TRENDS IN SCIENCES 2026; 23(4): 12261
https://doi.org/10.48048/tis.2026.12261
REVIEW ARTICLE

Calcium Signaling Pathways in Physiological Regulation and Disease Development: A Comprehensive Review

Aswin Rafif Khairullah[1], Dea Anita Ariani Kurniasih[2], Ilma Fauziah Maruf[3], Bima Putra Pratama[4], Mohammad Sukmanadi[5,*], Arif Nur Muhammad Ansori[6,7,8], Imam Mustofa[9], Bantari Wisynu Kusuma Wardhani[3], Riza Zainuddin Ahmad[1], Eny Martindah[1], Sri Mulyati[9], Wita Yulianti[10], Abdul Hadi Furqoni[11], Saifur Rehman[12], Syahputra Wibowo[13] and Fadhila Utari[3]

[1]Research Center for Veterinary Science, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia
[2]Research Center for Public Health and Nutrition, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia
[3]Research Center for Pharmaceutical Ingredients and Traditional Medicine, National Research and Innovation Agency (BRIN), Bogor, West Java 16911, Indonesia
[4]Research Center for Process Technology, National Research and Innovation Agency (BRIN), Banten 15314, Indonesia
[5]Division of Basic Veterinary Medicine, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Mulyorejo, East Java 60115, Indonesia
[6]Postgraduate School, Universitas Airlangga, Kampus B Dharmawangsa, East Java 60286, Indonesia
[7]Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Uttarakhand 248007, India
[8]Medical Biotechnology Research Group, Virtual Research Center for Bioinformatics and Biotechnology, East Java 60493, Indonesia
[9]Division of Veterinary Reproduction, Faculty of Veterinary Medicine, Universitas Airlangga, Kampus C Mulyorejo, East Java 60115, Indonesia
[10]Research Center for Biota Systems, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia
[11]Center for Biomedical Research, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia
[12]Department of Pathobiology, Faculty of Veterinary and Animal Sciences, Gomal University, Dera Ismail Khan 27000, Pakistan
[13]Eijkman Research Center for Molecular Biology, National Research and Innovation Agency (BRIN), West Java 16911, Indonesia

([*]Corresponding author's e-mail: moh-s@fkh.unair.ac.id)

Received: 13 October 2025, Revised: 24 October 2025, Accepted: 4 December 2025, Published: 1 January 2026

Abstract

Calcium ions (Ca^{2+}) are universal signaling molecules that play a central role in physiological processes, including muscle contraction, hormone secretion, gene regulation, energy metabolism, and neurotransmission. This review aims to integrate the SOCE-MCU-CaM axes to provide a systems-level view of Ca^{2+} regulation from the plasma membrane to the ER/SR, mitochondria, and nucleus in physiology and pathology. The Ca^{2+} signaling pathway encompasses ion transport by Ca^{2+} pumps and Na^{+}/Ca^{2+} exchangers, ion flow through plasma-membrane channels and the endoplasmic/sarcoplasmic reticulum (ER/SR), and interactions with binding proteins such as calcineurin and calmodulin (CaM), which trigger downstream programs including NFAT, CREB, and MAPK. Maintenance of cytosolic and mitochondrial Ca^{2+} homeostasis depends on pathways such as the mitochondrial calcium uniporter (MCU) and store-operated calcium entry (SOCE) via STIM1/Orai1; their coordinated action links Ca^{2+} transients to metabolism and

gene control. Dysregulation of Ca^{2+} signaling contributes to chronic diseases, including neurodegeneration (Alzheimer's, Parkinson's), cardiovascular disease (heart failure, arrhythmia, hypertension), cancer (breast, lung, colorectal), and metabolic/endocrine disorders (diabetes and insulin resistance). Unchecked Ca^{2+} accumulation or pathway imbalance promotes oxidative stress, apoptotic activation, impaired energy metabolism, and cellular dysfunction, while mutations in Ca^{2+}-related genes alter cardiac contractility and other physiological regulation. Therapeutic approaches include Ca^{2+}-channel modulation, targeting STIM1, Orai1, and MCU, and epigenetic strategies that leverage Ca^{2+}'s influence on gene expression, with the goal of restoring network-level Ca^{2+} equilibrium and improving cell function. A clearer understanding of Ca^{2+} mechanisms and pathway cross-talk will support the development of more precise and effective interventions.

Keywords: Calcium signaling, Physiology, Pathology, Targeted therapy, Disease

Introduction

Calcium ion (Ca^{2+}) is a universal signaling molecule that has a central role in regulating various cellular physiological processes [1]. Ca^{2+} functions as a second messenger, converting both internal and external stimuli into certain physiological and biochemical reactions, such as energy metabolism, hormone release, muscle contraction, and gene transcription [2]. Rapid and regulated changes in intracellular Ca^{2+} concentrations enable cells to adjust their biological activity in response to changes in the environment, preserving organ function and homeostasis [3]. The ability of calcium to create intricate signaling patterns - pulsatile, oscillatory, and spatial - each of which has distinct functional implications in cell regulation. This feature makes it unique as a signaling mediator [4].

Apart from its function in healthy physiology, calcium signaling also plays a part in a number of pathogenic processes. Ca^{2+} dysfunction or dysregulation can trigger or worsen chronic disease conditions, including neurodegenerative disorders such as Alzheimer's and Parkinson's, cardiovascular diseases such as arrhythmias and heart failure, and metabolic disorders such as diabetes mellitus [5-8]. At the molecular level, these illnesses are frequently linked to alterations in the expression or function of Ca^{2+}-handling proteins (ion channels, pumps, exchangers), Ca^{2+}-binding proteins (e.g., calmodulin), and Ca^{2+}-regulated enzymes (e.g., calcineurin) [9]. These alterations may result in a dysregulation of Ca^{2+} signaling, which impacts apoptosis, differentiation, proliferation, and other cellular processes, ultimately leading to the advancement of the disease [10].

Complex mechanisms that incorporate several Ca^{2+} sources and sensors are part of the calcium signaling cascade. Ca^{2+} is released or absorbed by the endoplasmic reticulum (ER) and mitochondria, which act as internal reservoirs in response to physiological demands [11]. Additionally, Ca^{2+} enters through plasma membrane pathways such as store-operated Ca^{2+} entry (SOCE) and voltage-gated calcium channels (VGCCs), which enable cells to react to changes in the extracellular environment [12]. The Na^{+}/Ca^{2+} exchanger and Ca^{2+} pumps like plasma membrane Ca^{2+}-ATPase (PMCA) and sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) dynamically maintain Ca^{2+} homeostasis [13]. Cells are able to precisely control Ca^{2+} fluctuations through the combination of these several pathways, maintaining appropriate physiological responses [14].

Ca^{2+} plays a role as a signaling mediator that extends beyond quick reactions; it also affects long-term control by triggering downstream signal transduction pathways [15]. A range of molecular targets, such as kinases, phosphatases, and transcription factors like Nuclear Factor of Activated T-cells (NFAT) and cAMP Response Element-Binding protein (CREB), interact with calcium-binding proteins like calmodulin to control gene expression and cell activity in a particular way [16]. Chronic cellular dysfunction can result from anomalies in this pathway, which explains how Ca^{2+} can act as a connection between environmental changes and long-term cellular adaptation [17].

This review aims to provide a comprehensive overview of the calcium signaling pathway, focusing on its regulatory mechanisms, physiological roles, and

association with the pathology of various diseases. The primary issues discussed are how disruption in calcium signaling affects the course of disease and how a better knowledge of this route could lead to the creation of more targeted treatment approaches. As a result, this paper offers a conceptual framework that can be applied to future studies and the creation of therapeutic measures that target the modification of Ca^{2+} signals. In particular, this review integrates the SOCE–MCU–CaM axes across the plasma membrane, ER/SR, mitochondria, and nucleus to address the current gap in compartment-spanning perspectives.

Data collection method

This review adopts a narrative, problem-focused search and synthesis strategy. Bibliographic searches were performed in PubMed/MEDLINE, Scopus, Web of Science, and Embase to identify publications from 1 January 2000 through 13 October 2025, using controlled vocabulary and free-text terms related to calcium signaling (e.g., "calcium signaling", "store-operated calcium entry", STIM1, Orai1, voltage-gated calcium channels, SERCA, PMCA, MCU, calmodulin [CaM], calcineurin, NFAT, CaMK) combined with disease terms (e.g., neurodegeneration, cardiac remodeling/arrhythmia, cancer, endocrine/metabolic dysfunction). Reference lists of sentinel articles were hand-searched to capture additional records. Inclusion criteria encompassed peer-reviewed mechanistic or disease-focused studies and reviews interrogating SOCE, VGCCs, SERCA/PMCA, the MCU complex, or CaM-dependent effectors in human, animal, or primary cell models; single case reports, non-mechanistic commentaries, and off-topic items were excluded. Titles and abstracts underwent screening followed by full-text appraisal; for each eligible study, we extracted variables on signaling nodes, experimental models and assays, principal mechanistic findings, disease context, and therapeutic leads, then synthesized them thematically along SOCE–MCU–CaM axes across organ systems. Formal risk-of-bias scoring was not performed given the narrative scope of this review; evidence weighting emphasized methodological rigor, reproducibility across models, and translational relevance.

Calcium signaling basics

Calcium signaling is a fundamental mechanism that allows cells to respond dynamically and specifically to internal and external stimuli. Numerous sources and regulatory mechanisms, such as the endoplasmic reticulum, mitochondria, membrane ion channels, calcium pumps, and exchangers, carefully control the intracellular Ca^{2+} ion concentration. Calcium-binding proteins like calcineurin and calmodulin (CaM) further convert these Ca^{2+} dynamics into physiological responses by activating downstream signaling pathways including cAMP Response Element-Binding protein (CREB), Nuclear Factor of Activated T-cells (NFAT), and Mitogen-Activated Protein Kinase (MAPK), which in turn coordinates a number of critical cellular functions.

Sources and regulation of Ca^{2+}

The concentration of Ca^{2+} in the cytosol is kept at a very low level, usually around 100 nM, to enable quick changes in response to stimuli [18]. These ions are crucial signaling mediators. Intracellular Ca^{2+} homeostasis is achieved through a complex coordination between internal reserves, flux from the extracellular environment, and active transport systems [19].

The endoplasmic reticulum (ER) functions as the main reservoir of intracellular Ca^{2+} [20]. The ER stores these ions, which are then released in response to physiological cues via certain channels such the ryanodine receptor (RyR) and the inositol 1,4,5-trisphosphate receptor (IP_3R) [21]. Additionally, mitochondria serve as crucial buffers, receiving calcium ions through the mitochondrial Ca^{2+} uniporter (MCU) and releasing them to facilitate apoptotic control and energy consumption [22]. These 2 organelles enable cells to control Ca^{2+} fluctuations in a specific spatial and temporal manner, leading to a precise cellular response [23].

Ion channels in the plasma membrane allow Ca^{2+} from the extracellular environment to enter, which is crucial in addition to internal reserves [24]. The ability to react quickly to changes in the environment is made possible by channels such SOCCs and VGCCs [25]. Ca^{2+}-binding proteins, including calmodulin, interpret the brief rise in cytosolic Ca^{2+} concentration caused by

channel activation to initiate downstream signaling cascades [26].

