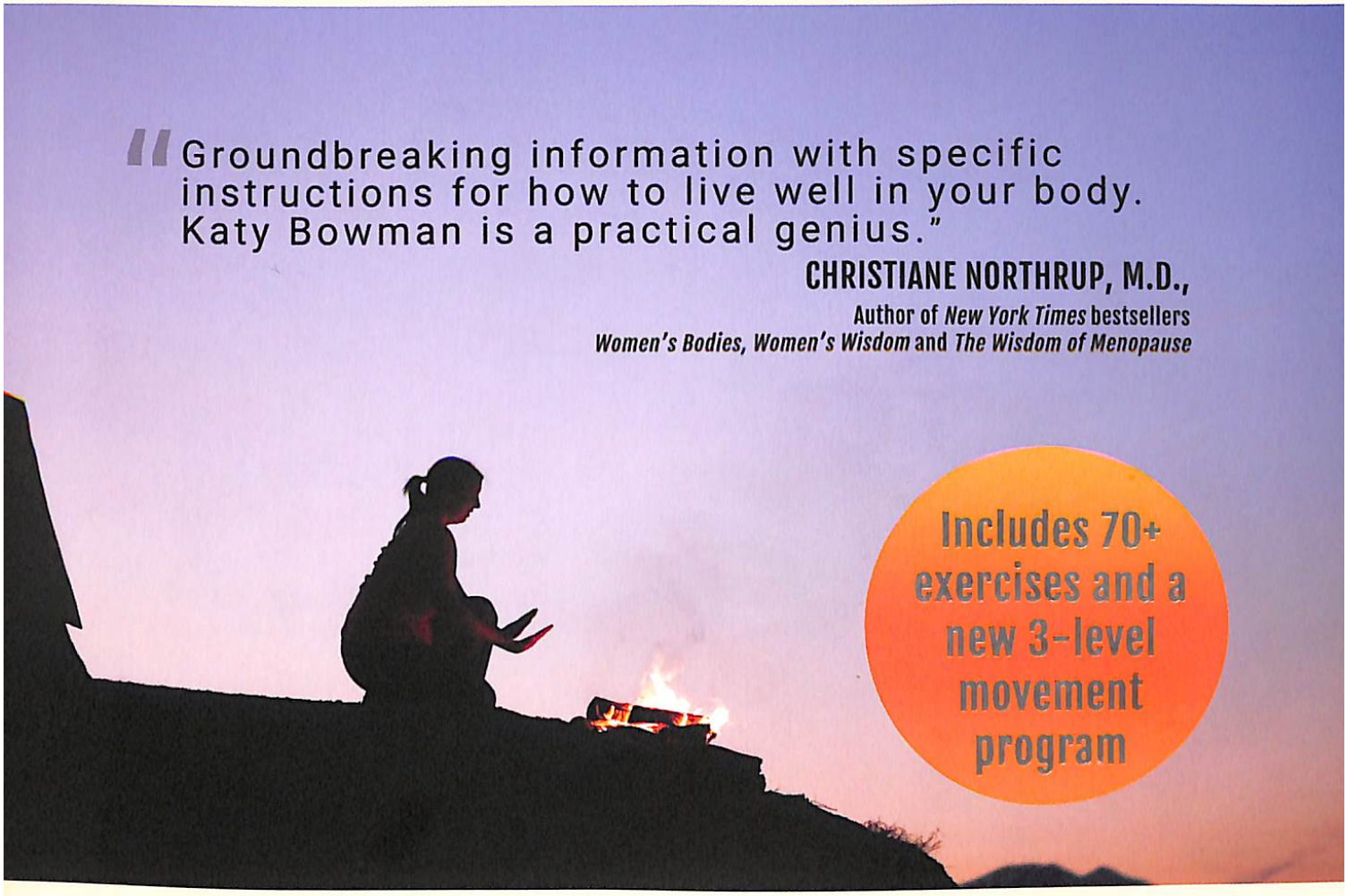
Previous chapters have described the physiological and clinical importance of electricity and magnetism. Little has been said about gravity, even though it is arguably the most potent physical influence in any human life.

Gravity pervades our bodies and our environment and affects our every activity. furniture, buildings, machinery,

MOVE YOUR DNA

RESTORE YOUR HEALTH THROUGH NATURAL MOVEMENT

EXPANDED EDITION



KATY BOWMAN

Your Weight.

For example, the way your foot is positioned while you're walking can create higher-than-normal loads within the knee. The more your feet turn out when you walk, the higher the loads placed on medial knee structures like the anterior cruciate ligament (ACL) and the medial meniscus. Do you need to lose thirty pounds to improve your knee loading? No. You can just start reducing the turnout of your foot.

Move Your DNA
Restore Your Health Through Natural Movement

Katy Bowman
2017

"Our bodies respond to mechanical input."

The conversion of mechanical input to "biochemical processes is called *mechanotransduction*."

Mechanotransduction **is the "process by which cells sense and then translate mechanical signals (compression, tension, fluid shear) created by their physical environment into biochemical signals, allowing cells to adjust their structure and function accordingly."**

"Gravity is one force your body responds to constantly."

"The loads created by gravity depend upon our physical position relative to the gravitational force."

The load created by gravity differs depending on alignment with the "perpendicular force of gravity."

"We experience load 100 percent of the time."

"The physical expression that is your body is the sum total of the loads experienced by your cells."

"Every unique joint configuration, and the way that joint configuration is positioned relative to gravity, and every motion created, and the way that motion was initiated, creates a unique load that in turn creates a very specific pattern of strain in the body." This is called "*load profile*."

Every load creates a "unique cellular deformation."

"It's not the *weight* that breaks you down, it's the *load* created by the way you carry it."

"Loads are often oversimplified to 'weight' because it makes them easier to understand, but there is much more going on with your sore knee (or foot, or back, or pelvic floor) than your weight."
"Weight is not the be-all and end-all of loads. When you want to improve your health, it's much more important to consider *how you carry* your weight than to spend hours contemplating the lone data point that is Your Weight."

"No matter the activity, when it comes to health, of utmost importance is the loads created."

"Every rate, size, and angle at which a force is being applied creates a unique environment for your cells."

"The timing and rates of loads are important because loads are *occurrences over a period of time*."

Each tissue type responds differently to a load, yet "they are all connected, which means that a load you perceive as only happening in one part of your body is actually affecting all other parts of you, and affecting each part uniquely."

"We should recognize our lack of health as a sign of a broken (mechanical) environment."

"With respect to disease, the human's internal mechanical environment has been the least-discussed environment of all—a staggering oversight when almost every cell in your body has specialized equipment *just to sense the mechanical environment*."

"You can eat the perfect diet, sleep eight hours a night, and use only baking soda and vinegar to clean your house, but without the loads created by natural movement, all of these worthy efforts are thwarted on a cellular level, and your optimal wellness level remains elusive."

"Human diseases are repeatedly explained to us in terms of their chemical or genetic makeup; meanwhile, we've completely ignored the load profile that the function of our body depends upon."

"Whether out of convenience or ignorance, we have failed to address the habitat ["habitual position relative to gravity"] in which our genes dwell, and the impact of the way we move on the state of our health."

"The loads that are perceived by your cells' mechanosensors, and the response triggered by the cell deformations—are collectively called the mechanome. A mechanome is the interplay between forces and biology."

"Movement, like food, is not optional."

"Movement is what most humans are missing more than any other factor, and the bulk of the scientific community has dropped the ball."

"A decrease in movement is associated with decreases in muscle size, vascularization, and the sensitivity in your proprioceptive system."

"Cellular loads are an inherent part of movement."

"Movement, position, and resting state of our musculoskeletal system are huge influencers of our mechanical environment."

"All movement and lack of movement create subtle differences in outcome in individuals and their genes."

"Our lack of movement input is slowly suffocating us on a cellular level."

The amount your joints move is integrated by your sensory system. "Movement provides information for the body. Movement is an environmental or epigenetic factor. Our movement environment has been polluted."

"If you want your health to change, you must change the way you move." Even tiny adjustments to your loading "can be worth millions in unspent healthcare dollars and bring about tremendous relief from your load-induced ailments."

"Tissues that spend most of their time in a fixed position will adapt to that position by making alterations that are fairly permanent."

"An under-moved area of the body will experience increases in the connective tissues." The author calls these "extra-connected" areas of the body "sticky spots."

Immobility-induced connective tissue growth creates a binding and "behaves much like scar tissue."

"On the cellular level, a sticky spot interferes with the transmission. Of forces throughout your tissues—mechanical signals that give cells context about loads placed upon them as well as position."

When a joint has a sticky spot, "you compensate by moving other joints," which may "come with a heavy dose of damage." Areas just outside of the sticky spot "experience unnaturally high loads."

Exercise cannot come close to restoring the tissues already adapted. "Exercise is good, but not good enough."

Small deformations translate into a constant stream of data to your brain and require constant communication throughout most of your body.

"We need a tool to measure the loads, both on the whole body and on every body part. The tool I use is alignment."

Muscles become physically shorter in response to "chronic joint positioning."

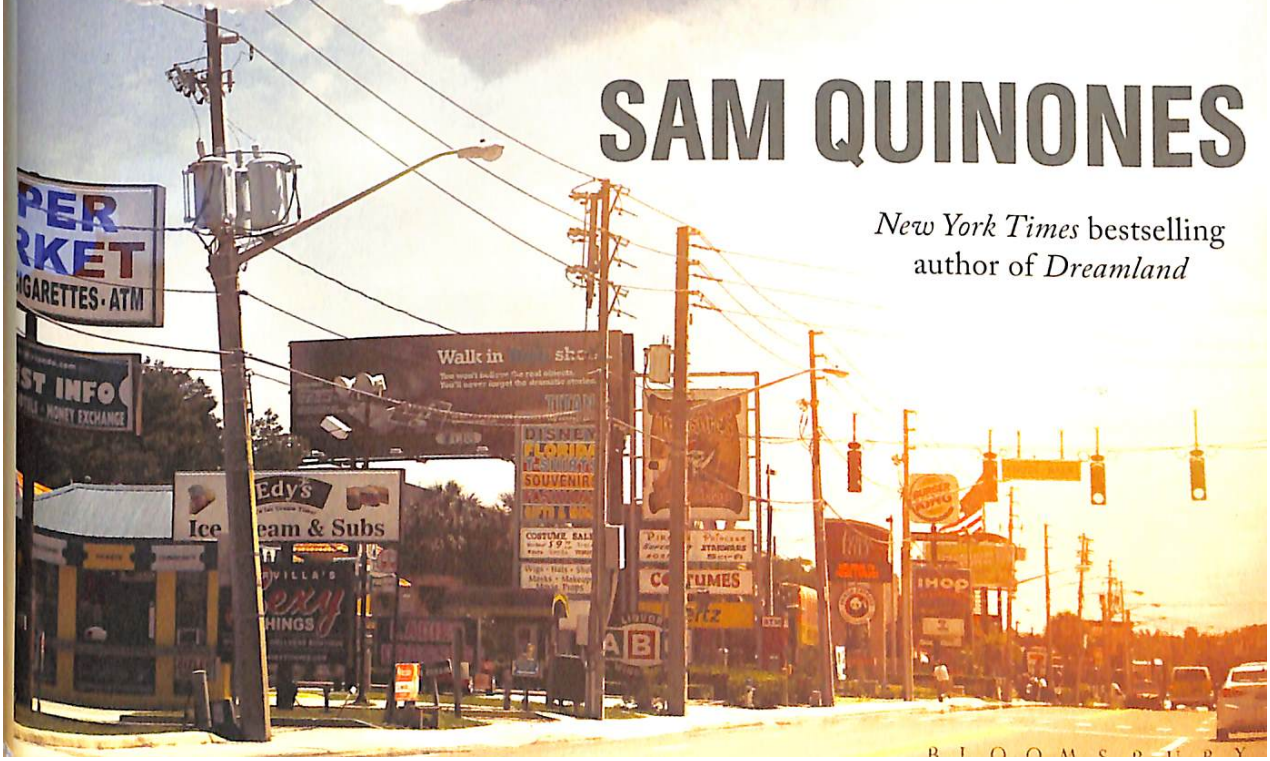
THE LEAST OF US

True Tales of America and Hope in the Time of Fentanyl and Meth

2021

SAM QUINONES

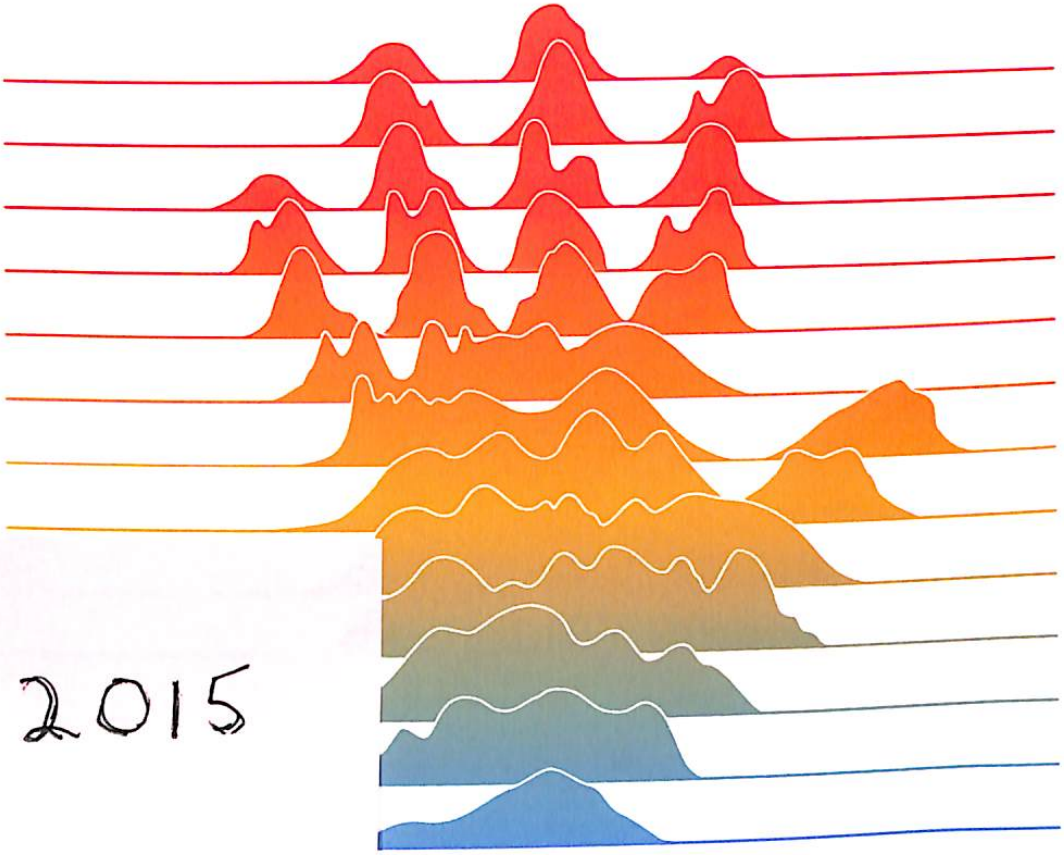
New York Times bestselling author of *Dreamland*



BLOOMSBURY

Touch

THE SCIENCE OF HAND, HEART, AND MIND



2015

David J. Linden

Author of the ***New York Times*** bestseller ***The Compass of Pleasure***

"[Linden is] an able guide to the world of touch.... The book will make you think more deeply about every itch, scrape, and caress." —***The Washington Post***

Nobel Prize in Medicine Awarded for Work on Senses

10/5/2021

WSJ

By Denise Roland
And Brianna Abbott

The Nobel Prize in physiology or medicine was jointly awarded to David Julius and Ardem Patapoutian for their work on how the human body senses temperature, touch and movement.

The Nobel Assembly said Monday that the scientists' discoveries had unlocked one of the secrets of nature by explaining the molecular basis for sensing heat, cold and mechanical force.

This basic understanding of how temperature and touch signal the nervous system is now being harnessed to research potential treatments for chronic pain and other medical conditions, the Nobel Assembly said.

"These sensations of heat and pain and touch, if those are all converted to electrical signals and sent to the brain, that opens up a whole new world of potential treatments," said Chad Bouton, a professor at the Feinstein Institutes for Medical Research in New York, whose work includes the use of stimulation of the brain to restore the sense of touch to patients who have lost it as a result of a stroke or injury. "It's all made possible by these critical discoveries," he added.

JONATHAN NACKSTRAND/AGENCE FRANCE-PRESSE/GETTY IMAGES

David Julius and Ardem Patapoutian were honored for explaining the molecular basis for sensing heat, cold and mechanical force. Above right, Thomas Perlmann, secretary of the Nobel Assembly.

Dr. Julius was born in 1955 in New York and is now a professor and chairman of the department of physiology at the University of California, San Francisco. Dr. Patapoutian was born in 1967 in Beirut. He moved to the U.S. in his youth and is currently a professor at Scripps Research in La Jolla, Calif.

While at UCSF in the late 1990s, Dr. Julius used capsaicin, a compound in chili peppers that causes a burning sensation, to identify a chemical receptor in nerve endings of the skin that responds to heat. In separate research, Dr. Patapoutian used pressure-sensitive cells to discover new receptors that respond to touch in the skin and internal organs.

Both the scientists' work involved identifying the specific genes involved in sensing either heat or touch and then figuring out what those genes did within cells.

Dr. Julius and his team assembled a library of millions of DNA fragments from sensory neurons and found a single gene that made cells sensitive to capsaicin. That gene directs nerve cells to make a so-called ion channel that opens up in response to capsaicin and high temperatures, allowing electrically charged particles called ions to flood into cells and send a pain message to the brain. That receptor was later named TRPV1.

"There is a time when you make a discovery where you are the only person on the planet, or at least you think you're the only person on the planet, who knows the answer to a particular question," Dr. Julius said in a media event. "And that's a really thrilling moment."

That discovery, published in a 1997 paper, sparked a wave of research by large drugmakers hopeful that blocking the TRPV1 receptor could treat chronic pain.

The work also paved the way for the discovery of other ion channels.

One of those channels was a cold-sensing receptor called TRPM8, which Drs. Julius and Patapoutian uncovered independently of one another, using menthol.

Dr. Patapoutian's work on touch uncovered two ion channels, named Piezo1 and Piezo2 after the Greek word for pressure, that open up in response to touch. He later showed that Piezo2 played a key role in how the body senses its position and movement. Subsequent work demonstrated how Piezo1 and Piezo2 help regulate bodily functions such as blood pressure and bladder control.

Dr. Patapoutian said that work was under way to find molecules that block the Piezo channels as these could form the basis of drugs for different types of pain.

569 results

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Drake LY, Pfeffer-Kleemann D, Zhang EY, Koloko Ngassie ML, Pabelick CM, Prakash YS.
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7 Mechanosensitive **PIEZO2** channels shape coronary artery development.
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8 Whole Exome Sequencing in 26 Saudi Patients Expands the Mutational and Clinical Spectrum of Diabetic Nephropathy.
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Medicina (Kaunas). 2025 May 29;61(6):1017. doi: 10.3390/medicina61061017.
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PMID: 40501713 Free PMC article. Preprint.