Maintenance of Ca^{2+} homeostasis depends not only on passive flux through the channels, but also through active transport mechanisms [27]. Ca^{2+} pumps, like the plasma membrane Ca^{2+}-ATPase (PMCA) and the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA), constantly transport Ca^{2+} from the cytosol to the ER or out of the cell, preserving a low basal concentration in the cytosol [28]. Furthermore, the Na^{+}/Ca^{2+} exchanger uses the sodium gradient to balance the Ca^{2+} concentration, promoting signal renewal and avoiding the buildup of potentially harmful Ca^{2+} [29].

Cells are able to produce dynamic and localized Ca^{2+} signals by the integration of internal reserves, external fluxes, and pump and exchanger activity [30]. This method highlights the significance of appropriate regulation to prevent dysfunction and pathology while explaining how Ca^{2+} can cause a range of physiological responses, from cell proliferation and neural signal transduction to muscular contraction and hormone release [31].

Ca^{2+} signal transduction mechanism

Cells must be able to convert variations in Ca^{2+} content into particular biological reactions in order for calcium signal transduction to occur [9]. Calmodulin (CaM) and other calcium-binding proteins are essential to this process. The EF-hand domain of this protein undergoes a conformational shift when calmodulin binds Ca^{2+}, activating several downstream effectors [32]. The Ca^{2+}-CaM complex activates calcineurin, a serine/threonine phosphatase, which is one of CaM's primary targets [33]. The transcription factor NFAT can enter the cell nucleus and affect the expression of genes that govern immunological responses, differentiation, and proliferation when calcineurin activation dephosphorylates it [34].

Along with the CaM-calcineurin route, Ca^{2+} also triggers the activation of several additional transcription factors and kinases, such as CREB and MAPK [35]. Changes in Ca^{2+} can activate MAPK, which can set off a cascade of phosphorylations that control cell division, growth, and death [36]. On the other hand, CREB activation through Ca^{2+}-dependent kinases permits control of gene expression involved in memory, metabolic adaptability, and synaptic plasticity [37].

Changes in Ca^{2+} concentration that take place in cellular microdomains can elicit distinct reactions from global changes due to the spatial and temporal specificity of the Ca^{2+} signal transduction pathway [20]. For instance, distinct signaling pathways may be triggered by local Ca^{2+} release close to neuronal synapses as opposed to Ca^{2+} release across the cytoplasm [38]. Cells can precisely customize their responses to physiological stimuli thanks to the intricate integration of these several pathways, which also explains how dysregulation of these pathways can result in a range of disease disorders [39]. As shown in **Figure 1**, cellular Ca^{2+} homeostasis emerges from membrane influx (VGCC, SOCE/STIM1-Orai1), ER release–reuptake (IP_3R/RyR, SERCA), extrusion (PMCA/NCX), and mitochondrial transport (MCU/NCLX), with decoding via CaM–calcineurin/NFAT and CaMK-CREB axes.

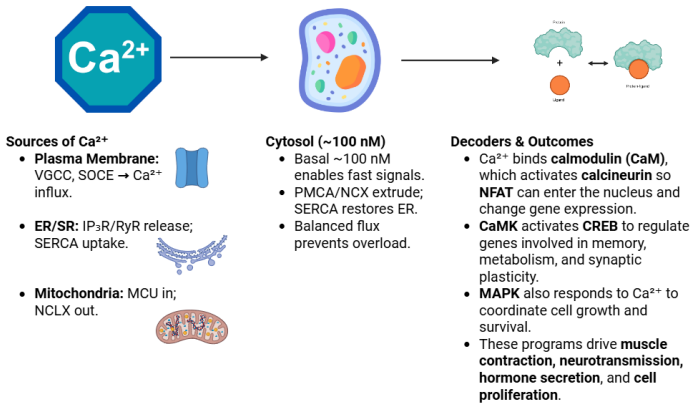


Figure 1 Cellular Ca^{2+} homeostasis.

Major calcium signaling pathways

The major calcium signaling pathways consist of mechanisms that allow cells to precisely regulate the flow and distribution of Ca^{2+}, both in the cytosol and internal organelles. The maintenance of calcium homeostasis, the coordination of numerous physiological processes, and the mediation of cellular responses to internal and external stimuli are all made possible by these pathways, which include Store-Operated Calcium Entry (SOCE), Mitochondrial Calcium Uniporter (MCU), and Ca^{2+} effectors like CaM. Understanding the processes underlying these pathways is essential for developing successful therapeutic strategies because dysfunction in them can lead to the development of a wide range of pathological illnesses, from cardiovascular ailments to neurodegenerative diseases. **Table 1** summarizes the major pathways and effectors in Ca^{2+} signaling that are essential for cellular physiological function.

Table 1 Physiological roles and pathological implications of calcium signaling pathways.

Ca^{2+} Pathway / Effectors	Mechanism	Key Molecules/Proteins	Physiological function	Implications of dysfunction / Pathology
Store-Operated Calcium Entry (SOCE)	Ca^{2+} depletion of the endoplasmic reticulum (ER) triggers STIM1 activation → interaction with Orai1 → entry of extracellular Ca^{2+} into the cytosol	STIM1 and Orai1	Maintains Ca^{2+} homeostasis, regulates proliferation, differentiation, secretion, and signal transduction.	STIM1/Orai1 mutation/dysregulation → immune disorders, muscle dysfunction, cardiac hypertrophy, arrhythmia, and tumor cell proliferation
Mitochondrial Calcium Uniporter (MCU)	Ca^{2+} ions enter the mitochondrial matrix through MCU → activation of TCA enzymes → ATP production	MCU, TCA enzymes, and electron transport chain	Regulates energy metabolism, ATP production, redox balance, apoptosis modulation, and mitochondrial function	Decreased MCU activity → cytosolic Ca^{2+} accumulation, energy disturbance, heart failure; Increased Ca^{2+} → neuronal apoptosis, neurodegeneration, and chronic oxidative stress
Calmodulin (CaM) and Ca^{2+} Effectors	Ca^{2+} binds to CaM → conformational changes → interactions with kinases, phosphatases, ion channels, and transcription factors	Calmodulin (CaM), kinases, phosphatases, MAPK, and calcineurin-NFAT	Mediating muscle contraction, hormone secretion, proliferation, differentiation, synaptic plasticity, and regulation of energy metabolism	CALM gene mutations → congenital arrhythmias, long QT syndrome, cardiac conduction disorders; MAPK/NFAT pathway dysregulation → proliferation/differentiation dysfunction

Store-Operated Calcium Entry (SOCE)

A calcium signaling route called SOCE is crucial for preserving intracellular Ca^{2+} homeostasis, particularly in non-excitable cells [40]. The depletion of Ca^{2+} stores in the ER initiates the SOCE mechanism by activating the Ca^{2+} sensor stromal interaction molecule 1 (STIM1) [41]. After detecting a drop in Ca^{2+} concentration, STIM1, which is found on the ER membrane, oligomerizes and moves to the area close to the plasma membrane [42]. Orai1, a specific Ca^{2+} channel in the plasma membrane, is contacted by STIM1 at this site, opening the channel and permitting Ca^{2+} ions from the extracellular environment to enter the cytosol [43]. The influx of Ca^{2+} through the SOCE not only restores ER stores but also produces cytosolic Ca^{2+} signals that control secretion, differentiation, proliferation, and downstream signal transduction [13].

SOCE dysfunction has been associated with various pathological conditions. STIM1 or Orai1 expression mutations or dysregulation can impact muscle and endothelial cell function and result in immunological diseases, including immunodeficiency [44]. Furthermore, SOCE dysregulation has been linked to the development of various cancer types, where increased Ca^{2+} flow through Orai1 promotes tumor cell migration and proliferation, as well as the

pathophysiology of cardiovascular diseases, including cardiac hypertrophy and arrhythmias [45]. Mechanistically, Orai1-mediated Ca^{2+} entry activates the Ca^{2+}/calmodulin-dependent phosphatase calcineurin, which dephosphorylates NFAT. Dephosphorylated NFAT translocates to the nucleus and induces the expression of pro-migratory and pro-invasive genes (e.g., cyclooxygenase-2 and autotaxin). This axis provides a direct link between enhanced SOCE and tumor cell migration, invasion, and metastatic progression. These results demonstrate that SOCE is a crucial signaling route with therapeutic implications in addition to being a homeostatic mechanism. As a result, SOCE regulation may be a target for clinical intervention in a number of disorders connected to Ca^{2+} [46].

Mitochondrial Calcium Uniporter (MCU)

The transmembrane protein complex known as the Mitochondrial Calcium Uniporter (MCU), which is found on the inner mitochondrial membrane, is essential for maintaining calcium homeostasis within the mitochondria [47]. MCU permits Ca^{2+} ions to enter the mitochondrial matrix, which controls energy generation by activating important tricarboxylic acid cycle (TCA) enzymes and oxidative phosphorylation [48]. Specifically, matrix Ca^{2+} entering via MCU acutely stimulates pyruvate dehydrogenase (PDH), isocitrate dehydrogenase (IDH), and α-ketoglutarate dehydrogenase (α-KGDH), thereby increasing NADH and $FADH_2$ supply to the electron-transport chain and coupling Ca^{2+} transients to oxidative phosphorylation and ATP output. MCU regulates mitochondrial Ca^{2+}, which supports energy metabolism and is also involved in apoptosis modulation, oxidative stress regulation, and mitochondrial function maintenance [49].

MCU malfunction has been linked to a number of clinical disorders. Reduced myocardial contractility and pathological cardiac remodeling are 2 ways that decreased MCU activity can cause cytosolic Ca^{2+} buildup and compromised cellular energy supply, both of which can lead to heart failure [51]. On the other hand, elevated mitochondrial Ca^{2+} resulting from MCU dysregulation can cause excessive permeability of the mitochondrial membrane, cause neuronal death, and contribute to the development of neurodegenerative illnesses including Parkinson's and Alzheimer's [52]. MCU dysregulation is also linked to mitochondrial malfunction and persistent oxidative stress, both of which are risk factors for cardiovascular and metabolic diseases [53].

Calmodulin and Ca^{2+} effectors

The ubiquitous calcium-binding protein CaM is essential for a variety of cellular functions as a modulator of Ca^{2+} signaling [54]. CaM can change its shape when it binds calcium ions because it contains 4 Ca^{2+} binding sites on its EF-hand domain [26]. Then, the active conformation of CaM interacts with several molecular targets, such as kinases, phosphatases, ion channels, and transcription factors, mediating a variety of physiological responses, ranging from the regulation of energy metabolism and synaptic plasticity to muscle contraction, hormone secretion, and cell proliferation [55].

There are important clinical ramifications to CaM's function as a Ca^{2+} effector. Calcium signaling failure may result from mutations in the CALM gene that impair CaM's capacity to connect with its targets or bind Ca^{2+} [56]. This condition has been linked to serious heart defects, including congenital arrhythmias, long QT syndrome, and cardiac conduction disorders [57]. According to genetic research, some mutations in CALM might cause aberrant activation or inhibition of downstream Ca^{2+} pathways, which can interfere with regular electrophysiological rhythms and cardiac contractions [58].

Furthermore, calcineurin-NFAT and MAPK are 2 more Ca^{2+}-dependent signaling pathways that can be impacted by CaM dysregulation, which can have an effect on organ functions, cell division, and proliferation [59]. As a result, calmodulin serves as a Ca^{2+} sensor as well as a vital connection between intracellular calcium variations and the genetic and functional control of cells [31]. The development of treatment approaches aimed at heart illnesses and diseases linked to calcium signaling dysregulation requires a comprehensive understanding of the function of CaM and related Ca^{2+} effectors.

The role of calcium signaling in normal physiology

Calcium signaling is a central mechanism in the coordination of various physiological processes, in

which fluctuations in intracellular Ca^{2+} concentration are translated into specific cellular responses. Calcium ions play an important role in muscle contraction, hormone secretion, regulation of energy metabolism, and nerve signal transmission, including synaptic plasticity and memory formation. Ca^{2+} is a crucial mediator in preserving proper physiological function and overall organismal homeostasis because of its capacity to control molecular and cellular network activities in a temporally and spatially specific manner. **Table 2** summarizes the role of Ca^{2+} as a key mediator in various physiological functions, the signaling mechanisms involved, the key molecules or proteins that regulate Ca^{2+} signaling, the main function of each process, and the implications if Ca^{2+} signaling dysfunction occurs.

Table 2 The role of Ca^{2+} signaling in normal physiological processes.

Physiological process	Ca^{2+} signaling mechanism	Key molecules / Proteins	Main function	Implications of dysfunction
Muscle contraction	- Depolarization of the plasma membrane triggers the release of Ca^{2+} from the RS via the RyR - Binding of Ca^{2+} to troponin C triggers cross-bridge cycling	RyR1 (skeletal muscle), RyR2 (heart), troponin C, SERCA, and VGCC	Regulates contraction and relaxation of skeletal and cardiac muscles, determining the strength and duration of contractions	Dysfunction causes impaired contractility, arrhythmias, and heart failure
Hormone secretion	- Depolarization of the plasma membrane opens VGCCs - Ca^{2+} activates the vesicle exocytosis machinery	VGCC, SNARE, and synaptotagmin	Triggers rapid and coordinated release of hormones (e.g. insulin and catecholamines)	Disorders cause abnormal hormone secretion, contributing to diabetes or an impaired stress response
Energy metabolism	- Ca^{2+} enters mitochondria through the MCU - Activates TCA enzymes: pyruvate, isocitrate, and α-ketoglutarate dehydrogenase	MCU and TCA dehydrogenase	Increases production of NADH/$FADH_2$, oxidative phosphorylation, and ATP; regulates redox balance	Excess Ca^{2+} → mitochondrial membrane depolarization, apoptosis; deficiency → decreased metabolism and cell energy capacity
Neurotransmission and memory	- Depolarization of the presynaptic terminal opens VGCCs - Ca^{2+} triggers neurotransmitter vesicle fusion via SNARE - Postsynaptic Ca^{2+} via NMDA receptors activates CaMKII	VGCC, synaptotagmin, SNARE, CaMKII, and NMDA receptor	Regulates neurotransmitter release, synaptic plasticity (LTP/LTD), long-term memory formation	Dysfunction → excitotoxicity, impaired neurotransmission, memory and learning, related to Alzheimer's and Parkinson's

Muscle contraction

Ca^{2+} is essential to the process of muscular contraction in both cardiac and skeletal muscles. Ca^{2+} is released from the sarcoplasmic reticulum (SR) through the ryanodine receptor (RyR1) in skeletal muscle when the plasma membrane depolarizes due to an action potential [60]. This ion can bind to troponin C due to an increase in cytosolic Ca^{2+} concentration. This causes a conformational shift in the troponin-tropomyosin complex, exposing the actin filament's active site [61]. This makes it possible to engage with myosin and start the cross-bridge cycle, which causes muscles to contract [62]. The sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) pumps Ca^{2+} back into the RS during contraction, enabling muscle relaxation [28].

The phenomenon of calcium-induced calcium release (CICR) is a component of the contraction process in heart muscle [63]. Extracellular Ca^{2+} can enter the cytosol when the cardiac cell membrane depolarizes, opening L-type VGCCs [64]. These Ca^{2+} ions subsequently trigger the ryanodine receptor (RyR2) to release more Ca^{2+} from the sarcoplasmic reticulum [65]. The strength and length of cardiac contraction are determined by these cytosolic Ca^{2+} oscillations, which also control troponin C binding and

facilitate myosin-actin contraction [66]. Inadequate control of Ca^{2+} through channels, pumps, or binding proteins can lead to cardiac failure, arrhythmias, or reduced contractility [67].

Hormone secretion

Ca^{2+} is the primary mediator in the method by which endocrine cells secrete hormones through the exocytosis process [68]. Generally speaking, physiological events like hormones, neurotransmitters, or metabolic alterations cause the plasma membrane of endocrine cells to depolarize. This opens VGCCs and permits Ca^{2+} to enter the cytosol from the external environment [69]. This increase in cytosolic Ca^{2+} serves as a signal to activate the exocytosis machinery, including the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins that regulate the fusion of secretory vesicles with the plasma membrane [70].

A conformation that permits vesicle-membrane fusion and hormone release into the bloodstream is induced when Ca^{2+} binds to vesicular calcium sensors, like synaptotagmin [71]. This mechanism ensures that hormone secretion occurs rapidly, coordinated, and according to physiological needs, whether it is the release of insulin from pancreatic β cells, the secretion of catecholamines from the adrenal medulla, or peptide hormones from other endocrine cells [72].

Hormone release can be disrupted by Ca^{2+} signaling dysfunction in endocrine cells, and this is linked to a number of clinical diseases [73]. One factor that contributes to the pathophysiology of diabetes mellitus is the dysregulation of Ca^{2+} in pancreatic β cells, which can result in aberrant insulin production [74]. Ca^{2+} disruptions in adrenal medullary cells can also impact catecholamine release and stress reactions [75].

Energy metabolism

Ca^{2+} has a major impact on mitochondrial function, which is the primary way it regulates cellular energy metabolism [76]. Ca^{2+} entering the mitochondrial matrix through the MCU activates a number of important TCA enzymes, including as α-ketoglutarate dehydrogenase, pyruvate dehydrogenase, and isocitrate dehydrogenase [77]. Oxidative phosphorylation and ATP synthesis are increased when these enzymes are activated because they produce more NADH and $FADH_2$, which in turn provide electrons to the electron transport chain [78].

The synthesis of energy is supported by mitochondrial Ca^{2+}, which also helps to maintain redox balance and stop oxidative stress from building up [79]. Excess Ca^{2+} can induce the inner mitochondrial membrane's permeability transition pore (PTP) to open, depolarizing the membrane, reducing ATP synthesis, and initiating the apoptotic process [80]. On the other hand, a lack of mitochondrial Ca^{2+} can impair organ function overall, lower cellular metabolic activity, and limit the body's ability to adjust to rising energy needs [81].

Neurotransmission and memory

Ca^{2+} controls the release of neurotransmitters at synapses, which is essential for neurotransmission and memory formation [82]. Ca^{2+} can enter the cytosol from the extracellular space when the action potential reaches the presynaptic terminal because the plasma membrane depolarizes, opening VGCCs [83]. Neurotransmitters are exocytosed into the synaptic cleft as a result of this rise in cytosolic Ca^{2+}, which causes ion binding to vesicle sensor proteins like synaptotagmin. This fusing of neurotransmitter vesicles with the plasma membrane is mediated by the SNARE complex [84].

Ca^{2+} plays a part in synaptic plasticity processes, including as long-term depression (LTD) and long-term potentiation (LTP), which are the molecular underpinnings of memory formation, in addition to controlling neurotransmitter release [85]. Glutamate receptor sensitivity and synaptic cytoskeleton remodeling are modulated by Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), which is activated by Ca^{2+} arriving through NMDA receptors on postsynaptic neurons [86]. This pathway's activation promotes long-term information storage and fortifies synaptic connections.

Dysfunction of Ca^{2+} signaling in the nervous system can lead to impaired neurotransmission, memory, and learning [87]. For instance, excessive or persistent dysregulation of Ca^{2+} can lead to neuronal excitotoxicity by activating proteases and producing free radicals, which is part of the pathophysiology of neurodegenerative illnesses including Parkinson's and

Alzheimer's [88]. On the other hand, intracellular Ca^{2+} shortage can interfere with the establishment of long-term memory by inhibiting LTP and synaptic plasticity [89]. **Figure 2** links these nodes to 4 canonical outputs - excitation-contraction coupling, neurotransmission and plasticity, endocrine secretion, and metabolic coupling - highlighting CICR (LTCC→RyR), synaptotagmin/SNARE-mediated exocytosis, NMDA-CaMKII signaling, and MCU-driven TCA/OXPHOS.

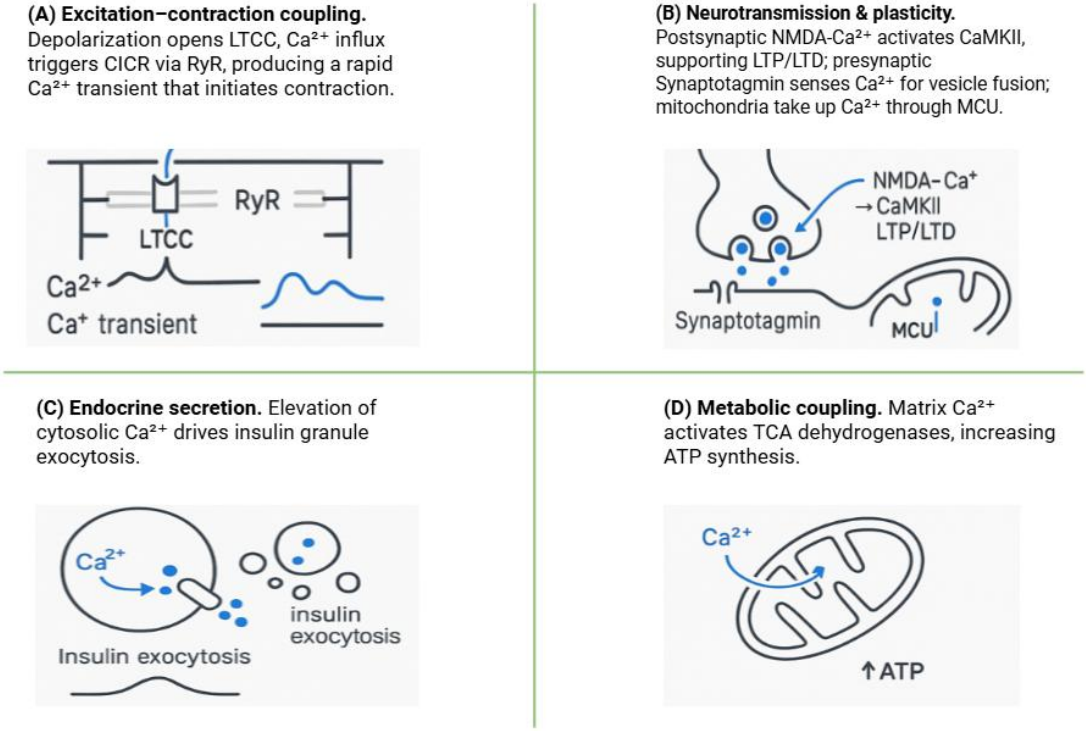


Figure 2 Physiological programs driven by Ca^{2+} signals.