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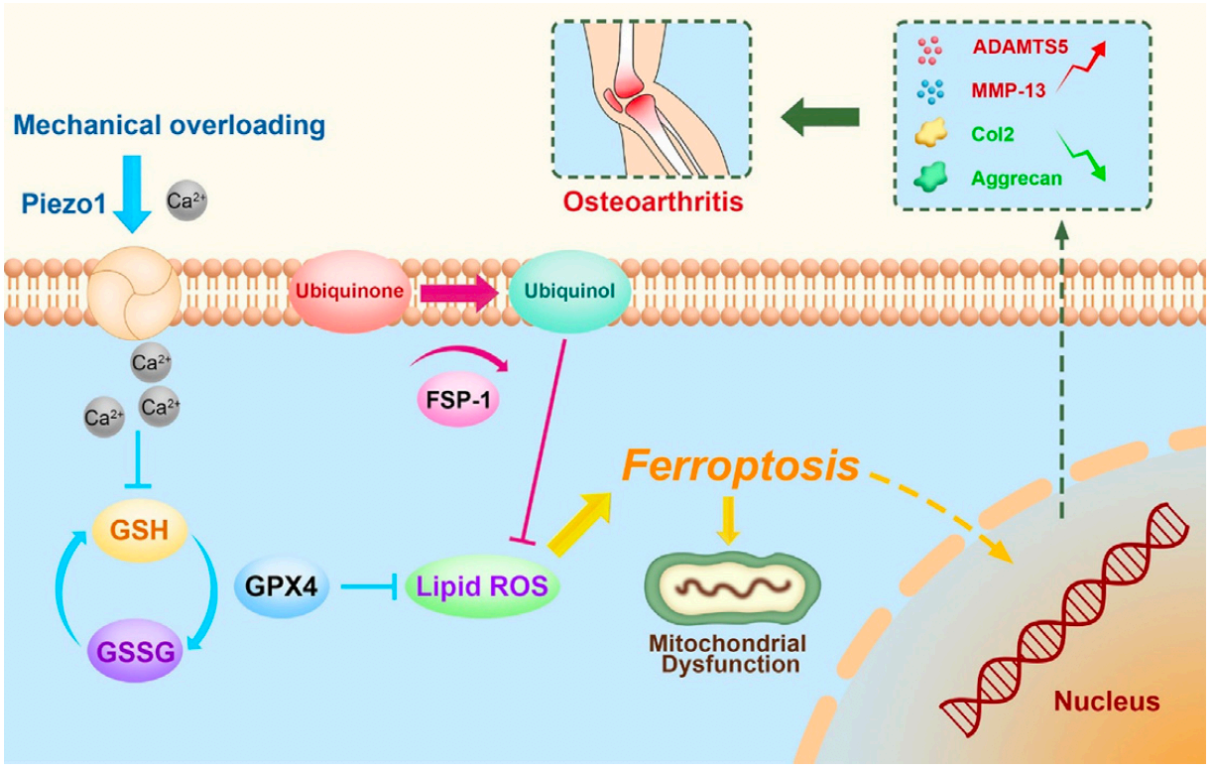
Yu D, Bae C.

Mechanical Overloading Induces Glutathione-Regulated Chondrocyte Ferroptosis in Osteoarthritis via Piezo1 Channel Facilitated Calcium Influx

Journal of Advanced Research
November 2022



A Simplified Model from Dan Murphy

Piezo1 is a **mechanoreceptor** that was mentioned in the **2021 Nobel Prize** in physiology or medicine.

Piezo1 receptors are found in the membrane of chondrocytes.

Mechanical loading (overloading) opens the Piezo1 receptor which allows excessive influx of Ca++ to enter into the cell. **[consider magnesium]**

The excessive intracellular Ca++ inhibits glutathione which increases chondrocyte oxidative stress, leading to osteoarthritis. **[consider glutathione supplements]**

CoQ10 blocks the oxidative stress driven ferroptosis cartilage damage.
[consider CoQ10; consider donating blood]

In an integrative narrative, this article has applications for the chiropractic subluxation and adjustment, Ca++ excess, Mg++ deficiency, glutathione status, and free radical damage. As such it would support not only the chiropractic adjustment, but also diet, nutrition, supplements, and laser therapy.

Spine (Phila Pa 1976). 2022 Mar 1;47(5):E203-E213. doi: 10.1097/BRS.0000000000004203.

Single Impact Injury of Vertebral Endplates Without Structural Disruption, Initiates Disc Degeneration Through Piezo1 Mediated Inflammation and Metabolism Dysfunction

Zhengang Sun [1], Xinfeng Zheng [2], Songbo Li [3], Baozhu Zeng [4], Jiaming Yang [4], Zemin Ling [5], Xizhe Liu [5], Fuxin Wei [4]

Affiliations

PMID: 34431832 PMCID: PMC8815838 DOI: 10.1097/BRS.0000000000004203

Free PMC article

Abstract

Study design: In vitro experimental study.

Objective: To establish an axial impact injury model of intervertebral disc (IVD) and to investigate if a single impact injury without endplate structural disruption could initiate intervertebral disc degeneration (IDD), and what is the roles of Piezo1 in this process.

Summary of background data: Although IDD process has been confirmed to be associated with structural failures such as endplate fractures, whether a single impact injury of the endplates without structural disruption could initiate IDD remains controversial. Previous studies reported that Piezo1 mediated inflammation participated in the progression of IDD induced by mechanical stretch; however, the roles of Piezo1 in IVD impact injury remain unknown.

Methods: Rats spinal segments were randomly assigned into Control, Low, and High Impact groups, which were subjected to pure axial impact loading using a custom-made apparatus, and cultured for 14 days. The degenerative process was investigated by using histomorphology, real-time Polymerase Chain Reaction(PCR), western-blot, immunofluorescence, and energy metabolism of IVD cell. The effects of Piezo1 were investigated by using siRNA transfection, real-time PCR, western-blot, and immunofluorescence.

Results: The discs in both of the impact groups presented degenerative changes after 14 days, which showed significant up-regulation of Piezo1, NLRP3 inflammasome, the catabolic (MMP-9, MMP-13), and pro-inflammatory gene (IL-1β) expression than that of the control group ($P < 0.05$), accompanied by significantly increased release of ATP, lactate, nitric oxide (NO), and glucose consumption of IVD cells at first 7 days. Silencing Piezo1 reduced the activation of NLRP3 inflammasome and IL-1β expression in the nucleus pulposus induced by impact injury.

Conclusion: It demonstrated that not only fracture of the endplate but also a single impact injury without structural impairment could also initiate IDD, which might be mediated by activation of Piezo1 induced inflammation and abnormal energy metabolism of IVD cells.Level of Evidence: N/A.

1,692 results

Page 1 of 34

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PMID: 40672277 Free PMC article. Preprint.

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Drake LY, Pfeffer-Kleemann D, Zhang EY, Koloko Ngassie ML, Pabelick CM, Prakash YS.
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Ma M, Li J, Li X, Jing M, Wang L, Jiang Y, Yang Z, He J, Wang M, Liu H, Chen Y, Mi K, Wang L, Fan J, Du H.
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PMID: 40653466 Free PMC article.

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Li R, Xia J, Shi C, Zhang K, Qu Y, He G, Fu Z, Deng L, Liu R, Wang X, Cai G, Dong Z, Li P, Chen X, Hong Q.
J Adv Res. 2025 Jul 11:S2090-1232(25)00540-5. doi: 10.1016/j.jare.2025.07.015. Online ahead of print.
PMID: 40653265 Free article.

10 SIRT4 Regulated by a Mechanosensor, **PIEZO1** Shows a Protective Function to Suppress Ox-LDL Uptake in Endothelial Cells.
Kopych V, Da Costa ADS, Park K.
Tissue Eng Regen Med. 2025 Jul 11. doi: 10.1007/s13770-025-00733-w. Online ahead of print.
PMID: 40643822

Excessive Mechanical Stress-induced Intervertebral Disc Degeneration is Related to Piezo1 Overexpression Triggering the Imbalance of Autophagy/Apoptosis in Human Nucleus Pulposus

Arthritis Research & Therapy
May 23, 2022; Vol. 24; No. 1; Article 119

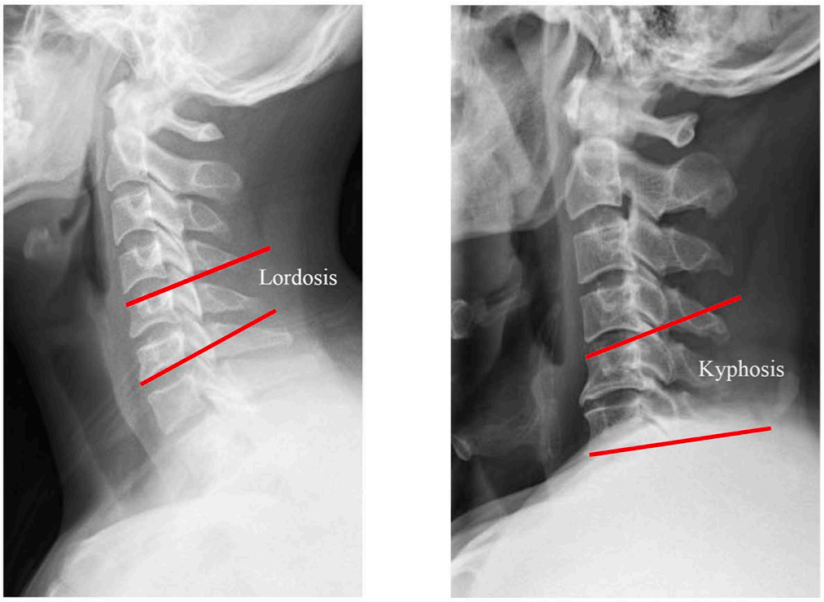
Sheng Shi, Xing-Jian Kang, Zhi Zhou, Zhi-Min He, Shuang Zheng, Shi-Sheng He

This study aimed to investigate the effect of the ***Piezo1*** mechanoreceptor on the mechanical stress-induced intervertebral disc degeneration (IVDD) and explore the possible mechanism. Immunohistochemistry staining antibodies against ***Piezo1*** were used in the analysis.

Cervical nucleus pulposus (NP) samples were collected via surgery from 26 patients (12 men and 14 women; age range: 22–65 years).

"In order to explore whether mechanical stress treatment can affect Piezo1 expression and cell function of NP cells, a mechanical compression with different intensity and/or duration was conducted on human NP cells."

Cervical lordosis was assessed with x-rays using the protocol established by Deed Harrison, DC, and colleagues in the journal *Clinical Biomechanics* in 2001: [Harrison DE, Harrison DD, Janik TJ, William Jones E, Cailliet R, Normand M. Comparison of axial and flexural stresses in lordosis and three buckled configurations of the cervical spine; Clinical Biomechanics; May 2001; Vol.16; No. 4; pp. 276–784.]



The angle between the superior endplate of the rostral vertebra and the inferior endplate of the caudal vertebra on the lateral x-ray was measured.

The expression of ***Piezo1***, cervical curvature, and the stiffness of the nucleus pulposus (NP), was performed in normal and degenerated human intervertebral discs.

"Mechanical stress plays a crucial role in the pathogenesis of intervertebral disc degeneration (IVDD)."

"Intervertebral disc degeneration (IVDD) is the leading cause of degenerative spine diseases such as discogenic pain and disc herniation, which reduces the quality of life and increases the socioeconomical burden."

- "The onset and development of IVDD is a complex process involving numerous factors such as biomechanics, aging, genetic factors, nutrition, inflammation, and so on."

- "Mechanical stress as part of the biomechanical factors may contribute to playing a particularly prominent role in the pathogenesis of IVDD."

The nucleus pulposus (NP) "is considered to be the most crucial component for maintaining the pressure gradient and ensuring the infiltration and diffusion of metabolites and nutrients."

- "Abnormal mechanical load can promote cell death in the NP, cause matrix metabolism disorders, and hasten the process of IVDD." **[Important]**

    - "Compressive forces by bad postures or kyphosis may lead to intense stresses that act on the NP." **[Key Point]**

    - "Mechanical stress caused by kyphosis has been linked to the pathological process of IVDD." **[Key Point]**

"The mechanosensitive Piezo1 ion channel can sense the changes in mechanical stress and convert the mechanical signals into chemical signals." **[Key Point]**

- ***Piezo1*** is a new mechanosensitive ion channel, which can "sense the changes of mechanical stress and convert the mechanical signals into electrical or chemical signals."

- "[Piezo1] is widely distributed in a variety of different tissues including bone, articular cartilage and the intervertebral disc."

Findings:

- "Intradiscal pressure was shown to be definitely higher in forward leaning from a sitting position than in relaxed sitting, which indicates that intradiscal

pressure increases with application of compression and is dependent on the lifestyle."

- "The expression of Piezo1 had obviously increased in the NP tissues of the IVDD patients when compared to that of the control group."
- The expression of Type-II Collagen significantly declined in the IVDD group when compared to that in the control group.
- "The protein levels of Type-II Collagen and Aggrecan were markedly suppressed after mechanical stress."

  [Aggrecan and **Type-II Collagen** form the major structural component of cartilage and the intervertebral disc].
- "Apoptosis was significantly increased in mechanical stress-treated NP cells and could be restricted when Piezo1 was inhibited."

Chiropractic Mechanical Connection:

- "The lateral radiograph revealed the local cervical curvature was significantly lower [kyphotic] in the high grade IVDD group."
- "Excessive mechanical stresses are found in the kyphotic areas of sagittal cervical spine when compared to the normal lordosis."
- "The increased mechanical stress induced by kyphosis was considered to be a risk factor for the development of IVDD or disc herniation."
- Cervical kyphosis resulted in the up-expression of ***Piezo1*** and the down-expression of Type II Collagen.
  - This increased nucleus pulposus stiffness and increased degeneration of human intervertebral discs.
- "The upregulated expression of Piezo1, poor curvature [kyphosis], and increased extracellular matrix (ECM) stiffness in the degenerated human NP."
- Increased **Piezo1** expression reduced **Type-II Collagen** in the degenerated human NP tissue, along with more kyphotic angle in the cervical spine, reveals that the "Piezo1 sensing the excessive stress partly attributed to poor curvature may affect the ECM homeostasis and further change the mechanical properties of NP." **[Key Point]**
- "Our data provide the evidence that Piezo1 upregulation under excessive compression can promote the apoptosis and senescence of NP cells, secrete

pro-inflammatory cytokines, and reduce the synthesis of ECM by mitochondrial dysfunction and the suppression of autophagy in NP."

- "The up-regulation of the mechanosensitive [calcium] ion channel Piezo1 by excessively external compressive stress can increase pro-inflammatory cytokines, and induce mitochondrial dysfunction, which may trigger the apoptosis and senescence of human NP cells via suppressing autophagy and resulting in the loss of ECM."

- This research confirms that "overactivated Piezo1 by excessive compression inhibits the synthesis of major parts in ECM involving the collagen II and aggrecan."

- The upregulation of Piezo 1 enhanced the apoptosis of NP cells and promotes the apoptosis and senescence of NP cells. **[Key Point]**

- "[Both] apoptosis and autophagy were induced by moderate mechanical compression in NP cells."

PUTTING IT ALL TOGETHER

Cervical kyphosis drives the following:

- Increases the load on the Piezo1 mechanoreceptor.
- Opens the Ca++ ion channel.
- The Ca++ influx damages the mitochondria.
- Damaged mitochondria increase inflammatory cytokine production.
- Damaged mitochondria reduce cell repair and the reusing of old and damaged cells or parts of cells. This is **autophagy**.
- Reduced autophagy increases **apoptosis** and **senescence**, leading to cell death.
- **Apoptosis** and **Senescence** reduce the production of **Type-II Collagen** and **Aggrecan,** which degrades the **extracellular matrix.**
- The results are acceleration of degenerative disc disease and spinal stiffness.

This supports correcting cervical kyphosis (we use Dennerolls from CBP), correct subluxations, take Mg++ (blocks the Ca++ ion channel), use low-level laser therapy (improves mitochondria health and physiology), take mitochondria health supplements (like CoQ10, PQQ, acetyl-l-carnitine, alpha-lipoic acid, etc.).

See the following picture:

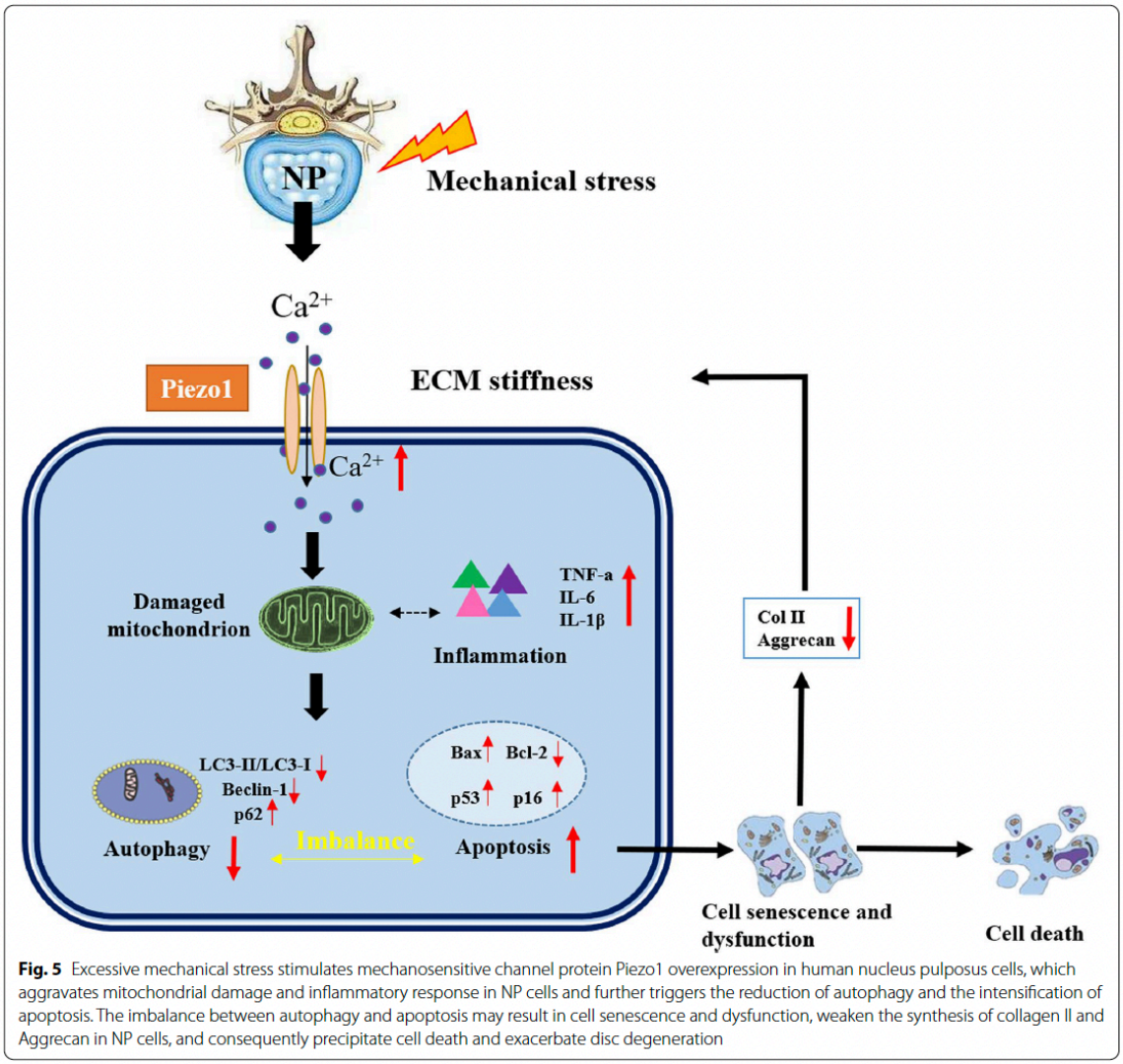


Fig. 5 Excessive mechanical stress stimulates mechanosensitive channel protein Piezo1 overexpression in human nucleus pulposus cells, which aggravates mitochondrial damage and inflammatory response in NP cells and further triggers the reduction of autophagy and the intensification of apoptosis. The imbalance between autophagy and apoptosis may result in cell senescence and dysfunction, weaken the synthesis of collagen II and Aggrecan in NP cells, and consequently precipitate cell death and exacerbate disc degeneration

Other *Article Reviews* on Piezo1 mechanoreceptors include:
Article Review 16-23:
Mechanical Loading Induces Piezo1 Calcium Influx and Osteoarthritis

Article Review 42-23:
Injury Initiates Disc Degeneration Through Piezo1 Mediated Inflammation

Other *Article Reviews* on cervical kyphosis include:
Article Review 24-11:
Is the Kyphosis Cause or Effect of Disc Degenerative Disease

Article Review 52-13:
Focal Kyphosis correction and Neurological Outcomes

Article Review 2-23:
Improvement in Cervical Curve in the Management of Lumbar Radiculopathy

The Emerging Role of Piezo1 Channels in Skeletal Muscle Physiology

Biophysics Review
September 29, 2023;Vol 15; 15; No. 5; pp. 1171-1184

Timur Mirzoev

Piezo1 channels are mechanically activated (MA) cation channels that are involved in sensing of various mechanical perturbations, such as membrane stretch and shear stress, and play a crucial role in cell mechanotransduction.

In response to mechanical stimuli, these channels open up and allow cations to travel into the cell and induce biochemical reactions that can change the cell's metabolism and function.

Skeletal muscle cells/fibers inherently depend upon mechanical cues in the form of fluid shear stress and contractions (physical exercise).

For example, an exposure of skeletal muscles to chronic mechanical loading leads to increased anabolism and fiber hypertrophy, while prolonged mechanical unloading results in muscle atrophy.

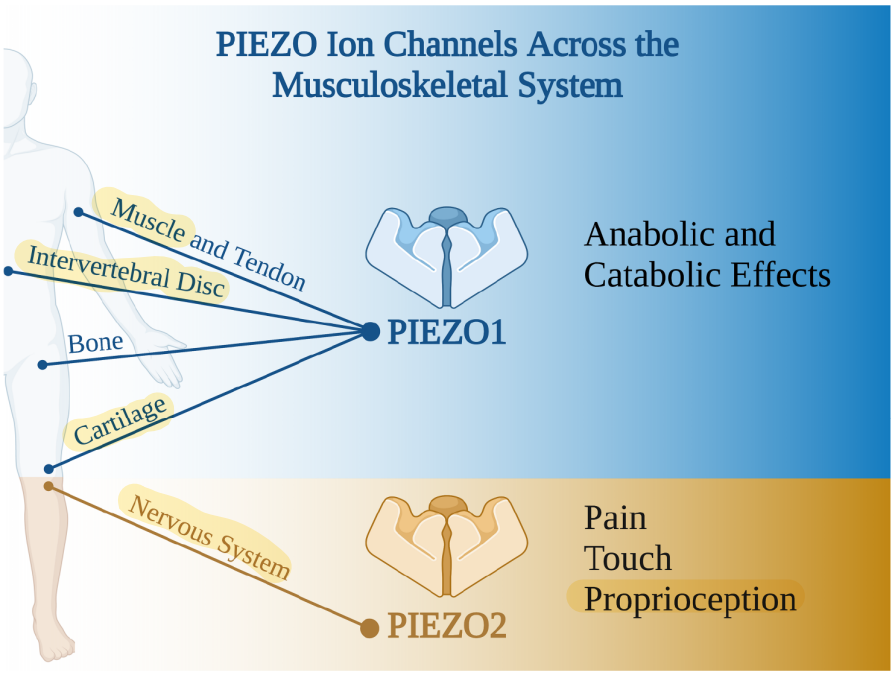
MA Piezo1 channels have recently emerged as key mechanosensors that are capable of linking mechanical signals and intramuscular signaling in skeletal muscle cells/fibers.

This review will summarize the emerging role of Piezo1 channels in the development and regeneration of skeletal muscle tissue as well as in the regulation of skeletal muscle atrophy.

In addition, an overview of potential Piezo1-related signaling pathways underlying anabolic and catabolic processes will be provided.

The Role of PIEZO Ion Channels in the Musculoskeletal System
March 14, 2023

Alireza Savadipour, Daniel Palmer, Erica Ely, Kelsey Collins, et. al.



AMERICAN JOURNAL OF PHYSIOLOGY
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american physiological society

PIEZO1 and PIEZO2 are mechanosensitive cation channels that are highly expressed in numerous tissues throughout the body and exhibit diverse, cell-specific functions in multiple organ systems.

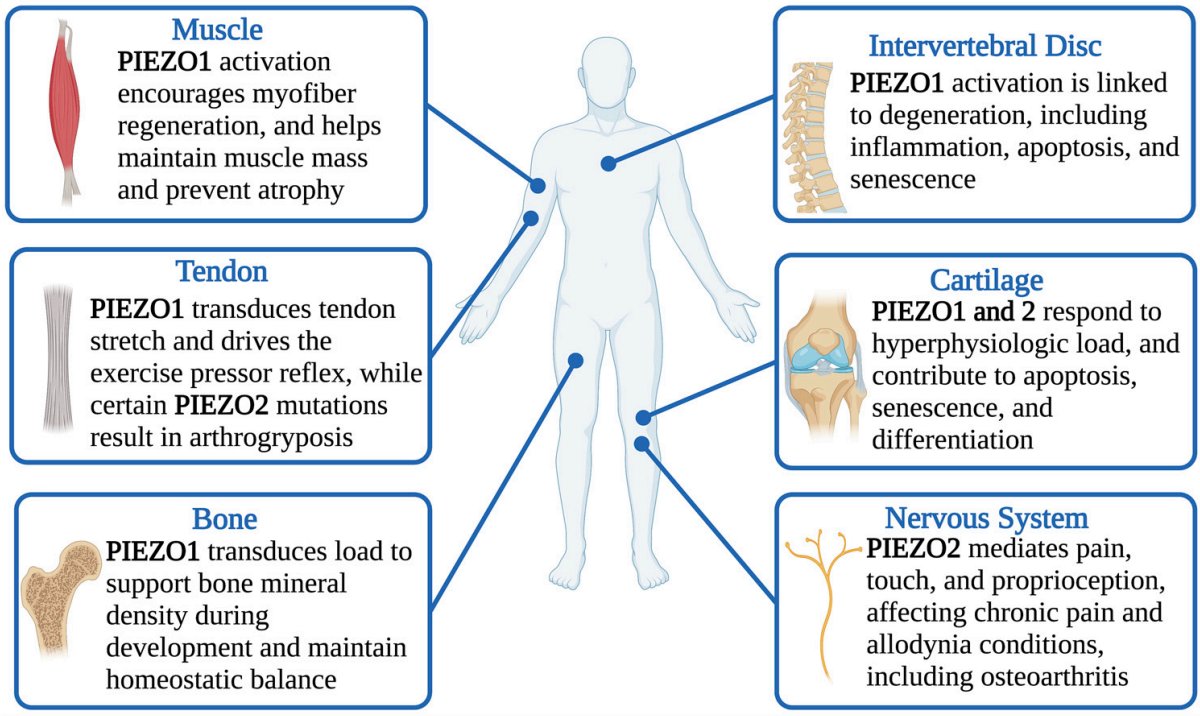
Within the musculoskeletal system, PIEZO1 functions to maintain muscle and bone mass, sense tendon stretch, and regulate senescence and apoptosis in response to mechanical stimuli within cartilage and the intervertebral disc.

PIEZO2 is essential for transducing pain and touch sensations as well as proprioception in the nervous system, which can affect musculoskeletal health.

PIEZO1 and PIEZO2 have been shown to act both independently as well as synergistically in different cell types.

Conditions that alter PIEZO channel mechanosensitivity, such as inflammation or genetic mutations, can have drastic effects on these functions.

PIEZO1 and PIEZO2 Regulate Essential Musculoskeletal Functions



Muscle
PIEZO1 activation encourages myofiber regeneration, and helps maintain muscle mass and prevent atrophy

Tendon
PIEZO1 transduces tendon stretch and drives the exercise pressor reflex, while certain **PIEZO2** mutations result in arthrogryposis

Bone
PIEZO1 transduces load to support bone mineral density during development and maintain homeostatic balance

Intervertebral Disc
PIEZO1 activation is linked to degeneration, including inflammation, apoptosis, and senescence

Cartilage
PIEZO1 and 2 respond to hyperphysiologic load, and contribute to apoptosis, senescence, and differentiation

Nervous System
PIEZO2 mediates pain, touch, and proprioception, affecting chronic pain and allodynia conditions, including osteoarthritis

Potential PIEZO-Related Therapies Include:

Targeted PIEZO Inhibition
Control PIEZO1 and 2 sensitivity through regulated use of inhibitors such as GsMTx4

Inhibit VGCCs or TRPV4
Inhibit voltage gated cation channels (VGCCs) or TRPV4 to modulate PIEZO activity

Dietary Supplementation
Increase omega-3/ omega-6 dietary fatty acid ratio to decrease PIEZO1 and 2 sensitivity

life

MDPI

Review

Voltage-Gated Ion Channels in Neuropathic Pain Signaling

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Abstract: Neuropathic pain is a chronic and debilitating disorder of the somatosensory system that affects a significant proportion of the population and is characterized by abnormal responses such as hyperalgesia and allodynia. Voltage-gated ion channels, including sodium (Na_V), calcium (Ca_V), and potassium (K_V) channels, play a pivotal role in modulating neuronal excitability and pain signal transmission following nerve injury. This review intends to provide a comprehensive analysis of the molecular and cellular mechanisms by which dysregulation in the expression, localization, and function of specific Na_V channel subtypes (mainly $Na_V1.7$ and $Na_V1.8$) and their auxiliary subunits contributes to aberrant neuronal activation, the generation of ectopic discharges, and sensitization in neuropathic pain. Likewise, special emphasis is placed on the crucial role of Ca_V channels, particularly $Ca_V2.2$ and the auxiliary subunit $Ca_V\alpha_2\delta$, whose overexpression increases calcium influx, neurotransmitter release, and neuronal hyperexcitability, thus maintaining persistent pain states. Furthermore, K_V channels (particularly K_V7 channels) function as brakes on neuronal excitability, and their dysregulation facilitates the development and maintenance of neuropathic pain. Therefore, targeting specific K_V channel subtypes to restore their function is also a promising therapeutic strategy for alleviating neuropathic pain symptoms. On the other hand, recent advances in the development of small molecules as selective modulators or inhibitors targeting voltage-gated ion channels are also discussed. These agents have improved efficacy and safety profiles in preclinical and clinical studies by attenuating pathophysiological channel activity and restoring neuronal function. This review seeks to contribute to guiding future research and drug development toward more effective mechanism-based treatments by discussing the molecular mechanisms underlying neuropathic pain and highlighting translational therapeutic opportunities.

Keywords: voltage-gated ion channels; neuropathic pain; calcium channels; Ca_V channels; potassium channels; K_V channels; sodium channels; Na_V channels; PROTACs

Academic Editors: Carlo Musio and Marzia Martina

Received: 27 January 2025
Revised: 30 April 2025
Accepted: 8 May 2025
Published: 30 May 2025

Citation: Felix, R.; Corzo-Lopez, A.; Sandoval, A. Voltage-Gated Ion Channels in Neuropathic Pain Signaling. *Life* **2025**, *15*, 888. https://doi.org/10.3390/life15060888

1. Introduction

The somatosensory system enables us to perceive and interact with our environment and body through highly specialized peripheral sensory neurons in the skin, muscles, joints, and internal organs that detect touch, pressure, pain, and temperature. These neurons detect environmental stimuli, convert them into action potentials (APs), and transmit them to the brain via the spinal cord (SC). These same neurons transmit pain signals through the peripheral nerves to the SC, where second-order neurons transfer them to the thalamus. The thalamus receives these signals and projects them to the primary somatosensory cortex, where the information is integrated [1] (Figure 1).

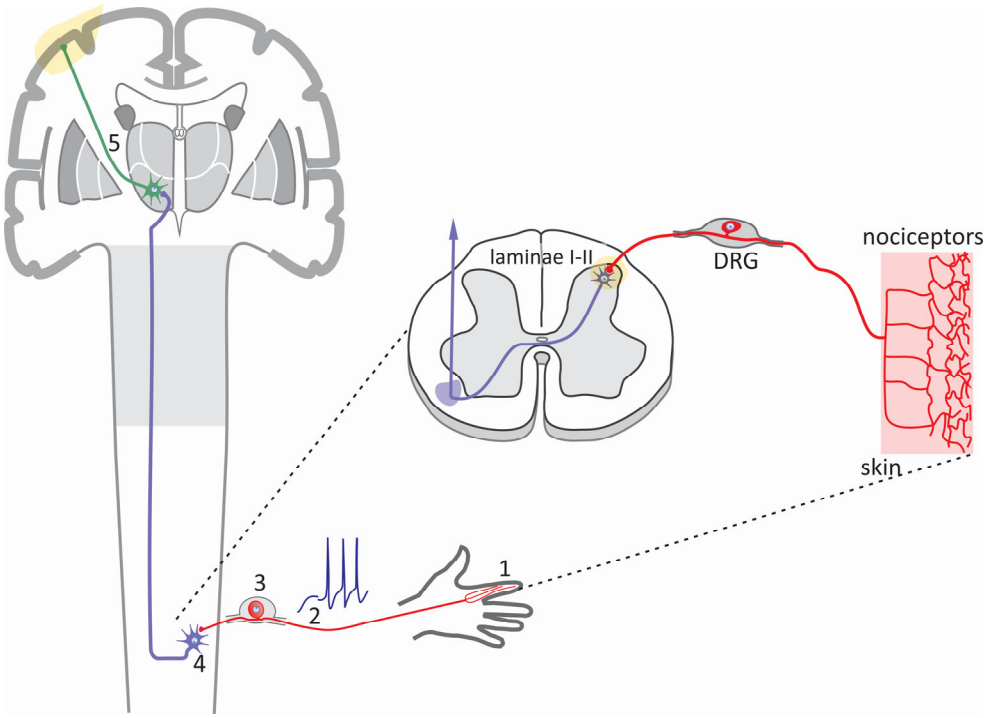

Figure 1. The sensory pathway. The somatosensory system comprises an intricate network of sensory receptors distributed throughout the skin, muscles, joints, and internal organs. These receptors include nociceptors activated in response to noxious stimuli and generate pain signals. The information generated in the periphery (1) is transmitted as action potentials (2), primarily via primary afferent fibers of the Aδ and C type that have a peripheral axon innervating the distal regions, to the DRG (3), where the soma of the sensory neurons are located. The pain signals then travel to the second-order neurons in the laminae I-II of the spinal cord (4). Finally, these signals are transmitted to third-order neurons in the thalamus (5) and then to the primary somatosensory cortex to be integrated.

Neuropathic pain is a disorder of the somatosensory system that affects ~10% of the general population. It is more frequent in women and in individuals over 50 years of age and most frequently affects the lower back, upper and lower limbs, and the neck [2,3]. It is characterized by abnormal responses to stimuli, including hyperalgesia, an increased painful response to painful stimuli, and allodynia, the presence of pain associated with innocuous stimuli. Different conditions may cause neuropathic pain, with diabetes mellitus being one of the most significant [3]. However, neuropathic pain may also occur as a result of herpes virus infections, acquired immunodeficiency syndrome, or have a traumatic origin. Likewise, autoimmune disorders such as Guillain–Barré syndrome and multiple sclerosis, as well as some oncological treatments, may also cause peripheral neuropathy [1,3].

It is well-known that the changes responsible for neuropathic pain mechanisms lie in altered gene transcription or protein functional expression/localization in sensory neurons. Interestingly, after damage to peripheral sensory fibers, alterations in the different subunits that compose voltage-gated ion channels may contribute to the changes in pain transmission observed in allodynia and hyperalgesia, as we shall discuss next [1,4].

2. Voltage-Gated Sodium (Na_V) Channels and Neuropathic Pain

2.1. Structure and Function of Na_V Channels

Na_V channels play a relevant role in the development and maintenance of neuropathic pain. These proteins are essential components of the excitability machinery in excitable cells, including neurons, and alterations in their expression or function after nerve injury

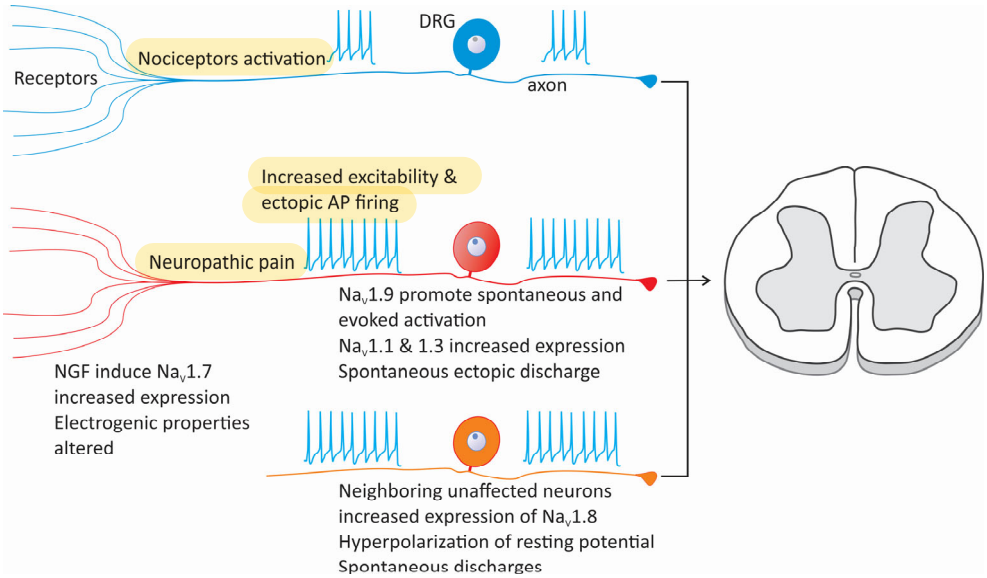

Figure 3. Changes in Na_V channel expression and cellular excitability in neuropathic pain. Alterations in the expression of various subtypes of sodium channels, such as $Na_V1.1$, $Na_V1.3$, $Na_V1.7$, $Na_V1.8$, and $Na_V1.9$, can increase cellular excitability, reducing the activation threshold of nociceptors. Similarly, after nerve injury, neurons adjacent to the damaged area may experience changes in the expression of Na_V channels, particularly $Na_V1.3$ and $Na_V1.8$, which causes the development of ectopic foci of neuronal activity. On the other hand, the expression of $Na_V1.8$ channels in neurons neighboring an injured nerve can also be compromised, contributing to the maintenance of neuropathic pain.

$Na_V1.9$ channels are expressed primarily in nociceptive neurons, where they play a relevant role in pain signaling, especially in neuropathic pain conditions [24,27]. In addition to those reviewed in the preceding sections, these channels generate APs and amplify pain signals, especially after nerve injury. While $Na_V1.9$ channels mediate TTX-R sodium currents that are crucial for maintaining neuronal excitability under physiological conditions [41,45], under pathological conditions, sodium currents through these channels can become dysregulated and contribute to chronic pain states. Numerous studies suggest that $Na_V1.9$ channels favor spontaneous and evoked activation in DRG neurons, which, in abnormal conditions, leads to exacerbated pain perception [24,27].