Calcium signaling dysfunction in disease

One of the main contributing factors to the pathophysiology of many chronic diseases has been found to be the dysregulation of Ca^{2+} signaling. Significant physiological abnormalities can result from abnormal Ca^{2+} fluctuations, which can impact a wide range of cellular and tissue activities, including neurons, cardiomyocytes, and endocrine cells. Along with upsetting ionic homeostasis, this disruption sets off the activation of pathogenic signaling pathways that are linked to endocrine dysfunction, diabetes, cardiovascular disease, cancer, and neurodegeneration. The development of more targeted diagnostic and treatment approaches requires a comprehensive understanding of the mechanisms underlying Ca^{2+} dysregulation in the setting of disease. **Table 3** presents a summary of the mechanisms of Ca^{2+} signaling dysfunction in various types of diseases, the molecules and pathways involved, the physiological impact or pathological consequences that arise, and potential therapeutic targets.

Table 3 Ca^{2+} signaling dysfunction and its role in the pathogenesis of various diseases.

Types of disease	Mechanism of Ca^{2+} dysfunction	Related molecules/Pathways	Impact / Consequences	Therapeutic target
Neurodegeneration (Alzheimer's and Parkinson's)	Excessive cytosolic Ca^{2+} accumulation, disruption of ion channels, Ca^{2+} pumps, glutamate receptors, and	L-type calcium channels, mitochondria, proteases, phospholipases, and NMDA receptors	Oxidative stress activation, neuronal apoptosis, abnormal tau phosphorylation, β-amyloid	Modulation of Ca^{2+} channels, mitochondrial stabilization, and

Types of disease	Mechanism of Ca^{2+} dysfunction	Related molecules/Pathways	Impact / Consequences	Therapeutic target
	mitochondrial homeostasis		plaques, synaptic damage, and impaired memory and motor function	inhibition of excitotoxicity
Cardiovascular disease (Hypertrophy, heart failure, and arrhythmia)	Chronic cytosolic Ca^{2+} elevation, impaired Ca^{2+} efflux from the sarcoplasmic reticulum	SERCA, RyR, L-type calcium channels, SOCE, and MCU	Asynchronous contractions, cell hypertrophy, mitochondrial oxidative stress, apoptosis activation, and atrial/ventricular fibrillation	Activation/modulation of SERCA, RyR, L-type channels to improve contractility and prevent arrhythmias
Cancer (Breast, lung, and colorectal)	Cytosolic Ca^{2+} dysregulation, excessive SOCE, mitochondrial MCU, and interactions with oncogenic pathways	VGCC, STIM1/Orai1, MCU, PI3K/AKT, and MAPK	Increased proliferation, migration, invasion, metastasis, and apoptosis resistance	SOCE inhibitors, MCU modulation, and inhibition of specific Ca^{2+} channels

Neurodegeneration

Ca^{2+} signaling dysfunction is a central mechanism in the pathogenesis of various neurodegenerative diseases, including Alzheimer's and Parkinson's [9]. Excessive cytosolic Ca^{2+} buildup is the outcome of Ca^{2+} dysregulation in Alzheimer's disease, which is caused by disruption of ion channels, Ca^{2+} pumps, and glutamate receptors [90]. This rise in Ca^{2+} damages the cytoskeleton, cell membranes, and organelles, including mitochondria, by causing the activation of proteases, phospholipases, and free radicals [91]. Additionally, aberrant tau protein phosphorylation and β-amyloid plaque development are brought on by chronic Ca^{2+} buildup, which leads to neuronal degeneration and compromised synaptic function [92].

Dopaminergic neurons in the substantia nigra pars compacta are extremely susceptible to Ca^{2+} stress in Parkinson's disease [93]. L-type Ca^{2+} channel dysfunction and mitochondrial homeostasis dysregulation raise intracellular Ca^{2+} load, which sets off oxidative stress, depolarization of the mitochondrial membrane, and apoptotic pathway activation [94]. Both the motor and non-motor symptoms that are typical of Parkinson's disease are caused by the unchecked buildup of Ca^{2+}, which damages synapses and kills dopaminergic neurons [95].

Cardiovascular disease

Ca^{2+} signaling dysfunction is a major factor in the pathogenesis of various cardiovascular diseases, including cardiac hypertrophy, heart failure, and arrhythmias [96]. Through the sarcoplasmic reticulum's CICR mechanism, which binds to troponin C and ion return to the reticulum via SERCA, cytosolic Ca^{2+} variations in a healthy myocardium control cardiac contraction and relaxation [97]. Chronic increases in cytosolic Ca^{2+} or defective Ca^{2+} emptying result from dysfunction in this control, which can be caused by mutations in Ca^{2+} regulatory proteins or by dysregulation of the SOCE and MCU pathways. These conditions cause asynchronous contractions and cellular hypertrophy [98].

Excessive cytosolic Ca^{2+} buildup in heart failure reduces cardiac contractility and raises mitochondrial oxidative stress, which lowers ATP synthesis and initiates the apoptotic pathway [99]. Additionally, aberrant depolarization and spontaneous release of Ca^{2+} from the sarcoplasmic reticulum are 2 ways whereby Ca^{2+} dysregulation in cardiac conduction cells and Purkinje tissue leads to arrhythmias, such as atrial and ventricular fibrillation [100].

Pathological cardiac remodeling is also influenced by disruption in Ca^{2+} signaling [50]. Hemodynamic load-induced cardiac hypertrophy raises Ca^{2+} channel expression and activity, intensifying maladaptive growth signals and raising the risk of chronic heart failure [101]. Therefore, pharmaceutical interventions that aim to improve contractility, prevent arrhythmias, and restrict cardiac remodeling should focus on modulating the Ca^{2+} signaling pathway, which includes the activity of SERCA, RyR, and L-type channels [102].

Cancer

The pathogenesis and progression of cancer are significantly influenced by Ca^{2+} signaling dysregulation, which controls the proliferation, migration, invasion, and death of tumor cells [103]. Dysregulation of plasma Ca^{2+} channels and organelles, such as VGCCs, SOCE via STIM1/Orai1, and MCU, can lead to abnormal intracellular Ca^{2+} fluctuations [104]. Overactivity of these pathways causes pro-proliferative and anti-apoptotic genes to be expressed, activates Ca^{2+}-dependent kinases and phosphatases, and raises cytosolic Ca^{2+} [36].

Upregulation of SOCE via STIM1/Orai1 has been linked to aggressive cell migration, tissue invasion, and metastasis in a number of cancer types, including colorectal, lung, and breast malignancies [105]. Furthermore, MCU-mediated dysregulation of mitochondrial Ca^{2+} influences ATP synthesis, redox balance, and apoptosis resistance, all of which promote tumor cell survival in oxidatively challenged conditions [106]. Dysfunction of Ca^{2+} signaling also interacts with other oncogenic pathways, including MAPK and PI3K/AKT, which increase the capacity of cancer cells to proliferate and adapt metabolically [107].

There is a lot of therapeutic potential in targeting Ca^{2+} signaling in cancer cells, whether via SOCE suppression, MCU regulation, or blocking particular Ca^{2+} channels [108]. These treatments can prevent metastasis, improve sensitivity to chemotherapy, and decrease tumor growth [109]. Therefore, a better comprehension of Ca^{2+} dysregulation in cancer creates prospects for the creation of more targeted and efficient molecular mechanism-based treatments.

Diabetes and endocrine disorders

Ca^{2+} signaling dysfunction plays a critical role in the pathogenesis of metabolic and endocrine disorders, including diabetes mellitus and pancreatic hormone dysfunction. Proper cytosolic Ca^{2+} fluctuations are necessary for insulin production in response to glucose in pancreatic β cells [110]. Increased glucose causes the cell membrane to depolarize, opening VGCCs that let Ca^{2+} in and cause insulin vesicle fusion through SNARE proteins [111]. Insulin secretion is inhibited and hyperglycemia is exacerbated by Ca^{2+} dysregulation, which manifests as either reduced Ca^{2+} flow or compromised cytosolic equilibrium [112].

Systemic metabolic balance may also be upset by Ca^{2+} dysregulation, which also influences the release of other hormones such as glucagon, catecholamines, and thyroid hormones [113]. Cell dysfunction may worsen as a result of oxidative stress, reduced ATP synthesis, and apoptosis pathway activation brought on by excessive mitochondrial Ca^{2+} buildup or diminished MCU activity in endocrine cells [114]. This disorder raises the risk of cardiometabolic problems in addition to affecting glucose homeostasis [115]. Figure 3 maps disease-relevant perturbations (↑/↓ SOCE; RyR leak; SERCA downregulation; VGCC variants; MCU↑/NCLX↓; CaM/CaMK/calcineurin mis-signaling) onto neurodegeneration, cardiac remodeling/arrhythmia, cancer, and endocrine dysfunction, with directionality indicated.

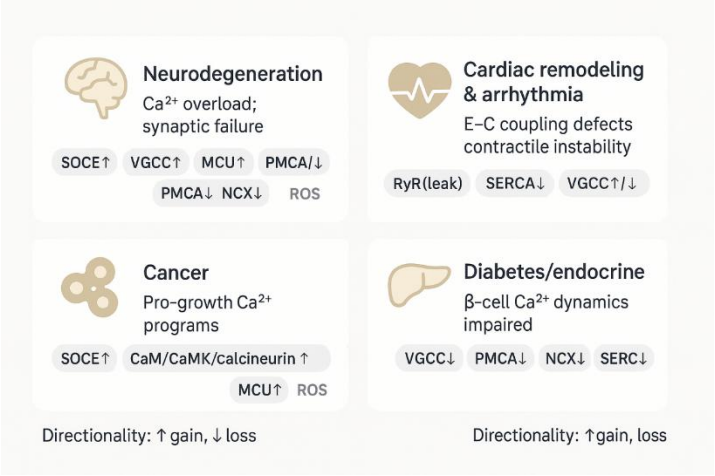


Figure 3 Pathological perturbations of Ca^{2+} signaling across diseases.

Therapeutic approaches and interventions

Therapeutic strategies that target Ca^{2+} signaling have promising prospects for the treatment of numerous illnesses linked to this ion's dysfunction. Intervention tactics include direct Ca^{2+} channel manipulation, controlling certain molecular targets like STIM1, Orai1, and MCU, and using epigenetic techniques to take advantage of Ca^{2+}'s impact on gene expression. In addition to restoring calcium homeostasis, these strategies seek to enhance tissue and cellular capabilities compromised by Ca^{2+} signaling dysregulation, laying the groundwork for the creation of more targeted and potent novel treatments.