2.3. The Role of the Na_V Channel Auxiliary Subunits in Neuropathic Pain

Furthermore, as already mentioned, $Na_V\beta$ auxiliary subunits regulate the kinetic properties and voltage dependence of the ion-conducting subunits of Na_V channels [9,46,47]. Therefore, alterations in the functional expression of these proteins may influence the development of neuropathic pain due to their central role in the excitability of sensory neurons. On the other hand, it has also been observed that the expression of the auxiliary subunits $Na_V\beta_2$ and $Na_V\beta_3$ can be augmented after peripheral nerve injury, both in injured sensory neurons and neighboring uninjured nerve cells. This could be associated with neuronal hyperexcitability and the development of ectopic activity [48].

Previous work on $Na_V\beta_2$ subunit expression has revealed that this protein is upregulated following peripheral nerve injury, which may affect neuronal excitability [48]. This idea is supported by results obtained in $Na_V\beta_2$ null mice, showing decreased Na_V TTX-S channel expression in DRG neurons [10,49]. Remarkably, mechanical allodynia associated with peripheral nerve injury was attenuated in the knockout animals, consistent with the role of this protein in neuropathic pain [10,49].

The auxiliary subunit $Na_V\beta_3$ may also play a role in neuropathic pain. As discussed above, there is evidence that peripheral nerve injury induces an increase in currents passing

At the molecular level, VX-548 exhibits potent state-dependent inhibition of $Na_V1.8$ channels, characterized by a "reverse use dependence" mechanism. This means that it binds tightly to the channels in their resting (closed) state, but this inhibition can only be rapidly relieved by extensive and prolonged depolarizations. Consequently, VX-548 maintains tonic inhibition of these channels under physiological conditions. This unique mechanism distinguishes VX-548 from other Na_V channel inhibitors and supports its consistent and selective analgesic effect [75,76].

The clinical success of VX-548 validates $Na_V1.8$ channels as a viable pharmacological target for treating acute pain, confirming their central role in peripheral nociceptive signaling. Furthermore, initial data from the evaluation of VX-548 in managing pain in DPN and LSR suggest that $Na_V1.8$ channels also play a relevant signaling role during the development of neuropathic pain. However, further studies are required to validate this idea.

The treatment of neuropathic pain aimed at the selective inhibition of $Na_V1.8$ channels offers several advantages. These compounds provide analgesia and may improve tolerability compared to other therapies. By targeting peripherally located Na_V channels, these blockers may minimize the central side effects typically seen with more broad-spectrum Na_V channel inhibitors. Preclinical and clinical research will contribute to a better understanding of their role and effectiveness in broader pain management contexts.

On the other hand, therapy targeting the molecular mechanisms associated with neuropathic pain involving $Na_V1.9$ channels is still in development. Finding compounds that may alter $Na_V1.9$ currents has proven difficult [61]. This is because the expression of these channels in heterologous systems is complex and tends to run down quickly in sensory neurons [77]. An innovative strategy was developed in which individual voltage-sensor paddles from $Na_V1.9$ were transplanted into chimeric constructs of voltage-gated (K_V) channels to identify toxins that may interact with native $Na_V1.9$ channels [78]. Although this study showed that $Na_V1.9$ channels have a distinctive pharmacological profile and that the voltage-sensor paddles could be promising targets, it was unclear to what extent the chimeric channels reproduced the pharmacological properties of native channels.

3. Voltage-Gated Calcium (Ca_V) Channels in Neuropathic Pain

3.1. Structure and Function of Ca_V Channels

Ca_V channels are the preferential route for the entry of calcium ions into excitable cells. These channels are activated in response to the depolarization of the plasma membrane and, thus, allow for the selective entry of calcium. In this way, Ca_V channels contribute to determining cell excitability. Additionally, calcium entering cells acts as a second chemical messenger that initiates and regulates multiple physiological processes, including gene expression and neurotransmitter release, among many others. Therefore, Ca_V channels play a dual role by linking electrical signals at the cell surface with biochemical responses within the cell [79–82].

Based on their biophysical and pharmacological properties, voltage-gated calcium (Ca_V) channels have been classified into T, L, N, P, Q, and R subtypes. However, the most used classification is based on the voltage range at which they apparently activate, separating them into the following two categories: low- and high-threshold channels, LVA and HVA, respectively. The T-type channel is the only low-threshold channel described, while the L-, N-, P-, Q-, and R-type channels are considered to be high-voltage-activated channels [79–84] (Figure 4A).

Likewise, it is known that the $Ca_V\alpha_2\delta$ auxiliary subunits favor the membrane expression of Ca_V channels (Figure 4A). Four subtypes of these proteins have been described ($Ca_V\alpha_2\delta$-1 to $Ca_V\alpha_2\delta$-4), encoded by independent genes (*CACNA2D*). These genes are initially translated into precursor proteins that are proteolytically processed, giving rise to two peptides, $Ca_V\delta$ and $Ca_V\alpha_2$, with the first anchored to the plasma membrane through a GPI motif and the second being completely extracellular, which remain linked by a disulfide bond [88]. The $Ca_V\alpha_2$ peptide is highly glycosylated and contains diverse functional regions, including von Willebrand factor A (vWFA) motifs, a metal-ion-dependent adhesion site (MIDAS), and four cache regions. Similarly to the $Ca_V\beta$ subunit, the $Ca_V\alpha_2\delta$ subunits promote and stabilize the expression of Ca_V channels on the cell surface [79,85,89].

Finally, eight $Ca_V\gamma$ subunits have been identified, which, according to phylogenic analyses, belong to a protein subfamily originating from a single gene. Biochemical and electrophysiological studies have shown the physical and functional interactions of these subunits with the Ca_V channel complex [90–93]. On the other hand, it is known that the $Ca_V\gamma_2$ subunit can also bind to proteins containing the PDZ domain and that it participates in the intracellular trafficking of the AMPA receptor [94].

In mammals, ten different $Ca_V\alpha_1$ subunits encoded by independent genes (*CACNA1*) are expressed, which, from a molecular point of view, group Ca_V channels into three subfamilies [81,82]. The first (Ca_V1) includes L-type channels with four members ($Ca_V1.1$ to $Ca_V1.4$). The Ca_V2 subfamily has three members ($Ca_V2.1$ to $Ca_V2.3$), which give rise to currents through P/Q-type, N-type, and R-type neuronal channels, respectively. P- and Q-type channels result from the alternative splicing of the *CACNA1A* gene encoding the $Ca_V2.1\alpha_1$ subunit [95,96].

Lastly, the Ca_V3 subfamily groups low-activation-threshold channels and consists of three members, $Ca_V3.1$ to $Ca_V3.3$ (Figure 4A). These channels allow for a basal calcium influx called a window current, which helps to maintain the resting membrane potential. Likewise, since they are activated at more negative potentials than the other Ca_V channels, they can significantly influence cell excitability, contributing to the generation of APs and rhythmic electrical activity [79–82].

It is widely accepted that Ca_V channels may play a key role in the fundamental mechanisms of neuropathic pain. The contribution of these proteins to cell excitability and neurotransmission, as well as their potential role in the treatment of the condition, stresses the need to understand neuropathic pain at the cell and molecular levels [82,85,97]. The association of Ca_V channels with the pathogenesis of the disease occurs predominantly through the HVA channels of the P/Q- ($Ca_V2.1$) and N-types ($Ca_V2.2$) and the ancillary $Ca_V\alpha_2\delta$ subunit. However, it has also been reported that the LVA channels of the $Ca_V3.2$ class may also contribute significantly to the pathophysiology of the condition [98–100].

As mentioned above, the entry of calcium ions in response to the activation of Ca_V2 channels determines the release of neurotransmitters. The calcium that enters the nerve terminal promotes the assembly of a subset of scaffolding proteins essential for anchoring synaptic vesicles containing neurotransmitters to the cell membrane and their eventual fusion [87,101,102] (Figure 4B). Therefore, alterations in the functional expression of Ca_V2 channels will alter synaptic transmission and consequently may affect pain signaling.

3.2. Role of Different Ca_V2 Channel Subunits in Nociceptive Pathways and Neuropathic Pain

Ca_V channels regulate neuronal excitability, synaptic transmission, and pain signaling. As we will see below, there are three subtypes of Ca_V2 channels. Among them, $Ca_V2.1$ (P/Q-type) and $Ca_V2.2$ (N-type) are particularly important in neurotransmission between primary afferent fibers and neurons of the SC's dorsal horn.

Ca_V2 channels contribute to the onset and maintenance of neuropathic pain through different cellular and molecular processes. Firstly, these channels are decisive in synaptic transmission, since their activation gives rise to transient increases in the concentration of intracellular calcium in the nerve terminals, which favors the release of neurotransmitters. In pathological conditions, however, synaptic transmission in sensory neurons may be altered, increasing the release of chemical pain mediators such as glutamate and substance P and inducing central sensitization, one of the main features of neuropathic pain. Second, the activity of Ca_V2 channels can be regulated by phosphorylation and other post-translational modifications, which may promote their functional expression during neuropathic pain. Finally, transient increases in intracellular calcium can cause, in pathological conditions, changes in gene expression patterns that promote the activation of transcription factors that target genes associated with chronic pain [103] (Figure 5A).

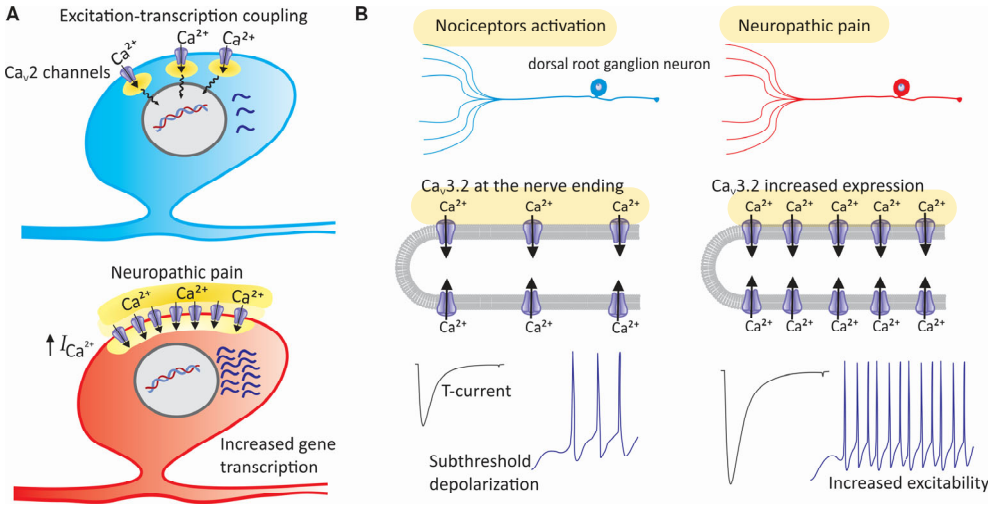

Figure 5. Contribution of Ca_V channels to the pathogenesis of neuropathic pain. (**A**) In addition to its effects on the release of neurotransmitters, alteration in the expression of Ca_V2 channels participates in the pathophysiology of neuropathic pain by affecting the excitation–transcription coupling. This fundamental cell process links electrical activity in excitable cells to gene transcription. This implies that the calcium, once inside the cells, can activate transcription factors, either directly or through protein kinases and second messengers that control the activity of these factors. (**B**) Overexpression of Ca_V3 channels in sensory neurons during neuropathic pain increases their excitability, decreases the firing threshold of afferent fibers, and favors repetitive firing.

The contribution of $Ca_V2.1$ (P/Q-type) channels to pain perception is being studied in detail and is beginning to be revealed. These channels are crucial for neurotransmitter release in the CNS, and pharmacological studies suggest their involvement in the pathophysiology of pain. While initial studies showed that intrathecal injections of specific blockers, such as AgaIVA, did not have an apparent effect on $Ca_V2.1$ channels in neuropathic pain [104–106], subsequent research has indicated that they may influence descending pathways that modulate pain transmission in some areas of the brain [107,108]. Likewise, studies conducted in $Ca_V2.1\alpha_1$ subunit knockout mice have revealed alterations in their response to nociceptive stimuli [109]. However, eliminating the pore-forming subunit of $Ca_V2.1$ channels does not significantly modify the response to thermal stimuli [109].

$Ca_V2.2$ channels are predominantly expressed in the presynaptic nerve terminals of central and peripheral neurons [110]. They are crucial for releasing neurotransmitters relevant to generating pain signals, such as glutamate and GABA. In addition, the activity of these channels is modulated by the activation of various G protein-coupled receptors (GPCRs) involved in nociception, including opioid, cannabinoid, neuropeptide Y, and

substance P receptors [111,112]. Research has shown a significant relationship between the knockout of $Ca_V2.2$ channels and neuropathic pain, consistent with their contribution to the molecular pathophysiology of this condition. Multiple studies suggest that the genetic ablation of these channels can result in reduced pain responses across various models of neuropathic pain [113,114]. The absence of $Ca_V2.2$ channels affects the release of substance P and CGRP, and this reduction in neurotransmitter release contributes to a decrease in overall pain signaling.

$Ca_V2.2$ channels are concentrated in nerve terminals located in laminae I and II of the dorsal horn of the spinal cord, where they transmit pain signals arriving on C and Aδ fibers. Interestingly, these channels in primary afferent fibers contribute to developing allodynia and hyperalgesia after nerve injury [115], as discussed below.

Several studies have shown that mutually exclusive splicing patterns in the gene encoding the $Ca_V2.2\alpha_1$ subunit modulate the function of N-type channels in sensory neurons and can influence pain transmission. In particular, an exon 37a-containing isoform whose expression is restricted to DRGs correlates closely with significantly larger N-type currents in nociceptive neurons [116,117]. The preferential inclusion of exon 37a in sensory neurons generates a module in the C-terminus of the $Ca_V2.2\alpha_1$ subunit that mediates channel inhibition in a voltage-independent manner, which requires tyrosine kinase activation [118,119]. Furthermore, exon 37a enhances the μ-opioid-receptor-mediated inhibition of N-type channels [120], contributing to defining the molecular nature of the voltage-independent inhibition of N-type channels in the pain pathway.

Likewise, research in animal pain models has shown that the expression of the $Ca_V2.2\alpha_1$ subunit is significantly increased [100]. Mice subjected to partial sciatic nerve ligation showed an increased current amplitude through N-type channels and increased mRNA levels for the gene encoding the $Ca_V2.2\alpha_1$ protein in DRG neurons [121,122]. Likewise, in a chronic constrictive nerve injury model, the $Ca_V2.2\alpha_1$ protein was upregulated in lamina II of the SC dorsal horn [123]. Furthermore, in nerve ligation models, a significant increase in the expression of $Ca_V2.2$ channels with a subsequent increase in the amplitude of the current was reported, which further facilitated the excitatory synaptic transmission of Aδ and C fibers in the SC dorsal horn [122].

Research on the cellular and molecular bases of neuropathic pain has shown that ubiquitination may contribute to its establishment and maintenance by regulating the turnover of synaptic proteins. Specifically, it has been described that the active zone protein RIM1α participates in the development of the condition by binding and positively regulating the expression of $Ca_V2.2$ channels. It is also known that RIM1α-associated spinal allodynia is mediated by Fbxo3, a protein that reduces the Fbxl2-dependent ubiquitination of RIM1α. When deubiquitinated, RIM1α can bind directly to these channels, increasing its expression in the nerve terminals of the dorsal horn of the SC [124].

The activation of nociceptin opioid peptide (NOP) receptors, also known as opioid-like receptor 1 (ORL-1), results in the G protein-dependent regulation of $Ca_V2.2$ channels [125–127]. This results in a decreased current amplitude, with consequent alterations in presynaptic calcium levels and impairment in neurotransmission [128]. Due to the widespread expression of both NOP and $Ca_V2.2$ channels in the brain, dorsal horn of the SC, and DRG, alterations in this system result in different neurological conditions, including neuropathic pain. As mentioned, $Ca_V2.2$ channels are crucial for pain processing by controlling the synaptic strength on C and Aδ afferent fibers. Thus, reducing calcium influx by activating NOP receptors may decrease the release of CGRP and substance P, neurotransmitters involved in pain signaling. This is beneficial in neuropathic pain, where the expression of $Ca_V2.2$ channels is generally upregulated [126,129].

3.3. The Role of the $Ca_V\alpha_2\delta$-1 Auxiliary Subunit in Neuropathic Pain

The $\alpha_2\delta$ subunits of Ca_V2 channels have been shown to play crucial roles in nociceptive signaling [130–133]. As mentioned earlier, these proteins are essential in the function and regulation of these channels by contributing to the intracellular trafficking, voltage dependence, and kinetics of the currents [134–138]. In particular, the $Ca_V\alpha_2\delta$-1 subunit, which is expressed in excitable cells, including neurons, is essential for presynaptic functions such as synapse formation, the regulation of synaptic plasticity, and the control of the calcium concentration in the synaptic cleft [138–140]. The protein contains several functional regions that allow for interactions with the channel complex and other synaptic molecules. Research on the structure of $Ca_V\alpha_2\delta$ has identified a von Willebrand factor A (VWA) region along with four cache domains. The VWA region is critical for interaction with the $Ca_V\alpha_1$ subunit [138].

It has been reported that $Ca_V\alpha_2\delta$ expression may increase at both the mRNA and protein levels in sensory neurons after spinal nerve ligation and in animal models of diabetic neuropathy [130,141–145]. This change is accompanied by AP discharges in the injured neurons due to an increase in the functional expression of $Ca_V2.2$ channels mediated by the exacerbated expression of the $Ca_V\alpha_2\delta$ subunit. Consistent with this, genetic ablation of the $Ca_V\alpha_2\delta$-1 subunit significantly decreased the expression of $Ca_V2.2$ channels on the cell membrane of DRG neurons and in the dorsal horn of the SC [146]. This alteration in neuronal excitability can affect the release of neurotransmitters associated with neuropathic pain pathways [122]. Interestingly, mice overexpressing $Ca_V\alpha_2\delta$-1 exhibit neuropathic pain symptoms without nerve damage, whereas $Ca_V\alpha_2\delta$-1-deficient mice show deficits in sensitivity after nerve injury [147–149].

Several studies support an important role of the interaction between the $Ca_V\alpha_2\delta$-1 subunit and thrombospondin-4 (TSP4), a glycoprotein found in the extracellular matrix, in nerve-injury-induced neuropathic pain, mediated through aberrant excitatory synapse formation and presynaptic neurotransmission in the SC [150–152]. Peripheral nerve injury induces the upregulation of both proteins in the SC that precedes the onset and correlates with the duration of neuropathic pain [130,141–143,153–155]. The inhibition of this regulation or the genetic ablation of $Ca_V\alpha_2\delta$-1 or TSP4 prevent the onset and development of the disease [152,155,156]. The mechanism by which an exaggerated expression of TSP4 alters the function of Ca_V channels remains to be established. In this regard, it has been reported that TSP4 can differently affect the distinct types of channels in sensory neurons, decreasing the currents passing through HVA channels and increasing those flowing through LVA channels [154], which is paradoxical given that, unlike what occurs with HVA channels, a clear role for auxiliary subunits, including $Ca_V\alpha_2\delta$-1, in the functional expression of LVA channels has not yet been established. Further research is required to better understand the origin of this discrepancy.

Similarly, research has demonstrated that the $Ca_V\alpha_2\delta$-1 subunit interacts with N-methyl-D-aspartate receptors (NMDARs) to create a complex that increases their activity by promoting their trafficking to synapses [157,158]. NMDARs are preferentially expressed in postsynaptic neurons, but are also present in presynaptic neurons, influencing neurotransmitter release and synaptic plasticity [159]. The activation of presynaptic NMDARs leads to increased calcium and the exocytosis of secretory vesicles, resulting in greater glutamate release. Under normal conditions, NMDARs are inactive; however, these receptors become tonically active in neuropathic pain [160]. Notably, models of neuropathic pain have shown an elevated expression of $Ca_V\alpha_2\delta$-1/NMDAR complexes, indicating their potential involvement in pain mechanisms [149].

have shown that knocking down USP5 results in an increased ubiquitination of $Ca_V3.2$, decreased protein levels of the channel, and reduced whole-cell currents [170–172]. Conversely, increasing USP5 activity leads to greater activity of $Ca_V3.2$ channels in models of neuropathic pain.

3.5. Ca_V Channels as Potential Therapeutic Targets for Neuropathic Pain

Gaining insight into the function and potential of Ca_V channels as therapeutic targets has offered valuable information for managing chronic pain conditions. For instance, $Ca_V2.2$ channels are key in pain signaling because they help release neurotransmitters from sensory neurons. Blocking these channels can prevent the release of neuropeptides that transmit pain, making them a promising target for treating neuropathic pain.

Several studies stress significant advancements in studying $Ca_V2.2$ channels for treating neuropathic pain. Ziconotide, a synthetic version of the marine peptide ω-conotoxin MVIIA, has been established as an effective blocker of these channels for treating severe chronic pain [111,173]. It is administered intrathecally and has shown efficacy in several neuropathic pain models. The mechanism of ziconotide involves blocking calcium entry, which is crucial for releasing the neuropeptides substance P and CGRP in sensory neurons [174].

Furthermore, in animal models, treatment with ziconotide can prevent hyperalgesia and allodynia, confirming the role of $Ca_V2.2$ channels in establishing neuropathic pain. Ziconotide is about ten times more potent than intrathecally administered morphine [175]. However, its clinical use is limited by side effects [111]. Leconotide is a newer blocker of $Ca_V2.2$ channels, which has emerged as an alternative to ziconotide. This compound has been shown to have antihyperalgesic effects and offers a better side effect profile [176]. On the other hand, an alternative for pain relief has focused on developing small molecules that function as inhibitors of $Ca_V2.2$ channel activity. These molecules aim to provide similar benefits to ziconotide and leconotide without the disadvantages associated with peptide administration. Some of these peptides have been designed to disrupt the coupling of the main subunit $Ca_V\alpha_1$ with other intrinsic or extrinsic proteins in the channel complex. In this context, various studies suggest that collapsin response mediator protein 2 (CRMP-2) is an important molecular interactor of $Ca_V2.2$, regulating its function and, consequently, the release of neurotransmitters in sensory neurons. The overexpression of CRMP-2 increases the current density through $Ca_V2.2$ channels and enhances the release of CGRP, which participates in pain transmission.

It has also been reported that disrupting the CRMP-2/$Ca_V2.2$ complex with specific peptides, such as TAT-CBD3, Ct-dis, and R9-CBD3-A6K, reduces the excessive neurotransmitter release associated with chronic pain, showing antinociceptive effects in neuropathic pain models [177–180]. Moreover, the potential of quinazolines and benzoylpyrazolines as agents that disrupt the coupling between $Ca_V\alpha_1$ and $Ca_V\beta$ subunits has been investigated. These compounds have shown the ability to decrease currents through $Ca_V2.2$ channels, alter their presynaptic localization, and inhibit the release of CGRP, exhibiting antinociceptive properties in various pain models, including neuropathic pain [181].

Likewise, Khanna and his colleagues also showed that the inhibition of the interaction between $Ca_V\alpha_1$ and $Ca_V\beta$ subunits reduces the excitability of DRG neurons, leading to a decrease in acute and neuropathic pain in several animal models [182]. Specifically, the authors developed a molecule identified as IPPQ that selectively binds to $Ca_V\beta$, inhibiting its coupling with the $Ca_V\alpha_1$ subunit of $Ca_V2.2$ channels. This leads to the delocalization of presynaptic channels, a decrease in the amplitude of calcium currents in sensory neurons, and a reduction in the release of the nociceptive neurotransmitter CGRP in the SC. This same research group recently designed a small peptidomimetic molecule derived from

species production and potentiating the release of proinflammatory cytokines in the central nervous system.

Voltage-gated H^+ channels allow for the flow of protons across the cell membrane in response to changes in electrical potential and play important roles in various cellular functions. When activated during membrane depolarization, they allow proton efflux, thus helping to maintain the acid–base balance within cells. Furthermore, Hv1 proton channels may directly influence neuronal excitability by conducting ions that depolarize the neuronal membrane. As mentioned above, they may also indirectly modulate excitability through their effects on ROS production, pH regulation, injury, and microglial activity.

The molecular structure of Hv1 channels differs from other voltage-gated ion channels due to their unique composition and function [262]. These channels consist solely of a voltage-sensing domain (VSD) composed of four transmembrane helices (S1–S4) and an additional amphipathic helix (S0) at the N-terminus. They are composed of two subunits, each with its own proton permeability pathway within the VSD [262,263]. The S4 helix in the VSD is crucial for sensing changes in transmembrane voltage. It undergoes outward displacement in response to depolarization, which changes the internal salt bridge network and reconfigures the proton permeability pathway [262]. The two subunits of Hv1 channels interact during the channel opening process, showing a positive cooperativity that modulates the voltage response of the two permeation pathways [264]. Furthermore, Hv1 channels exhibit unidirectional conductance, allowing protons to exit the cell but not enter it, which is essential for maintaining intracellular pH homeostasis.

The involvement of ROS in the development of neuropathic pain is reinforced by the fact that, following spinal cord injury, a large proportion of patients develop neuropathic pain [265]. Furthermore, NOX2-derived ROS in microglia have been associated with neuropathic pain induced by nerve injury [266]. It is also known that, in response to peripheral nerve injury, macrophages are recruited by DRGs and increase ROS production through a NOX2-dependent mechanism. Interestingly, $NOX2^{-/-}$ mice display a reduced neuropathic pain phenotype [267]. Given the established link between Hv1–NOX and NOX2 and the development of neuropathic pain, it was initially suggested that microglial Hv1 channels could initiate and maintain neuropathic pain after spinal cord injury [268].

Indeed, Hv1 channels are functionally expressed in spinal cord microglia and show significant upregulation following peripheral nerve injury [269]. Furthermore, the activation of these channels contributes to the onset of neuropathic pain by favoring the production of reactive oxygen species (ROS). This production of ROS is associated with astrocyte activation, which worsens pain sensitivity [269]. Likewise, Hv1-null mice display decreased pain sensitivity after nerve injury compared to wild-type mice. Together these data suggest that Hv1 channels are relevant in mediating pain responses through microglial and astrocytic interactions.

6. Voltage-Gated Ion Channel Dysregulation in Supraspinal Pathways

Pain transmission involves complex neural circuits that run from the periphery to the brain. While spinal mechanisms are crucial for the initial processing of nociceptive signals, supraspinal pathways, predominantly cortical and brainstem circuits, are essential for the integration, modulation, and conscious perception of pain.

The cortex plays a central role in pain perception, integrating sensory, emotional, and cognitive aspects. Key regions include the somatosensory cortices (S1 and S2), which are responsible for the sensory-discriminative aspects of pain, such as location and intensity. S1 receives nociceptive inputs from the thalamus, while S2 integrates information from multiple body regions. The insula and anterior cingulate cortex (ACC) provide pain's affective and emotional dimensions. The insula contributes to the subjective experience, while

the ACC is related to emotional and motivational responses. The prefrontal cortex participates in cognitive pain evaluation, including attention and modulation. Its dysfunction is associated with chronic pain.

The brainstem bridges cortical centers and spinal circuits, modulating pain through several structures, including the periaqueductal gray matter that integrates descending pain control signals, producing analgesia by inhibiting nociceptive neurons. The rostral ventromedial nucleus of the medulla oblongata contains neurons that facilitate and impede pain, exerting bidirectional control. Finally, the parabrachial area involves pain's affective and motivational aspects and contributes to the transition from acute to chronic pain.

While alterations in peripheral voltage-gated ion channels predominate in initiating neuropathic pain, supraspinal mechanisms may maintain pain through central sensitization and altered descending control. However, direct evidence for the involvement of voltage-gated ion channels in supraspinal pathways is scarce and contrasts with their well-documented contribution to peripheral and spinal mechanisms. In this context, it is worth noting that neuropathic pain may involve important changes in neuronal excitability and synaptic transmission along the peripheral and supraspinal pathways. Indeed, a key event in the development of neuropathic pain is central sensitization, which involves alterations in neuronal excitability and synaptic transmission. Though the involvement of voltage-gated ion channels has not been directly documented in the supraspinal context, their contribution to neuronal excitability suggests that they may be indirectly involved in neuropathic pain, as discussed below.

It has been documented that $Na_V1.3$ channels, especially in the thalamus, can generate and maintain neuropathic pain due to their role in central hyperexcitability [14,201]. Particularly, after a spinal cord injury, $Na_V1.3$ channel expression increases significantly in thalamic neurons, which is associated with increased spontaneous neuronal activity contributing to pain generation. Furthermore, it has been observed that spinal cord injuries can trigger supraspinal changes in Na_V channel expression in thalamic neurons [14,37,270].

Specifically, four weeks after injury, immunostaining for $Na_V1.3$ channels was significantly increased in neurons of the ventral posterolateral nucleus of the thalamus. Electrophysiological recordings from neurons in this region in SCI animals showed a high rate of spontaneous activity, independent of ascending afferent input. Interestingly, antisense oligonucleotides targeting $Na_V1.3$ channel messengers reduced their expression in the thalamus and reversed the increase in spontaneous activity. Furthermore, the exacerbated spontaneous activity persisted even after complete spinal cord transection, indicating that afferent input is not essential for maintaining thalamic hyperexcitability, suggesting that this region may function as an intrinsic pain generator [37,270] and supporting the finding that $Na_V1.3$ overexpression in the post-spinal cord injury thalamus contributes to spontaneous neuronal activity and neuropathic pain. Although further research is needed to fully understand Na_V channels' contributions to neuropathic pain, their involvement in central sensitization and hyperexcitability suggests a potential role in the molecular mechanisms of the condition.

On the other hand, T-type calcium channels, especially those of the $Ca_V3.2$ class, are not only involved in neuropathic pain at the peripheral level, but also appear to play a role at the supraspinal level. Specifically, it has been found that $Ca_V3.2$ channels are expressed in GABAergic neurons and contribute to high-frequency firing activity in the reticular thalamic nucleus and anterior pretectum (APT), a region involved in pain perception [162,271]. This activity is increased in animal models of neuropathic pain, while the specific elimination of $Ca_V3.2$ channels in APT neurons reduces mechanical allodynia.

Likewise, the upregulation of T-type channels in the anterior cingulate cortex (ACC) has been shown to alleviate neuropathic pain [272]. After chronic nerve constriction injury,

redundancy and overlap among these channels complicate efforts to identify the most relevant candidates and design selective modulators without off-target effects.

There is also a significant translational gap between animal models and humans. Many of the findings on the involvement of voltage-gated ion channels in neuropathic pain come from animal models, which may not fully replicate the human disease. Differences in ion channel expression and regulation may limit the translation of preclinical findings into effective clinical treatments.

On the other hand, nonselective ion channel blockers can be effective in animal models, but they often have a limited clinical efficacy and cause adverse effects. Therefore, developing more selective compounds that target peripheral channels without central or cardiac impacts remains a significant challenge. Likewise, following nerve injury, the functional expression of voltage-gated ion channels can change dynamically, influenced by inflammatory mediators and neuronal activity. Understanding these temporal and spatial changes is crucial for producing effective therapeutic responses.

Lastly, the proteins that form voltage-gated ion channel complexes are targets of post-translational modifications such as phosphorylation, ubiquitination, SUMOylation, and glycosylation, which affect their activity, intracellular trafficking, and half-life. Studying how these processes are affected during the development of neuropathic pain would be a topic of interest for future studies, especially considering its therapeutic potential (see below). Furthermore, it would be of great interest to expand our knowledge of how the release of cytokines and chemokines during neuroinflammation can affect the function and expression of ion channels and how these processes can contribute to the molecular pathophysiology of neuropathic pain. Likewise, studying how DNA methylation or histone acetylation and other epigenetic modifications can affect the expression patterns of ion channels is another topic of great relevance, since these modifications can affect pain perception and promote the development of neuropathic pain.

9.2. Small Molecules Versus Biologics in the Future of Voltage-Gated Ion Channel Therapies in Neuropathic Pain

Small molecules remain the primary and most promising approach to targeting voltage-gated ion channels in neuropathic pain. Recent advances include highly selective inhibitors for Na_V and Ca_V channels, with successful clinical trials generating significant momentum for this approach. Small molecules offer advantages such as oral bioavailability, ease of synthesis, and the ability to modulate channel activity or trafficking in a reversible and tunable manner.

Innovative small-molecule strategies are emerging, such as targeted protein degradation (PROTACs), which can selectively degrade specific ion channel subtypes and potentially offer longer-lasting effects [206–208,297]. Furthermore, small molecules are being developed to disrupt protein–protein interactions critical to channel function and trafficking, expanding the scope of therapeutic mechanisms. PROTACs in the ion channel field represent a novel strategy to modulate ion channel function by targeting the channel proteins rather than through traditional inhibition, potentially offering increased specificity and overcoming drug resistance mechanisms. They are small, heterobifunctional molecules designed to selectively degrade target proteins by exploiting the cell's ubiquitin–proteasome system (UPS). They are composed of two ligands connected by a linker—one ligand binds to the protein of interest, and the other recruits an E3 ubiquitin ligase. This proximity induces the ubiquitination of the target protein, marking it for degradation by the 26S proteasome, effectively reducing the cellular levels of the protein rather than simply inhibiting its function [206–208].

$Na_V1.7$ and $Na_V1.8$ are also susceptible to PROTAC-mediated targeted protein degradation. Engineered PROTACs have been used to induce the rapid and near-

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Journal of Orthopaedic Translation 53 (2025) 126–137

Contents lists available at ScienceDirect

Journal of Orthopaedic Translation

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-translation

Review Article

Electric currents in disc health: The role of ion channels in intervertebral disc pathophysiology

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ARTICLE INFO

Keywords:
Low back pain
Ion channels
Intervertebral disc degeneration
Epigenetics
Targeted therapy
Tissue engineering

ABSTRACT

Intervertebral disc degeneration (IVDD), which is known as a common global health concern, has been a significant factor in neck and back pain. The intervertebral discs are avascular structures consisting of the nucleus pulposus, annulus fibrosus, and cartilage endplate, which are crucial for regulating the spinal motion, withstanding stress, and buffering vibration. Due to their special anatomical structure and functional role, they are highly susceptible to stimulation by external factors. Ion channels are transmembrane proteins which have attracted significant attention and great progress in cardiovascular diseases and neurological diseases, and the importance of them in the pathophysiology of IVDD is gaining recognition. They function as a receptor to stimulate the influx of calcium within cells, which acts as a second messenger to activate downstream pathways and upregulate the expression of transcriptional protein, thereby triggering IVDD. This review classified the ion channel families into three types based on their primary activation mechanisms, and then described the regulation of ion channels from transcription and translation to trafficking and expression. Subsequently, the function of ion channels in the pathophysiology of IVDD as well as their potential and practicality in treatment were the main topics of this review. We hope this review could help understand and develop new, specific therapies for IVDD.

The translational potential of this article: Targeted therapeutic strategies for ion channels are particularly critical in the treatment of IVDD. Ion channel-targeted drugs and tissue engineering strategies for ion channels have emerged as novel therapeutic targets for intervening in IVDD by modulating calcium homeostasis, inflammatory responses, and extracellular matrix metabolism in disc cells. In addition, as the development of nanotechnology, the integration of ion channel-targeted therapies with advanced drug delivery systems represents a promising frontier in the treatment of IVDD. Nanoparticle-based carriers and hydrogel-mediated sustained-release platforms have emerged as complementary strategies to enhance drug bioavailability and spatiotemporal control within the avascular, mechanically stressed intervertebral disc microenvironment. Furthermore, systematic exploration of combination therapies integrating ion channel-targeted drugs with complementary pharmacological agents like anti-inflammatory drugs and growth factors warrants rigorous investigation to enhance therapeutic efficacy in IVDD management.

1. Introduction

Low back pain (LBP) is an extremely common symptom affecting individuals of all ages from youngsters to the elderly [1]. The Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019) showed that LBP was the ninth leading cause of disability-adjusted

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https://doi.org/10.1016/j.jot.2025.06.007
Received 1 January 2025; Received in revised form 24 May 2025; Accepted 10 June 2025

life-years (DALYs) in 2019, especially affects the 25-49-year age group [2]. The elements that make up the lumbar spine, such as soft tissues, vertebrae, sacroiliac joints, intervertebral discs, and neurovascular structures, are susceptible to numerous stressors, which can contribute to the LBP [3]. Among these, the intervertebral disc degeneration (IVDD) is considered to be the major culprit. Currently, most patients with IVDD have received conservative treatment such as bed rest, nonsteroidal anti-inflammatory drugs, and analgesics, or surgical interventions including lumbar discectomy and lumbar interbody fusion [4]. However, the application of oral NSAIDs is limited because of the gastrointestinal side effects they are linked to, and these drugs are primarily intended for the temporary relief of symptoms instead of targeting pathogenesis, thus remain unable to reverse the progression of IVDD [5]. In addition, despite the popularity and generally favorable outcomes of surgical interventions, the intervertebral disc's natural physiological structure cannot be fully restored, and there remains a probability of subsequent surgical interventions [6]. Given the high prevalence and negative effects of LBP, a novel therapeutic strategy that focuses on the mechanism of IVDD, aiming to delay or prevent its continued progression is desperately needed.

Intervertebral discs (IVDs) are fibrous cartilage structures located between two vertebrae in the spine, which are mainly composed of the translucent jelly-like nucleus pulposus (NP) tissue filled in the center, the outer annulus fibrosus (AF) tissue arranged in concentric circles, and the cartilaginous endplate (CEP) tissue which covers both top and bottom of the IVDs to separate the NP and the AF from adjacent vertebral bodies [7]. The pathogenesis of IVDD demonstrates multifactorial etiopathogenesis, characterized by a complex pathophysiological cascade involving dysregulated cellular metabolism, aberrant inflammatory mediator release, and disrupted extracellular matrix (ECM) homeostasis. Hypoxic/nutrient-deficient microenvironments disrupt cellular metabolism, triggering mitochondrial dysfunction and endoplasmic reticulum (ER) stress-induced apoptosis via caspase-3/9 activation [8]. Concurrently, NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) inflammasome activation by ECM fragments drives interleukin-1β/interleukin-18 (IL-1β/IL-18) maturation, exacerbating NF-κB-mediated overexpression of matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs-5 (ADAMTS-5), which degrade collagen and aggrecan [9]. ECM catabolism disrupts osmotic homeostasis and biomechanical integrity, further promoting apoptosis and inflammation. These pathogenic elements engage in reciprocal molecular cross-talk through self-amplifying signaling pathways, ultimately accelerating the destruction of intervertebral disc structure including decreased intervertebral height, endplate sclerosis, and osteophyte formation [10] (Fig. 1).

While the precise pathogenesis of intervertebral disc degeneration (IVDD) remains incompletely elucidated due to its multifactorial nature, emerging evidence underscores the critical involvement of ionic homeostasis dysregulation, particularly calcium ion (Ca^{2+}) imbalance, in driving disease progression. Notably, Ca^{2+} which has been recognized as the most extensively characterized secondary messenger system, exerts pivotal regulatory control over pathophysiological mechanisms underlying IVDD development [11]. Furthermore, emerging evidence substantiates that transmembrane channel-mediated disturbances in iron, copper, and potassium ionic gradients contribute to oxidative stress and disc matrix degradation in IVDD [12]. Since the pioneering application of the voltage-clamp technique in cardiac tissue research in 1964, the field of ion channel biology has witnessed remarkable advancements, particularly with the emergence and refinement of single-electrode patch-clamp methodologies [13,14]. As transmembrane protein complexes forming selective hydrophilic pores across lipid bilayers, ion channels exhibit precise ionic permeability critical for regulating cellular electrophysiological homeostasis [15]. Their fundamental role in orchestrating bioelectrical signaling has established ion channel dysfunction as a pathophysiological mechanism underlying various degenerative conditions, including cardiovascular disorders [16], neurological pathologies [17], oncogenesis [18], and musculoskeletal diseases [19]. In this review, we concentrated on the physiological and pathological functions of ion channels in IVDD, with the goal of elucidating novel therapeutic targets and providing novel insights for future investigative efforts.