Modulation of Ca^{2+} channels

Ca^{2+} channel modulation is a key therapeutic approach for the treatment of a number of cardiovascular conditions, including as hypertension and arrhythmias [116]. Myocardial contraction and vascular tone are significantly influenced by L-type Ca^{2+} channels found in cardiac muscle cells and vascular smooth muscle cells [117]. Increased smooth muscle and cardiac contractions due to excessive activation or dysregulation of these channels might raise blood pressure and increase the risk of arrhythmias [118].

The use of Ca^{2+} channel antagonists calcium channel blockers (CCBs) aims to inhibit the entry of Ca^{2+} into cells through L-type channels, thereby reducing heart muscle contractility, widening blood vessels, and stabilizing heart rhythm [119]. These medications have been demonstrated to be successful in lowering blood pressure in patients with hypertension, lessening the heart's stress, and shielding individuals with arrhythmias from tachycardia and atrial fibrillation episodes [120]. Furthermore, kinase activity and Ca^{2+}-dependent gene expression are 2 downstream signaling pathways that are impacted by Ca^{2+} channel regulation, which offers further protection against oxidative stress and abnormal cardiac remodeling [14].

Molecular target of Ca^{2+}

More specialized approaches to treating a variety of disorders linked to Ca^{2+} dysregulation are provided by therapeutic approaches that target important molecules in calcium signaling, such as STIM1, Orai1, and MCU. The SOCE pathway, which mediates the inflow of Ca^{2+} from the external environment when endoplasmic reticulum reserves are exhausted, is largely mediated by STIM1 and Orai1 [121]. This pathway's overactivation has been connected to immunological diseases, cancer, and heart hypertrophy [122]. Therapeutic potential in oncology and cardiovascular disease can be achieved by selectively inhibiting STIM1 or Orai1, which can stabilize cytosolic Ca^{2+} fluctuations, decrease the activation of maladaptive cell growth pathways, and prevent tumor cell migration and proliferation [123].

In the meantime, MCU is involved in the control of mitochondrial Ca^{2+}, which is necessary for the synthesis of ATP, the control of oxidative stress, and apoptosis [124]. Excessive mitochondrial Ca^{2+} accumulation or reduced Ca^{2+} uptake due to MCU dysfunction can result in cardiac failure, brain injury, and metabolic problems [125]. Through the use of inhibitors or selective agonists, MCU can be modified to directly regulate mitochondrial Ca^{2+} homeostasis, thereby restoring cellular energy capacity and lowering oxidative stress [126].

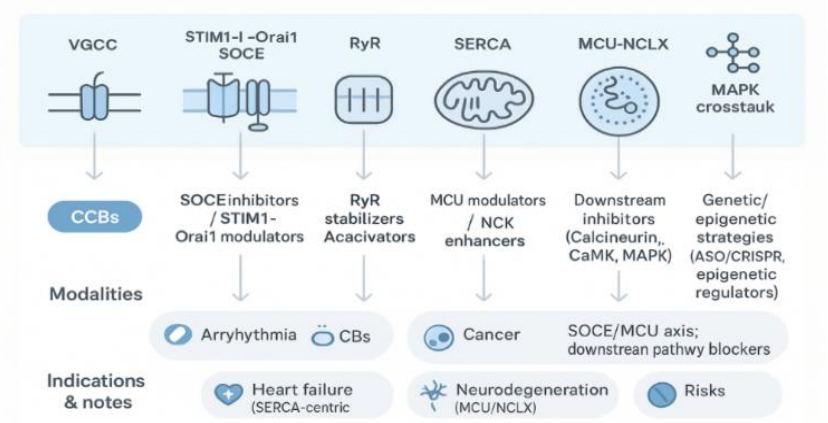
This molecular target-based method demonstrates that STIM1, Orai1, and MCU treatments influence downstream signaling cascades that are critical for cell proliferation, differentiation, contractility, and survival in addition to directly modulating Ca^{2+} fluctuations [127]. This approach lays the groundwork for the creation of safer and more efficient precision treatments for diseases linked to calcium signaling dysregulation, including metabolic, neurodegenerative, cardiovascular, and oncological conditions.

Epigenetic strategies

Through epigenetic pathways, Ca^{2+} affects the regulation of gene expression in addition to its involvement in cytosolic and mitochondrial signaling [128]. Variations in cytosolic Ca^{2+} can activate a number of transcription factors, such as NFAT, CREB, and myocyte enhancer factor 2 (MEF2), which directly control the expression of genes related to cell survival, proliferation, differentiation, and contractility [129]. This pathway, which connects Ca^{2+} fluctuations to chromatin changes and transcriptional activity, is

frequently activated by contact with Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) or phosphatases like calcineurin [130].

Ca^{2+} signaling is used in epigenetic-based treatment techniques that seek to precisely alter gene expression, for instance, by decreasing the production of pro-apoptotic genes or enhancing the activation of protective transcription pathways [131]. This approach may be used in cancer, neurological illnesses, and cardiovascular conditions where the course of the disease is aided by the deregulation of gene expression brought on by Ca^{2+} fluctuations [132]. For instance, CaMK/CREB regulation can support synaptic plasticity and memory function in neurodegenerative illnesses, while NFAT activation via Ca^{2+} can enhance cardiomyocyte cell regeneration following injury [133]. **Figure 4** summarizes the therapeutic landscape from membrane to nucleus - VGCC and SOCE modulators, RyR stabilizers, SERCA activators, MCU/NCLX targeting, and downstream inhibitors of calcineurin, CaMK, and MAPK - aligned to indications and biomarker readouts.



VGCC
- Voltage-gated Ca^{2+} channels drive fast Ca^{2+} entry during depolarization.
- Calcium-channel blockers (CCBs) reduce excitability and contractility.

STIM1–Orai1 SOCE
- STIM1 senses ER Ca^{2+} loss and opens Orai1 to refill stores and signal.
- SOCE inhibitors or STIM1–Orai1 modulators curb excessive Ca^{2+} influx.

RyR
- RyR releases Ca^{2+} from ER/SR; leak promotes arrhythmia and stress.
- RyR stabilizers/activators normalize release.

SERCA
- SERCA pumps Ca^{2+} back into ER/SR to restore baseline.
- SERCA enhancement can improve relaxation and heart failure.

MCU–NCLX
- MCU imports Ca^{2+} into mitochondria; NCLX exports it to prevent overload. Tuning this axis links Ca^{2+} signals to ATP supply; relevant in neurodegeneration and cancer.

MAPK crosstalk / downstream
- Ca^{2+} interfaces with MAPK, CaMK, and calcineurin–NFAT to control gene programs.Downstream inhibitors block maladaptive growth/ survival signaling.

Modalities / indications / notes
- Arrhythmia and heart failure (SERCA-centric); cancer; neurodegeneration (MCU/NCLX).
- Biomarkers: Ca^{2+} imaging, NFAT targets, p-CREB, mito-redox.
- Risks to monitor: hypotension, bradycardia/negative inotropy

Figure 4 Therapeutic targeting map of Ca^{2+} pathways.

Future research directions

Ca^{2+} signaling has been identified as a central mechanism regulating a wide range of physiological processes, from muscle contraction and hormone secretion to neurotransmission and energy metabolism [13]. Furthermore, dysregulation of Ca^{2+} plays a major role in the pathophysiology of a number of illnesses, such as cancer, diabetes, cardiovascular disease, and neurodegeneration [5-8]. These results highlight how crucial it is to fully comprehend Ca^{2+} dynamics in cellular and tissue settings, both in healthy and diseased settings.

Understanding the intricate relationships between Ca^{2+} signaling pathways, transcription factors, epigenetic modification, and downstream effects on different cell types is still difficult, despite the fact that prior research has shown important functions for molecules including STIM1, Orai1, MCU, and calmodulin [134]. These restrictions create the possibility of conducting more thorough studies on the coordination of Ca^{2+} variations in space and time, as well as their effects on the overall physiology of organs and systems.

Future studies should concentrate on developing novel technologies and experimental methodologies,

such as cellular proteomic and transcriptome analysis, *in vivo* Ca^{2+} imaging, and molecular and epigenetic target-based treatment approaches [14]. These investigations could help create novel treatments that restore Ca^{2+} homeostasis, uncover possible illness biomarkers, and offer more accurate insights into Ca^{2+} signaling pathways. Therefore, it is anticipated that additional study in this field will not only deepen our grasp of the scientific foundation but also open the door to more potent clinical treatments for disorders linked to calcium dysregulation.

Conslusions

This review synthesizes calcium signaling across cellular compartments to provide a systems-level account of how calcium regulates physiology and contributes to disease. The evidence indicates that pathogenesis more often reflects imbalance within an integrated network comprising store-operated calcium entry (SOCE), mitochondrial calcium uniporter (MCU)-mediated flux, and calmodulin (CaM)-driven transcriptional programs than defects in any single molecule. This network links plasma-membrane influx with calcium handling by the endoplasmic and sarcoplasmic reticulum, mitochondrial control of bioenergetics, and gene regulation in the nucleus.

Therapeutically, restoring network-level calcium balance is likely to be more effective than single-target blockade. Promising avenues include context-specific modulation of SOCE components such as STIM1 and Orai1, regulators of reticular calcium cycling such as SERCA and ryanodine receptors, mitochondrial transport via MCU and NCLX, and downstream calmodulin-dependent pathways including calcineurin-NFAT and CaMK-CREB. Future work should combine quantitative calcium imaging, multi-omics profiling of network nodes, and causal perturbation in human-relevant models to define biomarkers, stratify patients, and guide rational multi-node interventions. Viewed through this integrated lens, calcium signaling remains both a central regulator of normal physiology and a tractable target for next-generation therapies across neurodegenerative, cardiovascular, metabolic, and oncologic diseases.

Acknowledgements

The authors would like to express their sincere gratitude to the National Research and Innovation Agency (BRIN) and the Indonesia Endowment Fund for Education (LPDP) for financial support through the Research and Innovation for Advanced Indonesia (RIIM) Program – Competitive Wave 7, as stipulated in the Decree of the Deputy for Research and Innovation Facilitation of BRIN No. 61/II.7/HK/2024. The authors also acknowledge material and immaterial support from the Research Organization for Agriculture and Food (ORPP BRIN) and the valuable assistance of the Research Center for Mineral Technology, BRIN, in the preparation and completion of this manuscript. Collaborative contributions from Institut Teknologi Sumatera (ITERA) are gratefully appreciated.

Declaration of Generative AI in Scientific Writing

The authors declare that no generative AI tools were used in the writing or preparation of this manuscript.