2. Classification of ion channels

Ion channels are pore-forming proteins that provide the main pathways for ions to enter or leave the cells. Selectivity and gating are two common characteristics of ion channels. Selectivity allows specific ions to diffuse across membranes through their corresponding channels and prevents the passage of the others, while gating involves the mechanisms that regulate the closing and opening of channel gates [20]. In

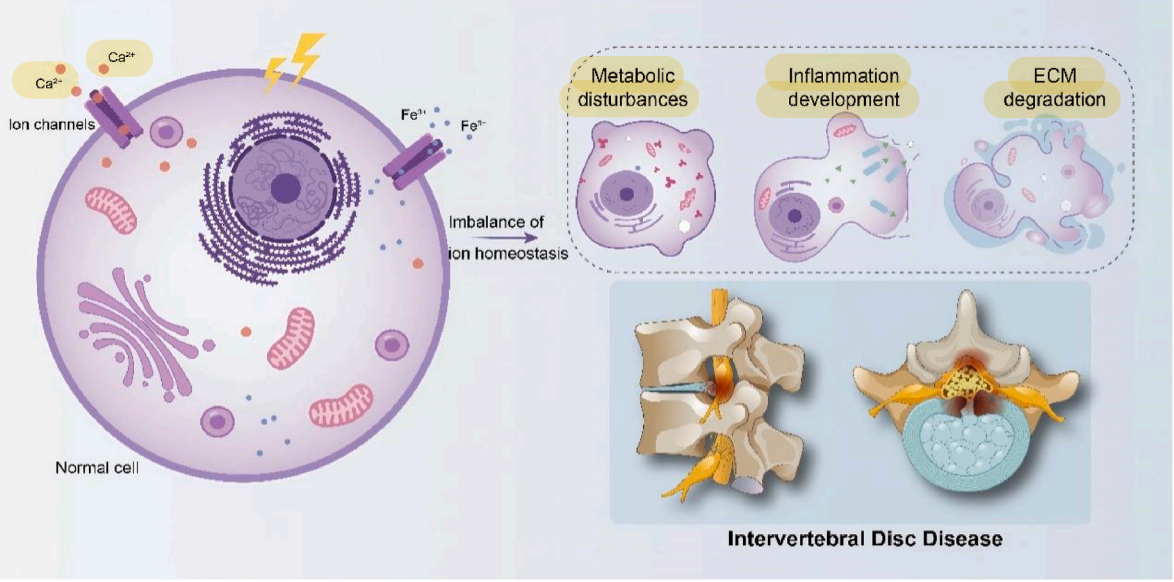

Fig. 1. An overview of ion channels mediating nucleus pulposus cell death as well as IVDD. Upon activation by diverse stimuli, ion channels located within the cellular membrane undergo activation-induced opening, facilitating transmembrane influx of divalent cations including Ca^{2+} and Fe^{3+}, causing an imbalance of ion homeostasis and triggering a cascade of pathophysiological events, thus resulting in IVDD related performance.

most current studies, ion channels families are usually separated into sodium, potassium, calcium ion channels according to their selectivity. In view of the fact that the IVD cells are subjected to threats such as hypoxia, mechanical load, low pH, hypertonicity, and other factors in the progression of IVDD, we tend to classify the ion channel families into three types based on the primary activation mechanisms, which are ligand-gated channels, proton-gated channels, and physical stimuli-gated channels [21](Table 1).

2.1. Ligand-gated channels

Ligand-gated channels (LGCs) are transmembrane channels that, upon binding to ligands of extra acellular domains, namely neurotransmitters, undergo conformational changes and open transmembrane domains (TMD), allowing ions to flow through the membrane along their electrochemical concentration gradients. According to the difference of TMD, they are mainly divided into three superfamilies: the ATP-gated purine receptors are homotrimers, the ionotropic glutamate receptors family are tetramers, and the Cys-loop receptors superfamily are pentamers [30]. For instance, ATP is well known for its function as the main source of cellular energy, while it can also act as a signaling molecule by activating nucleotide receptors which are referred to as purinergic P2 receptors under certain conditions, such as inflammation, hypoxia, and ischemia [31]. P2X7 receptors (P2X7R) are ATP-gated non-selective cation channels, which have been widely concerned because of their important role in multipling inflammatory and immune responses [32]. When the concentration of ATP exceed 100 μM, P2X7R are activated, resulting in a change in their molecular arrangement and the subsequent opening of ion channels, allowing potassium ions to exit and sodium and calcium ions to enter, which in turn induces alterations in the cell membrane potential, thereby affecting downstream Ca^{2+} signaling events [33]. Moreover, with the continuous action of ATP and its agonists, the TM1 and TM2 transmembrane segments of the P2X7R progressively open, forming larger membrane channels, which increased the cellular permeability to various ions and disrupted the equilibrium of intracellular small molecule metabolism, resulting in cell edema, cell necrosis, and cellular apoptosis [34].

2.2. Proton-gated channels

The functions of the proton-gated channels are primarily influenced by the protonation status of titratable groups distributed in discrete functional domains or throughout the protein. Acid-sensitive ion channels (ASICs) are typical proton-gated cation channels which belong to the voltage-insensitive, amiloride-sensitive epithelial Na channel/degenerin family. In mammals, ASICs are composed of five subunits—ACCN1a, ACCN1ab, ACCN2a, ACCN2b, and ACCN3, which form five distinct subunits: ASIC1a, ASIC1b, ASIC2a, ASIC2b, and ASIC3 [35]. ASICs function as the detectors with the pH range of 7 to 4.0, and are highly sensitive to the decreases in extracellular pH [36]. The drop in extracellular pH, which is triggered by acidosis, lactate, and arachidonic acid, causes ASICs to open and facilitates the passage of calcium, potassium, and sodium ions—with sodium ions being particularly selective [37]. There are accumulating studies highlighted that ASICs modulate cell behavior via mediating Na^{+} and Ca^{2+} influx, leading to cell membrane depolarization and intracellular Ca^{2+} accumulation, which is crucial in several degenerative disorders, such as IVDD, arthritis, Parkinson's disease, Huntington's disease, and multiple sclerosis [38].

2.3. Physical stimuli-gated channels

Physical stimuli-gated channels are specialized membrane proteins that open or close in response to specific physical forces including mechanical stress, temperature, or voltage, enabling cells to detect and adapt to environmental changes. Voltage-gated ion channels (VGICs) serve as fundamental regulators of bioelectrical signaling. Their voltage-sensing domains detect transmembrane potential changes, triggering pore opening/closing to permit selective ion flux (e.g., Na^{+}, K^{+}, Ca^{2+}) along electrochemical gradients. This mechanism underpins critical processes including action potential generation and synaptic transmission [39]. Temperature-gated ion channels operate through temperature-sensitive structural elements that modulate channel gating within physiological thermal ranges. A prominent family of temperature-gated channels is the Transient Receptor Potential (TRP) channel family. For instance, TRPV1 channels activate at noxious heat (>43 °C) and mediate thermal nociception, while TRPM8 responds to cooling (<25 °C) and mediates cold sensation [40]. These channels exhibit polymodal activation, often integrating thermal with chemical signals. Mechanosensitive ion channels (MSCs) are transmembrane proteins that convert mechanical stimuli, such as pressure, stretch, or shear stress, into electrochemical signals by allowing the flow of ions across cell membranes. These channels play critical roles in sensing touch, hearing, blood pressure regulation, and cellular responses to physical forces [41]. PIEZO, two-pore-domain potassium (K2P)

Table 1
Ion channels related to intervertebral disc degeneration.

Ion channels	Stimulating Factor	Selectivity	Cellular expression	Ref.
P2X7R	extracellular ATP	non-selective cation	immune cells, mast cells, glial cells, keratinocytes, retinal ganglion cells, intestinal epithelial cells, corneal cells, vascular endothelial cells, hepatocytes, fibroblasts, osteoclasts, skeletal muscle, vascular smooth muscle, and osteoblasts	[22]
ASICs	extracellular H^{+} (acidosis, lactate, arachidonic acid)	non-selective cation	central and peripheral neurons, taste receptor cells, cochlear hair cells, photoreceptors and retinal cells, testis, lung epithelial cells, adipose cells, pituitary gland, vascular smooth muscle cells, immune cells and bone	[23]
Voltage-gated sodium channels	depolarization	sodium selective	myocardium, skeletal muscle, neuroendocrine cells, neurons, glial cells	[24]
Voltage-gated calcium channels	depolarization	calcium selective	myocardium, smooth muscle, skeletal muscle, endocrine cells, neurons, sensory, spinal cord, lymphoid tissue	[25]
PIEZO1	mechanical stress (sheer stress, membrane stretch)	non-selective cation	urinary tract epithelial cells, renal epithelial cells, lung epithelial cells, vascular endothelial, red blood cells, adipocytes, myeloid cells, bone marrow cells, osteoblasts and osteocytes	[26]
K2P channels (TREK1)	mechanical stress (membrane stretch), heat, depolarization	potassium selective	neurons and glia cells, cardiac muscle cells, lung epithelial cells, intestinal epithelial cells, bladder cells, uterine cells, adrenal cortical cells and vascular endothelium	[27]
TRPV1	noxious heat (>43 °C), depolarization	non-selective cation	DRGs, brain, kidney, pancreas, testis, uterus, spleen, stomach, small intestine, lung and liver	[28]
TRPV4	mechanical stress (osmotic stress), heat (>24 °C–32 °C), constitutively active	non-selective cation	smooth muscle cells, epidermal keratinocyte cells, lung epithelial cells, cornea epithelial cells, pancreatic cells, urinary tract epithelial cells, osteoblasts and osteocytes	[29]

channels, OSCA/TMEM63 channels, and mechano-electrical transduction channel complex are currently recognized as mainly mechanosensitive ion channels. It is worth noting that this classification is not entirely accurate, as many channels may react to physical stimuli such as mechanical stress or voltage to some extent. For instance, ASICs are primarily activated by extracellular protonation states, while some studies have pointed out that they can also respond to mechanical stimulation of nerve endings [42].

3. The role of ion channels in IVDD

Emerging evidence indicates that ion channels may play a pathophysiological role in IVDD through their critical involvement in regulating transmembrane ion flux, thereby regulating the metabolism, inflammation, and structural integrity of intervertebral disc cells in response to various pathophysiological stimuli. The following summary summarized several ion channels linked to IVDD, categorized based on their major mechanisms of activation and discussed their specific mechanisms in IVDD (Table 2).

3.1. ATP-gated P2X7 receptor channels

A growing body of evidence has demonstrated the critical involvement of P2X7 receptors (P2X7R) in mediating cellular inflammatory responses. Under pathophysiological conditions, extracellular ATP accumulation triggers P2X7R activation through high-affinity binding, prompting its assembly into a macropore-forming cation channel. This structural reorganization enables coordinated K^+ efflux and Ca^{2+} dysregulation, with the former acting as a key trigger for NLRP3 inflammasome assembly [61]. Subsequent caspase-1 activation within the inflammasome complex catalyzes proteolytic maturation of pro-IL-1β and pro-IL-18, ultimately driving pyroptotic cell death and sustained release of bioactive cytokines that perpetuate sterile inflammation [62].

The association between P2X7R and IVDD has been well-established. Studies have revealed elevated expression of IL-1β, P2X7R, and NLRP3 inflammasome components in severely degenerated IVD tissues. Intriguingly, spatial localization studies reveal distinct cellular distributions: NLRP3 primarily resides in the cytoplasm, while P2X7R exhibits nuclear localization under basal conditions. The stimulation of P2X7R agonists and lipopolysaccharide can induce receptor translocation to the cytoplasm, facilitating colocalization with NLRP3 [43]. Emerging evidence suggests nuclear P2X7R may function as a membrane-bound signaling protein capable of regulating specific gene transcription, potentially playing an understudied role in maintaining NP homeostasis [63]. Further investigation is required to elucidate the full functional significance of nuclear P2X7R in disc biology.

Table 2
The role of ion channels in IVDD.

Ion channel	Mechanism	Function	Cell	Ref.
P2X7R	P2X7R/NLRP3/IL-1β pathway	Inflammatory response	IVD	[43]
ASIC1a	Ca^{2+}/calcium-dependent proteases and signaling	Cellular apoptosis	CEP	[44]
ASIC1a	Ca^{2+}/calpain and calcineurin	Cellular apoptosis	BMSC	[45]
ASIC1	ERK5 signaling pathway and mitochondrial dysfunction pathway	Cellular apoptosis	NP	[46]
ASIC1 and ASIC3	p53-p21/p27 and p16-Rb1 signaling	Cellular senescence	NP-MSCs	[47]
ASIC1 and ASIC3	ROS/NF-κB/NLRP3/IL-1β	Cellular inflammation and pyroptosis	NP	[48]
ASIC1a	NF-κB/increase MMP expression and activity	ECM degradation	CEP	[49]
PIEZO1	Ca^{2+}/ER stress and oxidative stress	Cellular senescence and apoptosis	NP	[50]
	Self-amplifying loop of NF-κB and periostin	Cellular senescence	NP	[51]
	Calpain2/BAX/Caspase3 pathway	Cellular apoptosis	AF	[52]
	Piezo1-iron-ferroptosis axis	Cellular ferroptosis	NP	[53]
	increase pro-inflammatory cytokines, and induce mitochondrial dysfunction	Cellular apoptosis and autophagy	NP	[54]
	Ca^{2+}/NF-κB/NLRP3	Inflammatory response	NP	[55]
	Ca2+/F-actin/Yap signaling axis	ECM degradation	CEP	[56]
TRPV4	ERK MAPK pathway	Cellular apoptosis	NP	[57]
TRPV2	PI3K/AKT signaling pathway and Cyt c and caspase proteins	Cellular apoptosis	NP	[58]
TRPV4	COX2/PGE2 and activated p38 MAPK	Inflammatory response	AF	[59]
TRPV4	increased expression of proteoglycan and Prg4	ECM degradation	CEP	[60]

3.2. Aid-sensitive ion channels

The IVD, which represents the largest non-vascular tissue in the body, relying primarily on the vertebral body's capillaries for nourishment, which diffuses to the NP cells through the CEP [64]. This special anatomical structure makes the IVD suffer from hypoxia for a long time, and glycolysis becomes the main energy source for the NPCs, coupled with the accumulation of lactate, which is the end product of glycolysis [65]. With the progression of calcification and degenerative changes in the cartilage endplate, the intervertebral disc's ability to exchange nutrients and metabolites with surrounding tissues becomes increasingly compromised. This progressive impairment results in the accumulation of acidic metabolites such as lactate, subsequently creating an acidic microenvironment characterized by reduced pH levels. Studies have shown that the pH of healthy IVDs is kept between 7.1 and 7.4, while in highly deteriorated discs, it can fall as low as 6.5, thereby activating the ASICs on the membrane of IVD [66]. Notably, degenerated IVD tissue demonstrates distinct spatial expression patterns: AF regions show predominant upregulation of ASIC1 and ASIC4, while NP compartments exhibit increased expression of ASIC1, ASIC2, and ASIC3 [67].

Emerging evidence indicated that ASICs regulate IVDD through multifaceted mechanisms. Primarily, ASIC activation under acidic microenvironments triggers intracellular Ca^{2+} influx, subsequently disrupting cellular metabolic homeostasis. Mechanistic studies reveal that ASIC1 channel activation facilitates calcium entry, which functions as a secondary messenger to disrupt the mitochondrial membrane potential. This process is mediated through dual pathways: the ERK5 signaling cascade and mitochondrial dysfunction, ultimately leading to mitochondria-mediated apoptosis of nucleus pulposus cells [44–47]. Secondary to the degenerative process, the inflammatory cascade significantly contributes to the pathogenesis and progression of IVDD. ASIC activation facilitates NF-κB and MAPK signaling pathway-mediated secretion of pro-inflammatory cytokines including IL-1β, IL-6, and TNF-α, thereby establishing a self-perpetuating inflammatory feedback loop [68]. Furthermore, extracellular lactate modulates intracellular reactive oxygen species (ROS) homeostasis via ASIC1 and ASIC3 channels, which subsequently activates the NLRP3 inflammasome complex. This molecular mechanism potentiates localized inflammatory amplification and promotes pyroptosis within the degenerative disc microenvironment [48]. In addition, ASICs contribute to structural deterioration of intervertebral discs by modulating ECM degradation. Mechanistically, ASIC1a has been demonstrated to regulate metabolic homeostasis in endplate chondrocytes. Exposure to acidic extracellular microenvironments suppressed anabolic factor expression while upregulating catabolic factors, effects that are mitigated by ASIC1a siRNA through inhibition of NF-κB transcriptional activity [49].

Concurrently, NP cells cultured under acidic conditions exhibit increased ASIC-3 expression at both transcriptional and translational levels. This upregulation promotes a catabolic phenotypic shift characterized by reduced aggrecan synthesis and elevated expression of matrix-degrading enzymes [69].

3.3. *PIEZO1*

The PIEZO channel family, comprising PIEZO1 and PIEZO2 subtypes, represents a class of mechanosensitive non-selective cation channels first identified as bona fide mechanical transducers in mammalian systems [70]. Compared to PIEZO2 which demonstrates more restricted tissue distribution, PIEZO1 exhibits broad expression patterns with particular enrichment in load-bearing musculoskeletal tissues [71]. This mechanotransduction channel can be activated by diverse physical stimuli including ultrasonic waves, tensile forces, and shear stress induced by fluid flow. Functionally, PIEZO1 demonstrates permeability to multiple divalent cations (Ca^{2+}, Mg^{2+}, Mn^{2+}, Ba^{2+}) and monovalent cations (Na^{+}, K^{+}, Cs^{+}), along with certain organic cationic molecules [72]. Of particular physiological significance is its role in mediating calcium influx, which modulates intracellular Ca^{2+} signaling cascades. This molecular mechanism enables PIEZO1 to serve as a critical mechanoelectrical transducer, converting extracellular mechanical stimuli into intracellular biochemical signals that regulate essential cellular processes including proliferation, differentiation, and tissue homeostasis [73,74].

In intervertebral disc cells, Piezo1 activation exacerbates disc degeneration by inducing NP and AF cell apoptosis and senescence, thereby disrupting cellular metabolic homeostasis. The stiffened ECM, a hallmark mechanical microenvironment in IVDD, triggers oxidative stress and endoplasmic reticulum (ER) stress through PIEZO1-mediated calcium influx. This pathway elevates intracellular Ca^{2+} and ROS levels, leading to mitochondrial Ca^{2+} overload and subsequent programmed necrosis via activation of the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling cascade. In addition, mechano-stress activates the NF-κB p65 transcriptional pathway through PIEZO1-Ca^{2+} signaling, upregulating periostin expression [50,75,76]. Secreted periostin from senescent NPCs further amplifies NF-κB p65 activation, establishing a self-sustaining loop that accelerates cellular senescence and IVDD progression [51]. In AF cells, PIEZO1 activation promotes apoptosis by enhancing Ca^{2+} influx and dysregulating calcium-dependent signaling. This process initiates the Calpain2/Bax/Caspase3 proapoptotic pathway, which drives caspase-3 activation and irreversible cell death [52]. Emerging evidence implicates PIEZO1 in ferroptosis, an iron-dependent regulated cell death mechanism characterized by ROS accumulation. Under mechanical stress, PIEZO1 acts as a critical iron transporter, and its pharmacological inhibition significantly reduces iron overload, mitigates mitochondrial ROS production, and suppresses ferroptosis-associated changes, thereby alleviating mechanical injury-induced IVDD [53,77].