CRediT Author Statement

Aswin Rafif Khairullah: Conceptualization, Literature review, and Writing – original draft. **Dea Anita Ariani Kurniasih**: Literature review, Data curation, and Writing – original draft. **Ilma Fauziah Ma'ruf**: Literature review, Data curation, and Writing – original draft. **Bima Putra Pratama**: Reference management, Data curation, and Validation. **Mohammad Sukmanadi**: Conceptualization, Supervision, Funding acquisition, and Writing – review and editing. **Arif Nur Muhammad Ansori**: Writing – review and editing, Validation, and Supervision. **Imam Mustofa**: Manuscript preparation, Critical review, and Validation. **Bantari Wisynu Kusuma Wardhani**: Manuscript preparation, Critical review, and Validation. **Riza Zainuddin Ahmad**: Methodological review, Critical revision, and Validation. **Eny Martindah**: Writing – review and editing, Supervision, and Validation. **Sri Mulyati**: Reference management, Resources, and Validation. **Wita Yulianti**: Manuscript preparation, Critical review, and Validation. **Abdul Hadi Furqoni**: Reference management, Resources, and Validation. **Saifur Rehman**: Project administration, Supervision, Writing – review and

editing, and Validation. **Syahputra Wibowo**: Writing – review and editing, Visualization, and Validation. **Fadhila Utari**: Manuscript preparation, Critical review, and Validation.

References

[1] P Köster, TA DeFalco and C Zipfel. Ca^{2+} signals in plant immunity. *The EMBO Journal* 2022; **41(12)**, e110741.

[2] G Bkaily and D Jacques. Calcium homeostasis, transporters, and blockers in health and diseases of the cardiovascular system. *International Journal of Molecular Sciences* 2023; **24(10)**, 8803.

[3] R Bagur and G Hajnóczky. Intracellular Ca^{2+} sensing: Its role in calcium homeostasis and signaling. *Molecular Cell* 2017; **66(6)**, 780-788.

[4] C Dai and RA Khalil. Calcium signaling dynamics in vascular cells and their dysregulation in vascular disease. *Biomolecules* 2025; **15(6)**, 892.

[5] E Murphy and JC Liu. Mitochondrial calcium and reactive oxygen species in cardiovascular disease. *Cardiovascular Research* 2023; **119(5)**, 1105-1116.

[6] G Bastioli, S Piccirillo, L Graciotti, M Carone, G Sprega, O Taoussi, A Preziuso and P Castaldo. Calcium deregulation in neurodegeneration and neuroinflammation in Parkinson's disease: Role of calcium-storing organelles and sodium-calcium exchanger. *Cells* 2024; **13(15)**, 1301.

[7] I Shemarova. The dysfunction of Ca^{2+} channels in hereditary and chronic human heart diseases and experimental animal models. *International Journal of Molecular Sciences* 2023; **24(21)**, 15682.

[8] J Zhu, P Xun, JC Bae, JH Kim, DJ Kim, K Yang and K He. Circulating calcium levels and the risk of type 2 diabetes: a systematic review and meta-analysis. *British Journal of Nutrition* 2019; **122(4)**, 376-387.

[9] RP Ureshino, AG Erustes, TB Bassani, P Wachilewski, GC Guarache, AC Nascimento, AJ Costa, SS Smaili and GJDS Pereira. The interplay between Ca^{2+} signaling pathways and neurodegeneration. *International Journal of Molecular Sciences* 2019; **20(23)**, 6004.

[10] S Ramos, J Gregório, AS Fernandes and N Saraiva. Association between dysregulated expression of Ca^{2+} and ROS-related genes and breast cancer patient survival. *Frontiers in Bioinformatics* 2025; **5(1)**, 1633494.

[11] A Wdowiak, A Podgórska and B Szal. Calcium in plants: An important element of cell physiology and structure, signaling, and stress responses. *Acta Physiologiae Plantarum* 2024; **46(1)**, 108.

[12] WA Catterall. Voltage-gated calcium channels. *Cold Spring Harbor Perspectives in Biology* 2011; **3(8)**, a003947.

[13] HO Gu, SW Noh, OH Kim and BC Oh. Crucial roles of calcium ATPases and phosphoinositides: Insights into pathophysiology and therapeutic strategies. *Molecules and Cells* 2025; **48(9)**, 100254.

[14] J Wang, J Pan, F Luan, H Shi, Y Xie, C Zhao, J Zou, Y Shi, D Guo, J Sun and X Zhang. From molecular chaos to precision medicine in the treatment of cardiac hypertrophy: A rational use of natural products by integrating artificial intelligence and multi-omics data. *Pharmacological Research* 2025; **219(1)**, 107898.

[15] E Perez-Rivera, C Plasencia and U Ros. The multifaceted role of calcium signaling in regulated necrosis. *Biomolecules* 2025; **15(6)**, 854.

[16] AP Kutschat, SA Johnsen and FH Hamdan. Store-operated calcium entry: Shaping the transcriptional and epigenetic landscape in pancreatic cancer. *Cells* 2021; **10(5)**, 966.

[17] J Xu, E Minobe and M Kameyama. Ca^{2+} Dyshomeostasis links risk factors to neurodegeneration in Parkinson's disease. *Frontiers in Cellular Neuroscience* 2022; **16(1)**, 867385.

[18] L Daverkausen-Fischer and F Pröls. Regulation of calcium homeostasis and flux between the endoplasmic reticulum and the cytosol. *Journal of Biological Chemistry* 2022; **298(7)**, 102061.

[19] X Zhou, Z Chen, L Xiao, Y Zhong, Y Liu, J Wu and H Tao. Intracellular calcium homeostasis and its dysregulation underlying epileptic seizures. *Seizure* 2022; **103(1)**, 126-136.

[20] F Moccia, AF Pla, D Lim, F Lodola and A Gerbino. Intracellular Ca^{2+} signalling: Unexpected new roles for the usual suspect. *Frontiers in Physiology* 2023; **14(1)**, 1210085.

[21] G Santulli, R Nakashima, Q Yuan and AR Marks. Intracellular calcium release channels: an update. *The Journal of Physiology* 2017; **595(10)**, 3041-3051.

[22] D D'Angelo and R Rizzuto. The Mitochondrial Calcium Uniporter (MCU): Molecular identity and role in human diseases. *Biomolecules* 2023; **13(9)**, 1304.

[23] Z Zayani, A Matinahmadi, A Tavakolpournegari and SH Bidooki. Exploring stressors: Impact on cellular organelles and implications for cellular functions. *Stresses* 2025; **5(2)**, 26.

[24] A Girault, A Ahidouch and H Ouadid-Ahidouch. Roles for Ca^{2+} and K^+ channels in cancer cells exposed to the hypoxic tumour microenvironment. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2020; **1867(4)**, 118644.

[25] G Bonsignore, S Martinotti and E Ranzato. Wound repair and Ca^{2+} signalling interplay: The role of Ca^{2+} channels in skin. *Cells* 2024; **13(6)**, 491.

[26] CF Yang and WC Tsai. Calmodulin: The switch button of calcium signaling. *Tzu Chi Medical Journal* 2021; **34(1)**, 15-22.

[27] AL Deluque, H Dimke and RT Alexander. Biology of calcium homeostasis regulation in intestine and kidney. *Nephrology Dialysis Transplantation* 2025; **40(3)**, 435-445.

[28] H Xu and H Van Remmen. The SarcoEndoplasmic Reticulum Calcium ATPase (SERCA) pump: A potential target for intervention in aging and skeletal muscle pathologies. *Skeletal Muscle* 2021; **11(1)**, 25.

[29] QS Liao, Q Du, J Lou, JY Xu and R Xie. Roles of Na^+/Ca^{2+} exchanger 1 in digestive system physiology and pathophysiology. *World Journal of Gastroenterology* 2019; **25(3)**, 287-299.

[30] S Ghosh, M Dahiya, A Kumar, M Bheri and GK Pandey. Calcium imaging: A technique to monitor calcium dynamics in biological systems. *Physiology and Molecular Biology of Plants* 2023; **29(12)**, 1777-1811.

[31] D Pikor, M Hurła, B Słowikowski, O Szymanowicz, J Poszwa, N Banaszek, A Drelichowska, PP Jagodziński, W Kozubski and J Dorszewska. Calcium ions in the physiology and pathology of the central nervous system. *International Journal of Molecular Sciences* 2024; **25(23)**, 13133.

[32] A Villalobo, H Ishida, HJ Vogel and MW Berchtold. Calmodulin as a protein linker and a regulator of adaptor/scaffold proteins. *Biochimica et Biophysica Acta (BBA) - Molecular Cell Research* 2018; **1865(3)**, 507-521.

[33] T Masaki and M Shimada. Decoding the phosphatase code: Regulation of cell proliferation by calcineurin. *International Journal of Molecular Sciences* 2022; **23(3)**, 1122.

[34] H-Y Pan, AV Ladd, MR Biswal and M Valapala. Role of nuclear factor of activated T cells (NFAT) pathway in regulating autophagy and inflammation in retinal pigment epithelial cells. *International Journal of Molecular Sciences* 2021; **22(16)**, 8684.

[35] H Tokumitsu and H Sakagami. Molecular mechanisms underlying Ca^{2+}/calmodulin-dependent protein kinase kinase signal transduction. *International Journal of Molecular Sciences* 2022; **23(19)**, 11025.

[36] DO Moon. Calcium's role in orchestrating cancer apoptosis: Mitochondrial-centric perspective. *International Journal of Molecular Sciences* 2023; **24(10)**, 8982.

[37] KH Zent and ML Dell'Acqua. Synapse-to-nucleus ERK→CREB transcriptional signaling requires dendrite-to-soma Ca^{2+} propagation mediated by L-type voltage-gated Ca^{2+} channels. *Journal of Neuroscience* 2025; **45(4)**, e1216242024.

[38] Y Bai, Z Zhou, B Han, X Xiang, W Huang and H Yao. Revisiting astrocytic calcium signaling in the brain. *Fundamental Research* 2024; **4(6)**, 1365-1374.

[39] L Yan, J Wang, X Cai, YC Liou, HM Shen, J Hao, C Huang, G Luo and W He. Macrophage plasticity: Signaling pathways, tissue repair, and regeneration. *MedComm* 2024; **5(8)**, e658.

[40] S Bollimuntha, B Pani and BB Singh. Neurological and motor disorders: Neuronal

store-operated Ca^{2+} signaling: An overview and its function. *Advances in Experimental Medicine and Biology* 2017; **993(1)**, 535-556.

[41] M Fahrner, H Grabmayr and C Romanin. Mechanism of STIM activation. *Current Opinion in Physiology* 2020; **17(1)**, 74-79.

[42] J Pacheco, L Dominguez, A Bohórquez-Hernández, A Asanov and L Vaca. A cholesterol-binding domain in STIM1 modulates STIM1-Orai1 physical and functional interactions. *Scientific Reports* 2016; **6(1)**, 29634.

[43] PS Yeung, M Yamashita and M Prakriya. Molecular basis of allosteric Orai1 channel activation by STIM1. *The Journal of Physiology* 2020; **598(9)**, 1707-1723.

[44] Q Lu, Y Ding, Y Zhang and S Liu. Viral subversion of host cell Ca^{2+} signaling through STIM1-Orai1-mediated SOCE: Mechanisms and implications. *Pharmacological Research* 2025; **218(1)**, 107846.

[45] P Mo and S Yang. The store-operated calcium channels in cancer metastasis: From cell migration, invasion to metastatic colonization. *Frontiers in Bioscience* 2018; **23(7)**, 1241-1256.