Moreover, Piezo1 channel activation mediates calcium ion influx that contributes to IVDD pathogenesis by exacerbating inflammatory responses and ECM degradation [54]. Mechanistically, the resultant intracellular Ca^{2+} surge triggers NF-κB pathway activation, which transcriptionally upregulates NLRP3 inflammasome components and IL-1β expression. Simultaneously, elevated Ca^{2+} acts as a secondary messenger facilitating NLRP3 inflammasome oligomerization, thereby amplifying IL-1β maturation and secretion [55]. Furthermore, Piezo1 orchestrates the Ca^{2+}/F-actin/YAP signaling axis that disrupts ECM homeostasis through downregulating collagen II and aggrecan synthesis while upregulating matrix-degrading enzymes (MMP-13 and ADAMTS-5) [56].

3.4. *Transient receptor potential (TRP) channels*

The TRP channel superfamily comprises seven distinct subfamilies: TRPA, TRPC, TRPM, TRPML, TRPN, TRPP, and TRPV. These transmembrane proteins function as nonselective cation channels localized primarily in the plasma membrane [78]. TRP channels demonstrate ubiquitous tissue distribution and are expressed across nearly all mammalian cell types. These polymodal channels are activated by a diverse array of physical and chemical stimuli, including thermal gradients, mechanical forces, voltage fluctuations, nociceptive signals, photic stimuli, and chemosensory inputs [79]. Functioning as calcium-permeable nonselective cation channels, TRP channels serve as critical mediators of extracellular calcium influx, thereby modulating intracellular calcium homeostasis [80].

TRP ion channels are critically involved in the pathophysiology of IVDD, primarily mediated through their regulatory effects on calcium signaling dysregulation, secretion of pro-inflammatory cytokines, and activation of matrix metalloproteinases. These molecular mechanisms collectively contribute to the disruption of cellular metabolic equilibrium, amplification of inflammatory cascades, and progressive degradation of ECM homeostasis characteristic of IVDD progression. Firstly, pathophysiological mechanical stress mediated by TRP channels initiated a cascade of cellular injury mechanisms culminating in programmed cell death. The study demonstrated that TRPV4 modulated COX2/PGE2 signaling and mediated cellular injury induced by supraphysiological dynamic compression, potentially through the ERK pathway [57]. Furthermore, another research revealed that NPCs exhibited significant alterations in spreading morphology under ECM elastic modulus conditions. This mechanical stimulation concurrently activated TRPV2 channels and initiated the PI3K/AKT signaling cascade. Concomitantly, mitochondrial cytochrome c (Cyt c) release triggered caspase activation, ultimately promoting NP apoptosis [58]. Secondly, TRP channels play a key role in mediating the inflammatory response associated with IVDD. Upon TRPV4 activation, intervertebral disc cells exhibited significant upregulation of IL-6 family cytokines (IL-6, IL-11, IL-16, and leukemia inhibitory factor), concurrent with downregulation of T cell-recruiting chemokines and monocyte-associated chemokines. Notably, dynamic and static compressive loading elicited distinct chemokine correlation profiles. Pharmacological inhibition of TRPV4 during dynamic loading disrupted the coordinated expression between LIF and other cytokines, whereas TRPV4 blockade under static loading significantly altered the regulatory association of IL-16 with VEGFA [59,81,82]. These findings suggest mechanosensitive TRPV4 signaling differentially modulates cytokine-chemokine crosstalk in a loading modality-dependent manner. Finally, TRPV4 critically regulated ECM synthesis and modulated intervertebral disc tissue mechanotransduction in response to biomechanical stress. Activation of the TRPV4 channel in NP cells induced ECM-related transcriptional activity. Mechanistically, transient TRPV4 stimulation initiated a signaling cascade characterized by sequential Ca^{2+} flux, NF-κB pathway activation, and IL-6 upregulation. Chronic TRPV4 agonism potentiated degenerative progression via pathological glycosaminoglycan deposition and concomitant biomechanical stiffening of ECM. Notably, targeted TRPV4 inhibition significantly attenuated load-induced matrix catabolism and preserved tissue homeostasis under sustained compressive stress [60,83](Fig. 2).

4. Regulation of ion channels

The regulation of ion channels encompasses a multilevel regulatory cascade spanning transcriptional regulation, translational processes, intracellular trafficking, and membrane expression. This intricate modulation system is further influenced by the interactions with the lipid bilayer composition and exogenous pharmacological agents (Fig. 3). Such comprehensive regulatory mechanisms enable multifaceted modulation of ion channel function, establishing these transmembrane proteins as highly promising therapeutic targets for IVDD management.

The primary mechanisms of epigenetic regulation—DNA

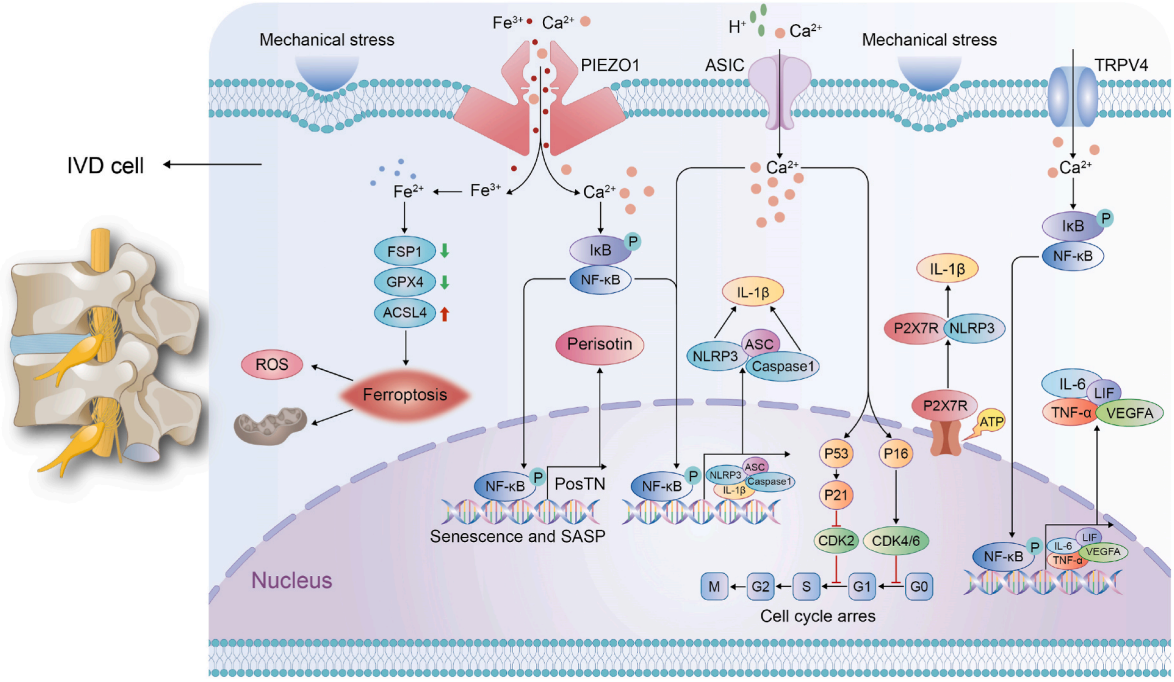

Fig. 2. The role of ion channels in IVDD. When activated by mechanical stress and extracellular H^+, ion channels distributed in IVD cell membrane including PIEZO1, ASIC and TRPV4 subsequently open and mediate the influx of Ca^{2+} and Fe^{3+}. Intracellular iron overload brought on by the Fe^{3+} influx ultimately results in ferroptosis as a stress response. The influx of Ca^{2+} activates the NF-κB pathway to mediates senescence, apoptosis and pyroptosis of IVD cells via transcriptionally upregulating downstream proteins and pro-inflammatory cytokines. P2X7R distributed on the cell nuclear membrane can also bind to NLRP3 to promote the release of IL-1β.

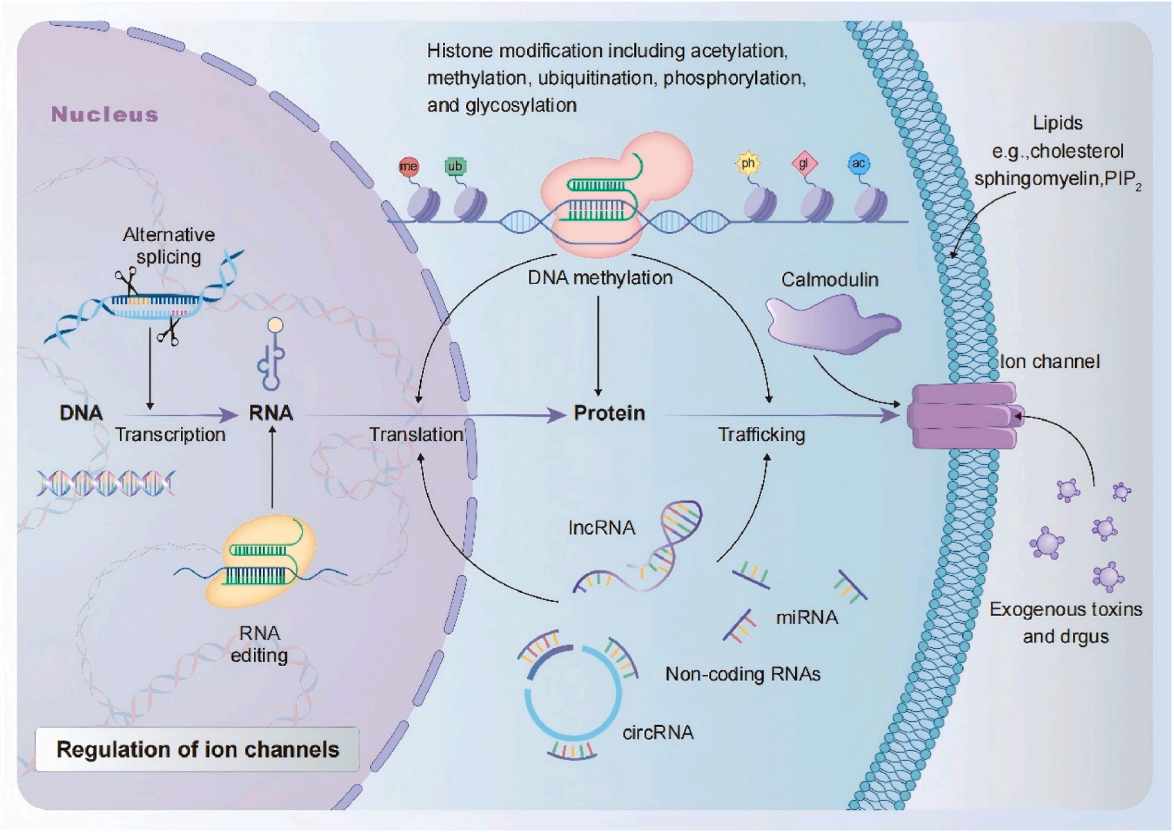

Fig. 3. Regulation of ion channels. Regulation of ion channels can occur at various steps from transcription and translation of the genetic code to trafficking of channel complexes and expression onto the plasma membrane, including alternative pre-mRNA splicing, RNA editing, epigenetic regulation, allosteric modulators, lipid environment, and exogenous drugs.

signaling pathways [103]. In the context of IVDD, circFOXO3 functioned as a ceRNA that sponged miR-185-3p and miR-939-5p, thereby relieving their inhibitory effects on ASIC1 expression. This regulatory axis culminates in ASIC1 upregulation and subsequent dysregulation of calcium ion homeostasis through enhanced Ca^{2+} influx, ultimately driving oxeiptosis in NPCs [104].

5. Possible therapeutic intervention

Ion channels are promising topics that may have important therapeutic implications for future research. Ion channels have been linked to the occurrence and prognosis of many diseases, especially neurodegenerative diseases and cardiovascular diseases (CVD). While a growing number of published studies now point to ion channels as a viable option for the treatment of IVDD.

5.1. Targeted drugs

Ion channel-related drugs are known for its applications in cardiovascular diseases and neurological diseases, such as hypertension and epilepsy. The European Society of Cardiology have stated that CVD medications like calcium channel blockers and antiarrhythmic drugs can also can affect cartilaginous tissues in addition to their own therapeutic effect [105]. Several studies have investigated how cardiovascular medications affect IVDD. Treatment with verapamil, a well-established blood pressure medication, effectively attenuated TBHP-triggered excessive generation of reactive oxygen species and suppressed NLRP3 inflammasome signaling. This therapeutic intervention consequently prevented cellular pyroptosis, apoptotic processes, and breakdown of extracellular matrix components [106]. Another calcium channel blocker nifedipine showed significant effect in the treatment of IVDD, resulting in altered cell calcium influx and downregulation of aggrecan and Col-II during dynamic compression [107]. In addition to CVD medications, the ion channels inhibitors have been shown to inhibit the progression of IVDD. For instance, GSMTx4, a selective PIEZO1 channel inhibitor, demonstrated significant anti-senescence effects by reducing senescence-associated β-galactosidase-positive cell populations. This compound effectively reversed the stiffness-dependent upregulation of MMP13 and POSTN expression in extracellular matrix environments [51]. Furthermore, Sa12b is a novel non-specific ASIC inhibitor that enhances the bioactivity of NP-MSCs (nucleus pulposus mesenchymal stem cells) in the severely acidic microenvironment of intervertebral discs by reducing Ca^{2+} influx through dual mechanisms of ASIC inhibition and Notch signaling pathway modulation [108] (Table 3).

Table 3
Ion channel drugs associated with IVDD.

Drug	Target	Function	Cell	Ref.
Verapamil	VGCC	targeted the Nrf2/TXNIP/NLRP3 axis to suppress ROS overproduction and pyroptosis	NP	[106]
Nifedipine	VGCC	altered cell calcium influx and down-regulated col 1a, aggrecan and ADAMTS-4	NP	[107]
GsMTx4	PIEZO1	reduced the number of β-Gal^{+} senescent cells and reversed the matrix stiffness-induced increase in expression of MMP13 and POSTN	NP	[51]
		alleviated AFCs apoptosis via inhibiting Calpain2/BAX/Caspase3 pathway	AF	[52]
GSK205	TRPV4	decreased NF-κB activity, IL-6 and VEGFA production, and degenerative changes to the ECM	AF	[83]
GSK2193874	TRPV4	reduced compression-induced NP cell damage and inflammation via ERK MAPK pathway	NP	[57]
Sa12b	ASICs	improved the biological activity of NP-MSCs by reducing Ca^{2+} influx and the Notch signaling pathway	NP-MSCs	[108]
Amiloride	ASIC1a and ASIC3	suppressed NLRP3 inflammasome activation and pyroptosis through the ROS/NF-κB signalling pathway	NP	[48]
APETx2	ASIC3	prevented the acidic pH induced proinflammatory and catabolic phenotype	NP	[69]
PcTx1	ASIC1 and ASIC3	alleviated premature senescence via inhibiting senescence programming pathways including p53-p21/p27 and p16-Rb1 signaling	NP-MSCs	[47]
	ASIC1a	decreased the activation of calpain and calcineurin and subsequent mitochondrial-mediated apoptosis	BMSC	[45]

5.2. Tissue engineering strategies

Current therapeutic approaches for IVDD, whether surgical or conservative, remain incapable of halting or reversing the underlying degenerative pathology. Mesenchymal stem cells (MSCs) have emerged as a promising regenerative strategy due to their potential to repopulate degenerated discs and restore ECM homeostasis. These multipotent adult stem cells, obtainable from bone marrow, adipose tissue, and muscular sources, exhibit self-renewal capacity and multilineage differentiation potential [109]. Notably, MSC differentiation into NP/AF-like phenotypes demonstrates enhanced synthesis of key ECM components, including collagen II and aggrecan, suggesting therapeutic potential for disc regeneration [110]. Preclinical and clinical studies have substantiated these regenerative properties [111]. However, the hostile microenvironment of degenerated discs—characterized by acidic pH, nutrient deprivation, and mechanical stress—compromises MSC viability, metabolic activity, and differentiation capacity. This necessitates tissue engineering approaches combining growth factors, biomaterial scaffolds, and cellular therapies [112].

Emerging evidence implicates ion channel modulation as a critical intervention point. The novel ASIC inhibitor Sa12b, isolated from *Sphex argentatus* venom, enhanced NP-MSC viability and bioactivity in acidic conditions by inhibiting ASICs and reducing calcium influx [108]. When integrated with RADA16-I self-assembling nanopeptides to form RAD/SA1 composites, this construct significantly outperformed conventional culture systems and RADA16-I alone in promoting NP-MSC proliferation and ECM synthesis—a process mediated through Ca^{2+}-dependent phosphorylation of ERK signaling pathways [113]. In addition, the mesenchymal stem cell differentiation can be controlled by mechanically stimulating ion channels. Innovative microgel platforms with upper critical solution temperature (UCST) properties demonstrate this principle: Adipose-derived MSCs (ADSCs) cultured on poly microgels exhibit omnidirectional stretching during thermoresponsive swelling, upregulating TRPV4 and Piezo1 channels. This mechanical priming promoted ADSC differentiation into NP-like cells with functional ECM remodeling capacity, offering a novel IVDD repair strategy [114] (Table 4).

6. Discussion and perspective

Intervertebral disc degeneration, as the predominant etiology of low back pain, substantially compromises patients' quality of life while imposing significant socioeconomic burdens. Contemporary therapeutic strategies, encompassing conservative management and surgical interventions, primarily provide transient symptomatic relief rather than addressing underlying pathological mechanisms. These approaches fail to halt disease progression or prevent IVDD development, underscoring the urgent need for pathogenesis-targeted therapies. Emerging insights from ion channel research in cardiovascular and neurological

Table 4
Summary of bioactive materials utilized to regulate ion channels in IVDD.

Bioactive materials	Target	Function	Cell	Ref.
RAD/SA1	ASICs	enhanced the Biological Activity of hNPMSCs via inhibiting the expression of p-ERK through Ca2+-dependent p-ERK signaling pathways	hNPMSCs	[110]
Injectable UCST Microgels	TRPV4 and Piezo1	upregulated TRPV4 and Piezo1 channel proteins and enhanced nucleus pulposus (NP)-like differentiation of ADSCs	adipose-derived mesenchymal stem cells	[114]
GM@CS-BP	ASIC3	maintained a balance between ECM synthesis and degradation by regulating the positive feedback between imbalanced oxygen metabolism in IVDs and inflammation	NP	[115]
Viscoelastic hydrogels	TRPV4	enhanced nucleus pulposus (NP)-like differentiation of ADSCs, coupled with an augmented secretion of aggrecan and type-II collagen	adipose-derived mesenchymal stem cells	[116]
HA hydrogel	TRPV1	altered glycosylation and modulated key inflammatory and signaling pathways, resulting in attenuation of inflammation and regulation of matrix components	NP and AF	[117]

pathologies have revealed promising therapeutic targets. Ion channels have been demonstrated to play a critical role in the pathogenesis of IVDD through their regulatory effects on cellular metabolic processes, modulation of inflammatory cascades, and maintenance the structural integrity of the intervertebral disc. In addition, the multifaceted regulatory capacity, combined with demonstrated druggability across multiple organ systems, positions ion channels as particularly viable therapeutic targets for IVDD intervention.