[46] Z Chao, Q Mei, C Yang, J Luo, P Liu, H Peng, X Guo, Z Yin, L Li and Z Wang. Immunological synapse: Structures, molecular mechanisms and therapeutic implications in disease. *Signal Transduction and Targeted Therapy* 2025; **10(1)**, 254.

[47] D Matuz-Mares, M González-Andrade, MG Araiza-Villanueva, MM Vilchis-Landeros and H Vázquez-Meza. Mitochondrial calcium: Effects of its imbalance in disease. *Antioxidants* 2022; **11(5)**, 801.

[48] C Delierneux, S Kouba, S Shanmughapriya, M Potier-Cartereau, M Trebak and N Hempel. Mitochondrial calcium regulation of redox signaling in cancer. *Cells* 2020; **9(2)**, 432.

[49] J Sun, G Gao, S Wang, H Liu and TS Tang. Decoding the influence of mitochondrial Ca^{2+} regulation on neurodegenerative disease progression. *Mitochondrial Communications* 2025; **3(1)**, 1-15.

[50] MP Lazaropoulos and JW Elrod. Mitochondria in pathological cardiac remodeling. *Current Opinion in Physiology* 2022; **25(1)**, 100489.

[51] P Wang, S Xu, J Xu, Y Xin, Y Lu, H Zhang, B Zhou, H Xu, SS Sheu, R Tian and W Wang. Elevated MCU expression by CaMKIIδB limits pathological cardiac remodeling. *Circulation* 2022; **145(14)**, 1067-1083.

[52] F Borbolis, C Ploumi and K Palikaras. Calcium-mediated regulation of mitophagy: Implications in neurodegenerative diseases. *npj Metabolic Health and Disease* 2025; **3(1)**, 4.

[53] J Wang, J Jiang, H Hu and L Chen. MCU complex: Exploring emerging targets and mechanisms of mitochondrial physiology and pathology. *Journal of Advanced Research* 2025; **68(1)**, 271-298.

[54] LM McAloon, AG Muller, K Nay, EL Lu, B Smeuninx, AR Means, MA Febbraio and JW Scott. CaMKK2: Bridging the gap between Ca^{2+} signaling and energy-sensing. *Essays in Biochemistry* 2024; **68(3)**, 309-320.

[55] JS Brzozowski and KA Skelding. The multi-functional calcium/calmodulin stimulated protein kinase (CaMK) family: Emerging targets for anti-cancer therapeutic intervention. *Pharmaceuticals* 2019; **12(1)**, 8.

[56] JW Hussey, WB Limpitikul and IE Dick. Calmodulin mutations in human disease. *Channels* 2023; **17(1)**, 2165278.

[57] DC Pipilas, CN Johnson, G Webster, J Schlaepfer, F Fellmann, N Sekarski, LM Wren, KV Ogorodnik, DM Chazin, WJ Chazin, L Crotti, ZA Bhuiyan and AL George. Novel calmodulin mutations associated with congenital long QT syndrome affect calcium current in human cardiomyocytes. *Heart Rhythm* 2016; **13(10)**, 2012-2019.

[58] B Badone, C Ronchi, MC Kotta, L Sala, A Ghidoni, L Crotti and A Zaza. Calmodulinopathy: Functional effects of CALM mutations and their relationship with clinical phenotypes. *Frontiers in Cardiovascular Medicine* 2018; **5(1)**, 176.

[59] R Ren, J Guo, Y Chen, Y Zhang, L Chen and W Xiong. The role of Ca^{2+} /Calcineurin/NFAT signalling pathway in osteoblastogenesis. *Cell Proliferation* 2021; **54(11)**, e13122.

[60] XQ Li, YM Zheng, J Reyes-García and YX Wang. Diversity of ryanodine receptor 1-

mediated Ca^{2+} signaling in systemic and pulmonary artery smooth muscle cells. *Life Sciences* 2021; **270(1)**, 119016.

[61] D Han, Y Lim, S Lee and SI Eyun. Troponin I - a comprehensive review of its function, structure, evolution, and role in muscle diseases. *Animal Cells and Systems* 2025; **29(1)**, 446-468.

[62] YS Borovikov, MV Tishkova, SV Avrova, VV Sirenko and OE Karpicheva. The twisting and untwisting of actin and tropomyosin filaments are involved in the molecular mechanisms of muscle contraction, and their disruption can result in muscle disorders. *International Journal of Molecular Sciences* 2025; **26(14)**, 6705.

[63] E Ríos. Calcium-induced release of calcium in muscle: 50 years of work and the emerging consensus. *The Journal of General Physiology* 2018; **150(4)**, 521-537.

[64] N Kumari, H Gaur and A Bhargava. Cardiac voltage gated calcium channels and their regulation by β-adrenergic signaling. *Life Sciences* 2018; **194(1)**, 139-149.

[65] TR Kolstad, J van den Brink, N MacQuaide, PK Lunde, M Frisk, JM Aronsen, ES Norden, A Cataliotti, I Sjaastad, OM Sejersted, AG Edwards, GT Lines and WE Louch. Ryanodine receptor dispersion disrupts Ca^{2+} release in failing cardiac myocytes. *Elife* 2018; **7(1)**, e39427.

[66] K Rayani, J Seffernick, AY Li, JP Davis, AM Spuches, F Van Petegem, RJ Solaro, S Lindert and GF Tibbits. Binding of calcium and magnesium to human cardiac troponin C. *Journal of Biological Chemistry* 2021; **296(1)**, 100350.

[67] A Njegic, C Wilson and EJ Cartwright. Targeting Ca^{2+} handling proteins for the treatment of heart failure and arrhythmias. *Frontiers in Physiology* 2020; **11(1)**, 1068.

[68] P Ježek, B Holendová, M Jabůrek, J Tauber, A Dlasková and L Plecitá-Hlavatá. The pancreatic β-Cell: The perfect redox system. *Antioxidants* 2021; **10(2)**, 197.

[69] YD Subbamanda and A Bhargava. Intercommunication between voltage-gated calcium channels and estrogen receptor/estrogen signaling: Insights into physiological and pathological conditions. *Cells* 2022; **11(23)**, 3850.

[70] M Lin, Q Zhu, J Wang, W Yang, H Fan, J Yi and M Jiang. Molecules involved in acrosomal exocytosis and cortical granule exocytosis. *Biotarget* 2017; **1(1)**, 11.

[71] AT Brunger, J Leitz, Q Zhou, UB Choi and Y Lai. Ca^{2+}-Triggered Synaptic Vesicle Fusion Initiated by Release of Inhibition. *Trends in Cell Biology* 2018; **28(8)**, 631-645.

[72] AJ Trexler and JW Taraska. Regulation of insulin exocytosis by calcium-dependent protein kinase C in beta cells. *Cell Calcium* 2017; **67(1)**, 1-10.

[73] MA Magnuson and AB Osipovich AB. Ca^{2+} signaling and metabolic stress-induced pancreatic β-cell failure. *Frontiers in Endocrinology* 2024; **15(1)**, 1412411.

[74] PV Dludla, SE Mabhida, K Ziqubu, BB Nkambule, SE Mazibuko-Mbeje, S Hanser, AK Basson, C Pheiffer and AP Kengne. Pancreatic β-cell dysfunction in type 2 diabetes: Implications of inflammation and oxidative stress. *World Journal of Diabetes* 2023; **14(3)**, 130-146.

[75] F De Nardi, C Lefort, D Bréard, P Richomme, C Legros and NC Guérineau. Monitoring the secretory behavior of the rat adrenal medulla by high-performance liquid chromatography-based catecholamine assay from slice supernatants. *Frontiers in Endocrinology* 2017; **8(1)**, 248.

[76] G Zhao, M Jia, S Zhu, H Ren, G Wang, G Xin, M Sun, X Wang, Q Lin, Q Jiang and C Zhang. Mitotic ER-mitochondria contact enhances mitochondrial Ca^{2+} influx to promote cell division. *Cell Reports* 2024; **43(10)**, 114794.

[77] D Zhang, F Wang, P Li and Y Gao. Mitochondrial Ca^{2+} Homeostasis: Emerging Roles and Clinical Significance in Cardiac Remodeling. *International Journal of Molecular Sciences* 2022; **23(6)**, 3025.

[78] D Nolfi-Donegan, A Braganza and S Shiva. Mitochondrial electron transport chain: Oxidative phosphorylation, oxidant production, and methods of measurement. *Redox Biology* 2020; **37(1)**, 101674.

[79] X Xu, Y Pang and X Fan. Mitochondria in oxidative stress, inflammation and aging: From mechanisms to therapeutic advances. *Signal Transduction and Targeted Therapy* 2025; **10(1)**, 190.

[80] G Quarato, F Llambi, CS Guy, J Min, M Actis, H Sun, S Narina, SM Pruett-Miller, J Peng, Z Rankovic and DR Green. Ca^{2+}-mediated mitochondrial inner membrane permeabilization induces cell death independently of Bax and Bak. *Cell Death & Differentiation* 2022; **29(7)**, 1318-1334.

[81] A Diaz-Vegas, P Sanchez-Aguilera, JR Krycer, PE Morales, M Monsalves-Alvarez, M Cifuentes, BA Rothermel and S Lavandero. Is mitochondrial dysfunction a common root of noncommunicable chronic diseases? *Endocrine Reviews* 2020; **41(3)**, bnaa005.

[82] J Mondal and JT Huse. Neurotransmitter power plays: The synaptic communication nexus shaping brain cancer. *Acta Neuropathologica Communications* 2025; **13(1)**, 85.

[83] C Costas-Ferreira and LRF Faro. Systematic review of calcium channels and intracellular calcium signaling: Relevance to pesticide neurotoxicity. *International Journal of Molecular Sciences* 2021; **22(24)**, 13376.

[84] Q Van Dinh, J Liu and P Dutta. Effect of calcium ion on synaptotagmin-like protein during pre-fusion of vesicle for exocytosis in blood-brain barrier. *Biochemistry and Biophysics Reports* 2020; **24(1)**, 100845.

[85] AH Bazzari and HR Parri. Neuromodulators and long-term synaptic plasticity in learning and memory: A steered-glutamatergic perspective. *Brain Sciences* 2019; **9(11)**, 300.

[86] AG Mohanan, S Gunasekaran, RS Jacob and RV Omkumar. Role of Ca^{2+}/calmodulin-dependent protein kinase Type II in mediating function and dysfunction at glutamatergic synapses. *Frontiers in Molecular Neuroscience* 2022; **15(1)**, 855752.

[87] A Uryash, V Flores, JA Adams, PD Allen and JR Lopez. Memory and learning deficits are associated with Ca^{2+} dyshomeostasis in normal aging. *Frontiers in Aging Neuroscience* 2020; **12(1)**, 224.

[88] S Khan, N Bano, S Ahamad, U John, NJ Dar and SA Bhat. Excitotoxicity, oxytosis/ferroptosis, and neurodegeneration: Emerging insights into mitochondrial mechanisms. *Aging and Disease* 2024; **16(5)**, 2504-2543.

[89] LA Koek, TM Sanderson, J Georgiou and GL Collingridge. The role of calcium stores in long-term potentiation and synaptic tagging and capture in mouse hippocampus. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences* 2024; **379(1906)**, 20230241.

[90] Y Wang, Y Shi and H Wei. Calcium dysregulation in Alzheimer's disease: A target for new drug development. *Journal of Alzheimer's Disease & Parkinsonism* 2017; **7(5)**, 374.

[91] Y Lai, FF Gao, RT Ge, R Liu, S Ma and X Liu. Metal ions overloading and cell death. *Cell Biology and Toxicology* 2024; **40(1)**, 72.

[92] R Rajmohan and PH Reddy. Amyloid-Beta and Phosphorylated Tau Accumulations Cause Abnormalities at Synapses of Alzheimer's disease Neurons. *Journal of Alzheimer's Disease* 2017; **57(4)**, 975-999.

[93] A Ni and C Ernst. Evidence That substantia nigra pars compacta dopaminergic neurons are selectively vulnerable to oxidative stress because they are highly metabolically active. *Frontiers in Cellular Neuroscience* 2022; **16(1)**, 826193.

[94] R Patil, H Wang, M Kazaleh, G Ailawadi and M Salmon. Dysregulation of mitochondrial homeostasis in cardiovascular diseases. *Pharmaceuticals* 2025; **18(1)**, 112.

[95] S Ramesh and ASPM Arachchige. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. *AIMS Neuroscience* 2023; **10(3)**, 200-231.

[96] I Shemarova. The dysfunction of Ca^{2+} channels in hereditary and chronic human heart diseases and experimental animal models. *International Journal of Molecular Sciences* 2023; **24(21)**, 15682.

[97] S Kurihara and N Fukuda. Regulation of myocardial contraction as revealed by intracellular Ca^{2+} measurements using aequorin. *The Journal of Physiological Sciences* 2024; **74(1)**, 12.

[98] N Kumari, N Pullaguri, SN Rath, A Bajaj, V Sahu and KKR Ealla. Dysregulation of calcium homeostasis in cancer and its role in chemoresistance. *Cancer Drug Resistance* 2024; **7(1)**, 11.

[99] HX Xu, SM Cui, YM Zhang and J Ren. Mitochondrial Ca^{2+} regulation in the etiology of heart failure: physiological and pathophysiological implications. *Acta Pharmacologica Sinica* 2020; **41(10)**, 1301-9.

[100] Y Du, LJ Demillard and J Ren. Sarcoplasmic reticulum Ca^{2+} dysregulation in the pathophysiology of inherited arrhythmia: An update. *Biochemical Pharmacology* 2022; **200(1)**, 115059.

[101] F Xiao, HL Li, JR Wang, HM Wu, YQ Cai, JW Wang, H Che, G Li, ZY Xia, ZB Xie and S Wang. Research progress on programmed cell death of cardiomyocytes in pressure-overload hypertrophic cardiomyopathy. *Apoptosis* 2025; **30(9-10)**, 2191-224.

[102] C Kho. Targeting calcium regulators as therapy for heart failure: focus on the sarcoplasmic reticulum Ca-ATPase pump. *Frontiers in Cardiovascular Medicine* 2023; **10(1)**, 1185261.

[103] A Alharbi, Y Zhang and J Parrington. Deciphering the Role of Ca^{2+} Signalling in Cancer Metastasis: From the Bench to the Bedside. *Cancers* 2021; **13(2)**, 179.

[104] M Calvo-Rodriguez, EK Kharitonova and BJ Bacskai. Therapeutic strategies to target calcium dysregulation in Alzheimer's disease. *Cells* 2020; **9(11)**, 2513.

[105] AS Hammad and K Machaca. Store operated calcium entry in cell migration and cancer metastasis. *Cells* 2021; **10(5)**, 1246.

[106] H Du, T Xu, S Yu, S Wu and J Zhang. Mitochondrial metabolism and cancer therapeutic innovation. *Signal Transduction and Targeted Therapy* 2025; **10(1)**, 245.

[107] H Sabit, S Abouelnour, BM Hassen, S Magdy, A Yasser, AS Wadan, S Abdel-Ghany, F Radwan, AI Alqosaibi, H Hafiz, OFA Awlya and B Arneth. Anticancer potential of prebiotics: Targeting estrogen receptors and PI3K/AKT/mTOR in breast cancer. *Biomedicines* 2025; **13(4)**, 990.

[108] X Liu, C Feng, L Yan, J Cao, X Zhu, M Li and G Zhao. Calcium channels as pharmacological targets for cancer therapy. *Clinical and Experimental Medicine* 2025; **25(1)**, 94.

[109] S Gross, P Mallu, H Joshi, B Schultz, C Go and J Soboloff. Ca^{2+} as a therapeutic target in cancer. *Advances in Cancer Research* 2020; **148(1)**, 233-317.

[110] AJ Trexler and JW Taraska. Regulation of insulin exocytosis by calcium-dependent protein kinase C in beta cells. *Cell Calcium* 2017; **67(1)**, 1-10.

[111] U Galicia-Garcia, A Benito-Vicente, S Jebari, A Larrea-Sebal, H Siddiqi, KB Uribe, H Ostolaza and C Martín. Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences* 2020; **21(17)**, 6275.

[112] C Klec, G Ziomek, M Pichler, R Malli and WF Graier. Calcium signaling in ß-cell physiology and pathology: A revisit. *International Journal of Molecular Sciences* 2019; **20(24)**, 6110.

[113] P Iglesias. Muscle in endocrinology: From skeletal muscle hormone regulation to myokine secretion and its implications in endocrine - metabolic diseases. *Journal of Clinical Medicine* 2025; **14(13)**, 4490.

[114] T Khan, R Waseem, Z Zehra, A Aiman, P Bhardwaj, J Ansari, MI Hassan and A Islam. Mitochondrial dysfunction: Pathophysiology and mitochondria-targeted drug delivery approaches. *Pharmaceutics* 2022; **14(12)**, 2657.

[115] JS Bhatti, GK Bhatti and PH Reddy. Mitochondrial dysfunction and oxidative stress in metabolic disorders - A step towards mitochondria based therapeutic strategies. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* 2017; **1863(5)**, 1066-1077.

[116] K Shah, S Seeley, C Schulz, J Fisher and SG Rao. Calcium channels in the heart: Disease states and drugs. *Cells* 2022; **11(6)**, 943.

[117] NR Tykocki, EM Boerman and WF Jackson. Smooth muscle ion channels and regulation of vascular tone in resistance arteries and arterioles. *Comprehensive Physiology* 2017; **7(2)**, 485-581.

[118] AKS Hamad. Caffeine and Arrhythmias: A critical analysis of cardiovascular responses and arrhythmia susceptibility. *Journal of the Saudi Heart Association* 2024; **36(4)**, 335-348.

[119] T Godfraind. Calcium channel blockers in cardiovascular pharmacotherapy. *Journal of Cardiovascular Pharmacology and Therapeutics* 2014; **19(6)**, 501-515.

[120] KE Jones, SL Hayden, HR Meyer, JL Sandoz, WH Arata, K Dufrene, C Ballaera, YL Torres, P Griffin, AM Kaye, S Shekoohi and AD Kaye. The evolving role of calcium channel blockers in hypertension management: pharmacological and clinical considerations. *Current Issues in Molecular Biology* 2024; **46(7)**, 6315-6327.

[121] E Zuccolo, U Laforenza, F Ferulli, G Pellavio, G Scarpellino, M Tanzi, I Turin, P Faris, A Lucariello, M Maestri, DA Kheder, G Guerra, P Pedrazzoli, D Montagna and F Moccia. Stim and orai mediate constitutive Ca^{2+} entry and control endoplasmic reticulum Ca^{2+} refilling in primary cultures of colorectal carcinoma cells. *Oncotarget* 2018; **9(57)**, 31098-31119.

[122] T Lu, Y Zhang, Y Su, D Zhou and Q Xu. Role of store-operated Ca^{2+} entry in cardiovascular disease. *Cell Communication and Signaling* 2022; **20(1)**, 33.

[123] Q Zhang, C Wang and L He. ORAI Ca^{2+} channels in cancers and therapeutic interventions. *Biomolecules* 2024; **14(4)**, 417.

[124] Y Liao, Y Hao, H Chen, Q He, Z Yuan and J Cheng. Mitochondrial calcium uniporter protein MCU is involved in oxidative stress-induced cell death. *Protein & Cell* 2015; **6(6)**, 434-442.

[125] B O'Rourke, D Ashok and T Liu. Mitochondrial Ca^{2+} in heart failure: Not enough or too much? *Journal of Molecular and Cellular Cardiology* 2021; **151(1)**, 126-134.

[126] C Li, J Sun, H Ling, Z Qin, X Zhu, X Fu, T Li and X Gan. MCU regulating bone remodeling and osteogenic function through mitochondrial calcium homeostasis and oxidative stress alteration. *Free Radical Biology and Medicine* 2025; **236(1)**, 87-97.

[127] A Michelucci, M García-Castañeda, S Boncompagni and RT Dirksen. Role of STIM1/ORAI1-mediated store-operated Ca^{2+} entry in skeletal muscle physiology and disease. *Cell Calcium* 2018; **76(1)**, 101-115.

[128] A Hernández-Oliveras and A Zarain-Herzberg. The role of Ca^{2+}-signaling in the regulation of epigenetic mechanisms. *Cell Calcium* 2024; **117(1)**, 102836.

[129] M Lisek, O Przybyszewski, L Zylinska, F Guo and T Boczek. The role of MEF2 transcription factor family in neuronal survival and degeneration. *International Journal of Molecular Sciences* 2023; **24(4)**, 3120.

[130] K Sałaciak, A Koszałka, E Żmudzka and K Pytka. The calcium/calmodulin-dependent kinases II and IV as therapeutic targets in neurodegenerative and neuropsychiatric disorders. *International Journal of Molecular Sciences* 2021; **22(9)**, 4307.

[131] C Gregório, SC Soares-Lima, B Alemar, M Recamonde-Mendoza, D Camuzi, PT de Souza-Santos, R Rivero, S Machado, A Osvaldt, P Ashton-Prolla and LFR Pinto. Calcium signaling alterations caused by epigenetic mechanisms in pancreatic cancer: From early markers to prognostic impact. *Cancers* 2020; **12(7)**, 1735.

[132] F Bi, C Gao and H Guo. Epigenetic regulation of cardiovascular diseases induced by behavioral and environmental risk factors: Mechanistic, diagnostic, and therapeutic insights. *FASEB BioAdvances* 2024; **6(11)**, 477-502.

[133] MJ Kipanyula, WH Kimaro and PFS Etet. The emerging roles of the calcineurin-nuclear factor of activated T-lymphocytes pathway in nervous system functions and diseases. *Journal of Aging Research* 2016; **2016(1)**, 5081021.

[134] S Patergnani, A Danese, E Bouhamida, G Aguiari, M Previati, P Pinton and C Giorgi. Various aspects of calcium signaling in the regulation of apoptosis, autophagy, cell proliferation, and cancer. *International Journal of Molecular Sciences* 2020; **21(21)**, 8323.