Ion channels exert stage-specific modulation of pathophysiological cascades during IVDD, with distinct regulatory patterns emerging in disease-specific microenvironments, where Ca^{2+} exerts pivotal regulatory control. The initial phase of IVDD is characterized by metabolic imbalances, compensatory adaptation to mechanical stress and acidic microenvironments, with calcium ions serving as crucial secondary messengers mediating cellular signaling pathways. ASIC1 channel activation facilitates calcium entry, leading to mitochondria-mediated apoptosis of nucleus pulposus cells via the ERK5 signaling cascade and mitochondrial dysfunction [46]. Meanwhile, the stiffened ECM triggered oxidative stress and ER stress through PIEZO1-mediated calcium influx, leading to mitochondrial Ca^{2+} overload and subsequent programmed necrosis [50]. When the degenerative process advances into an irreversible stage, the pathological progression becomes predominantly driven by the inflammatory cascade and catastrophic microarchitectural disintegration. Mechanistically, the pathological intracellular Ca^{2+} surge induces canonical NF-κB pathway activation through IκB kinase complex phosphorylation, leading to transcriptional upregulation of NLRP3 inflammasome core components and pro-IL-1β expression [55]. Furthermore, elevated cytosolic Ca^{2+} concurrently promoted NLRP3 inflammasome oligomerization via P2X7 receptor and mitochondrial ROS generation, thereby potentiating caspase-1-dependent IL-1β maturation and subsequent pyroptotic secretion [43]. Finally, Piezo1 orchestrates the Ca^{2+}/F-actin/YAP signaling axis that accelerate ECM catabolism through downregulating collagen II and aggrecan synthesis while upregulating matrix-degrading enzymes [56]. In summary, different ion channels play a role at different stages of IVDD, leading to corresponding pathological changes. It should be noted that the biomarkers for different stages of IVDD are still not very clear at present. Therefore, more research is needed to support the discovery of biomarkers for different stages of IVDD. Such research will help achieve stage-specific and sequential treatment of IVDD.

The regulation of ion channels occurs through multiple molecular mechanisms spanning from genomic expression to membrane localization. At the transcriptional level, alternative splicing of a single pre-mRNA transcript generates functionally distinct ion channel isoforms through precisely regulated mRNA processing [118]. RNA editing mechanisms further diversify protein products by introducing nucleotide modifications that alter coding sequences prior to translation. The research reported the use of CRISPR-Cas9 technology to successfully knock out TRPV4 in human AF cells, successfully reduced the stretch-induced upregulation of IL6, IL8 and COX2 gene expression, PGE2 release and p38 phosphorylation [59]. Another research developed multiplex CRISPR epigenome editing vectors that modulate endogenous expression of TRPA1, ASIC3, and Piezo2, abolishing degenerative IVD-induced mechanical nociception [119]. During protein synthesis and membrane trafficking, ion channels undergo essential co- and post-translational modifications including DNA methylation, histone modification, and non-coding RNA activity, which regulate gene expression through chromatin state modulation rather than altering DNA sequences. Common post-translational modifications include acetylation, methylation, ubiquitination, phosphorylation, and glycosylation. Allosteric regulation is achieved through calcium-dependent interactions with accessory proteins such as calmodulin, which induces conformational changes in channel gating properties [120]. In addition, the membrane lipid composition serves as a critical modulator of channel function, with specific lipid species exerting profound effects: PIP2 maintains voltage-gated channel activity through electrostatic interactions, cholesterol modulates mechanosensitive channels via membrane fluidity adjustments, and sphingomyelin-rich domains facilitate compartmentalized signaling [121]. Finally, ion channels are also regulated by exogenous toxins, and the development of related drugs has made them important targets for disease treatment. More mechanisms related to the regulation of ion channels in IVD need to be explored in the future, including alternative pre-mRNA splicing, RNA editing, histone modification, more non-coding RNAs, allosteric modulators, and lipid environment.

Emerging research highlights the therapeutic potential of ion channel-targeted pharmacological agents and bioactive materials for IVDD, though their clinical translation faces substantial limitations. Calcium channel blockers like nifedipine and verapamil exhibit established efficacy in hypertension management, while their application for IVDD requires rigorous preclinical and clinical validation to establish safety and efficacy profiles, particularly given systemic administration challenges posed by the disc's avascular architecture. The blood-disc barrier severely restricts therapeutic agent biodistribution, resulting in subtherapeutic concentrations at degenerative foci, while systemic verapamil use carries cardiovascular risks including bradycardia and conduction abnormalities, particularly in patients with preexisting cardiac comorbidities. Furthermore, monotherapeutic strategies targeting calcium homeostasis inadequately address IVDD's multifactorial pathophysiology involving inflammatory, oxidative, and biomechanical cascades. Parallel challenges exist for bioactive materials, where the disc's acidic, hypoxic, and hyperosmotic microenvironment compromises biomaterial integrity and homogeneous distribution, exacerbated by mechanical stresses during local injection [122]. Moreover, Current

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FASEB J. 2025 Jan 15;39(1):e70290. doi: 10.1096/fj.202400544RR.

Polyunsaturated fatty acids suppress PIEZO ion channel mechanotransduction in articular chondrocytes

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PMID: 39786170 DOI: 10.1096/fj.202400544RR

Abstract

Osteoarthritis (OA) is characterized by articular cartilage degeneration, leading to pain and loss of joint function. Recent studies have demonstrated that omega-3 (ω3) polyunsaturated fatty acid (PUFA) supplementation can decrease injury-induced OA progression in mice fed a high-fat diet. Furthermore, PUFAs have been shown to influence the mechanical properties of chondrocyte membranes, suggesting that alterations in mechanosensitive ion channel signaling could contribute to the mechanism by which ω3 PUFAs decreased OA pathogenesis. Here, we hypothesized that PUFAs may alter mechanical signaling through PIEZO1 (activated by changes in membrane tension) and TRPV4 (activated by physiologic mechano-osmotic signals), as these mechanosensitive cation channels have been shown to influence OA progression. Our results demonstrated that PUFAs reduced chondrocyte sensitivity to single-cell mechanical compression and to pharmacologic agonists of PIEZO1 and TRPV4, with ω3 PUFAs having the most significant effects overall. We also found that supplementation with ω6 PUFA linoleic acid (LA) altered the biophysical properties of chondrocytes, as evidenced by increased intracellular lipid droplet formation and more rapid membrane rupture in response to hypo-osmotic shock, suggesting that LA increases chondrocyte membrane susceptibility to damage. Our findings underscore the differential impacts of specific PUFAs on chondrocyte signaling and membrane properties and provide important considerations in the development of nutritional interventions to prevent or treat OA.

Keywords: PIEZO channels; TRPV4; articular cartilage; mechanosensitive ion channels; osteoarthritis; polyunsaturated fatty acids.

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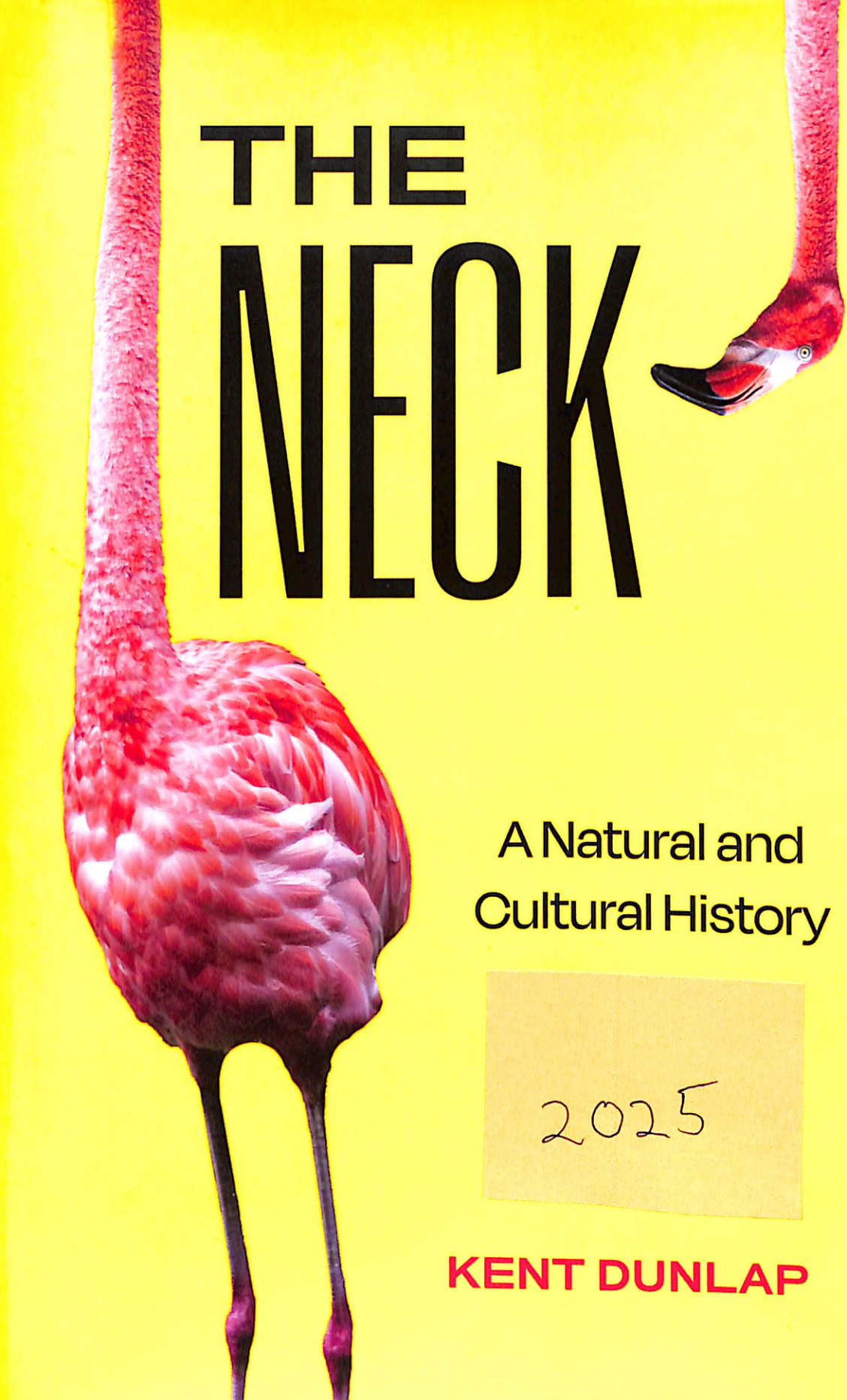

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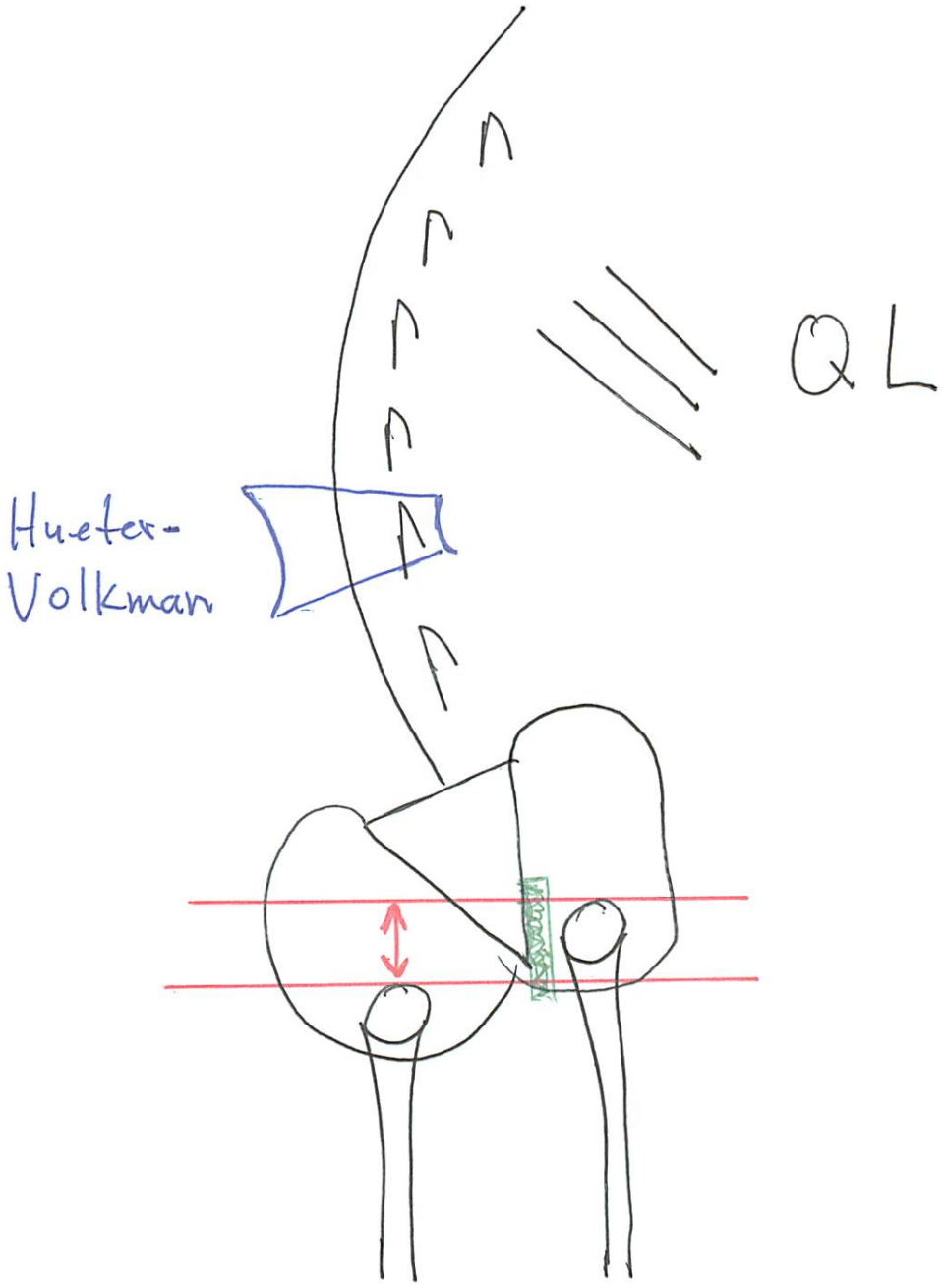
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John F. Kennedy's back: chronic pain, failed surgeries, and the story of its effects on his life and death

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The 35th president of the United States, John F. Kennedy (JFK), experienced chronic back pain beginning in his early 20s. He underwent a total of 4 back operations, including a discectomy, an instrumentation and fusion, and 2 relatively minor surgeries that failed to significantly improve his pain. The authors examined the nature and etiology of JFK's back pain and performed a detailed investigation into the former president's numerous medical evaluations and treatment modalities. This information may lead to a better understanding of the profound effects that JFK's chronic back pain and its treatment had on his life and presidency, and even his death.

https://thejns.org/doi/abs/10.3171/2017.2.SPINE151524

KEY WORDS JFK; John F. Kennedy; failed back surgery; Wilson plate; history; President Kennedy assassination

John Fitzgerald Kennedy (JFK), the 35th president of the United States and the youngest candidate elected to the Oval Office, was portrayed as a dynamic man full of vigor and youthful energy.[61] This aura of vitality belied the fact that he was patently unhealthy from an early age.[14,57] The full extent of his wide array of medical problems, especially relating to his time in the Oval Office, remained a secret as directed by the Kennedy family until 2001.[1] Low-back pain, just one of Kennedy's many medical problems, prompted a total of 4 largely unsuccessful surgeries. This pain affected him nearly continually from his undergraduate years at Harvard until the day of his assassination.

A Childhood of Poor Health: Numerous Illnesses and Hospitalizations

John Fitzgerald Kennedy was born the second of 8 children to Joseph P. Kennedy Sr. and Rose Fitzgerald Kennedy in Brookline, Massachusetts, on May 29, 1917. Several months shy of his 3rd birthday, young "Jack" contracted scarlet fever and was hospitalized; his condition ultimately deteriorated to the brink of death.[14,31,33,57,62] His childhood health troubles continued; he would be treated for a host of illnesses prior to his graduation from preparatory school.[1,14,21,24,57] In fact, Robert F. Kennedy would later recall that "when we were growing up together we used to laugh about the great risk a mosquito took in biting Jack Kennedy—with some of his blood the mosquito was almost sure to die."[51]

Collegiate Years: Origins of Low-Back Pain and First Consultation

Jack would add yet another entry to an already prodigious list of health problems during his undergraduate years at Harvard: low-back pain. The exact details of the inciting event remain murky, but the most commonly accepted account traces the onset of low-back pain to a football injury he sustained while at Harvard in 1937.[2,5,21,26,29,32,33,57]

Kennedy continued to be plagued with back pain after graduating from Harvard University in June 1940 and was referred to Dr. Gilbert "Ned" Haggart, an orthopedic spine specialist at the Lahey Clinic in Boston, who diagnosed him with a "very unstable lumbosacral joint." Dr. Haggart recommended a course of conservative treatment in the form of a manipulation of the back under anesthesia, which JFK underwent at the Lahey Clinic in 1940. Dr. Haggart also introduced the idea of a sacroiliac fusion if the conservative treatment failed.[22,23,29]

ABBREVIATIONS JFK = John F. Kennedy; PT = patrol torpedo.

ACCOMPANYING EDITORIAL See pp 245–246. DOI: 10.3171/2017.2.SPINE17229.
SUBMITTED December 21, 2015. **ACCEPTED** February 7, 2017.
INCLUDE WHEN CITING Published online July 11, 2017; DOI: 10.3171/2017.2.SPINE151524.

Sci Rep. 2024 May 23;14(1):11781. doi: 10.1038/s41598-024-62812-7.

Utilizing machine learning to predict post-treatment outcomes in chronic non-specific neck pain patients undergoing cervical extension traction

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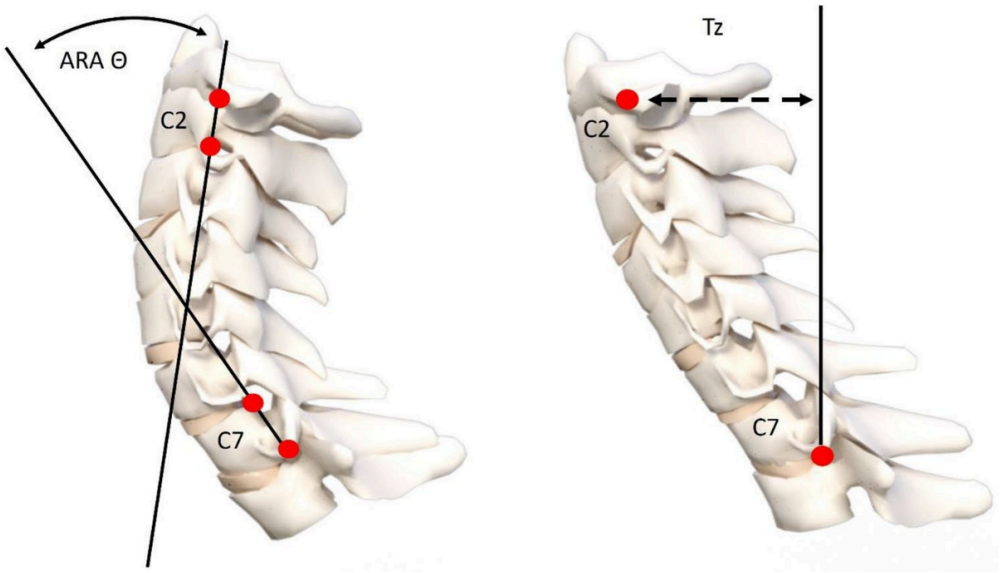

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