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TRPM8 Channels and SOCE: Modulatory Crosstalk between Na^+ and Ca^{2+} Signaling

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Abstract

The electrochemical driving forces across the plasma membrane both in excitable and non-excitable mammalian cells are finely regulated by different ion channels, pumps, and exchangers that are essential for a wide range of biological processes. The modulation between sodium (Na^+), calcium (Ca^{2+}), and intracellular downstream pathways is tightly linked through several mechanisms that generate spatiotemporal ion waves. Transient receptors potential melastatin 8 (TRPM8) channels and Store-operated Ca^{2+} entry (SOCE) are important players related to Na^+ and Ca^{2+} signaling. TRPM8 channels are non-selective ion-permeable channels exhibiting multi-gating mechanisms, being activated by innocuous cool to cold temperatures. The opening of these channels triggers Na^+ and Ca^{2+} influx, while the SOCE mediated by ORAI1-3 channels is 1000-fold more selective for ions Ca^{2+} than Na^+ ions. This feature makes the TRPM8 and SOCE relevant targets that integrate Na^+ and Ca^{2+} signaling. Although clear evidence of interaction between TRPM8 and SOCE modulating Na^+ and Ca^{2+} signaling remain not elusive, this review highlights the hypothesis that TRPM8 could be a crosstalk channel that links Na^+ and Ca^{2+} signaling. Recent evidence indicated that this link can be mainly mediated by the modulation of SOCE and the plasmalemma exchangers, Na^+/Ca^{2+} (NCX1-3), or via K^+-dependent Na^+/Ca^{2+} exchangers (NCKX1-6). Additionally, TRPM8 can interact with SOCE by alterations on GPCR $G\alpha_q$-subunit, cytosolic Ca^{2+} concentration, and PIP_2 levels. Therefore, providing a novel insight for further understanding of the structure-function relationships of these two cellular signaling pathways during the ionic influx and efflux is crucial. This review overviews the crosstalk between Na^+ and Ca^{2+} signaling in different cell types, highlighting the available evidence of the potential role of TRPM8 and SOCE in Na^+/Ca^{2+} pathways.

Keywords: Ca^{2+} and Na^+ signaling, TRPM8 channels, SOCE, ORAI channels, Channelopathies

Abbreviations: Ca^{2+}: Calcium; CMR1: Cold and Menthol Receptor 1; CRAC: Ca^{2+} Release-Activated Ca^{2+} channels; Cryo-EM: Cryo-Electron Microscopy; Cs^+: Cesium; ER: Endoplasmic Reticulum; GPCR: G Protein-Coupled Receptor; I_{CRAC}: Ca^{2+} Release-Activated Ca^{2+} Currents; I_{Na}: Sodium Currents; K^+: Potassium; MCU: Mitochondrial Ca^{2+} Uniporter; Na^+: Sodium; NCKX: K^+-dependent Na+/Ca^{2+} Exchangers; NCLX: Na^+-Li^+/Ca^{2+} Exchangers; NCX: Na^+/Ca^{2+} Exchangers; NHE: Na^+/H^+ Exchangers; PIP_2: Phosphatidylinositol 4,5-bisphosphate; Pirt: Phosphoinositide interacting regulator of TRP; SOCE: Store-Operated Ca^{2+} Entry; STIM1/2: Stromal Interaction Molecules 1-2; Thap: Thapsigargin; TRPM8: Transient Receptors Potential (TRP) Melastatin member 8

Cellular Na^+ and Ca^{2+} Signaling: Crosslinks and Pathways

The electrochemical driving forces across the plasma membrane mediated by ion channels, pumps, and exchangers are essential for cellular homeostasis, regulating a wide range of biological processes [1,2]. Although both excitable (e.g., neurons) and non-excitable (e.g., lymphocytes) cells manage their cellular functions through plasmalemmal ion flux, excitable cells change the membrane potential mediated by depolarization and voltage-gated ion channels, while non-excitable cells control this process by the different downstream processes and ligand-gated ion channels [2,3]. Sodium (Na^+) is the principal extracellular cation, being carried to the intracellular space mainly through inward Na^+ currents (I_{Na}) [2]. Pioneering studies documented that inhibition of I_{Na}, but not the calcium (Ca^{2+}) absence, abolished the action potential, indicating that Na^+ influx is essential for cell excitability, action

potential, and cellular functionality [4,5]. Additionally, the Na^+ driving forces also have been related to the function of several other ion transmembrane modes of transport, including 1) pumps (Na^+/K^+ ATPases); 2) Na^+/Ca^{2+} exchangers (NCX/NCKX); 3) Na^+/H^+ exchangers (NHE); 4) ligand-dependent channels (nicotinic acetylcholine receptors); and recently linked to the 5) transient receptors potential (TRP) melastatin member 8 (TRPM8), which are permeable both to the Na^+ and Ca^{2+} ion influx [2,6,7].

It's well established that Ca^{2+} handling is one of the most widespread transducing systems, regulating a wide range of cell biology ranging from cell fertilization and hormone exocytosis to cell death and hypomineralization during pathophysiological processes [8-10]. Ca^{2+} release-activated Ca^{2+} (CRAC) channels are mediated by the endoplasmic reticulum (ER) resident Ca^{2+} sensors stromal interaction molecules 1-2 (STIM1/2) and by a highly Ca^{2+}-selective conductance pore, known as ORAI (ORAI1-3) channels [11,12]. As shown in Figure 1, the ER-Ca^{2+} depletion elicits the Ca^{2+} influx through ORAI1-3 in many cells, including HEK-293, and both proteins orchestrally form the main store-operated Ca^{2+}

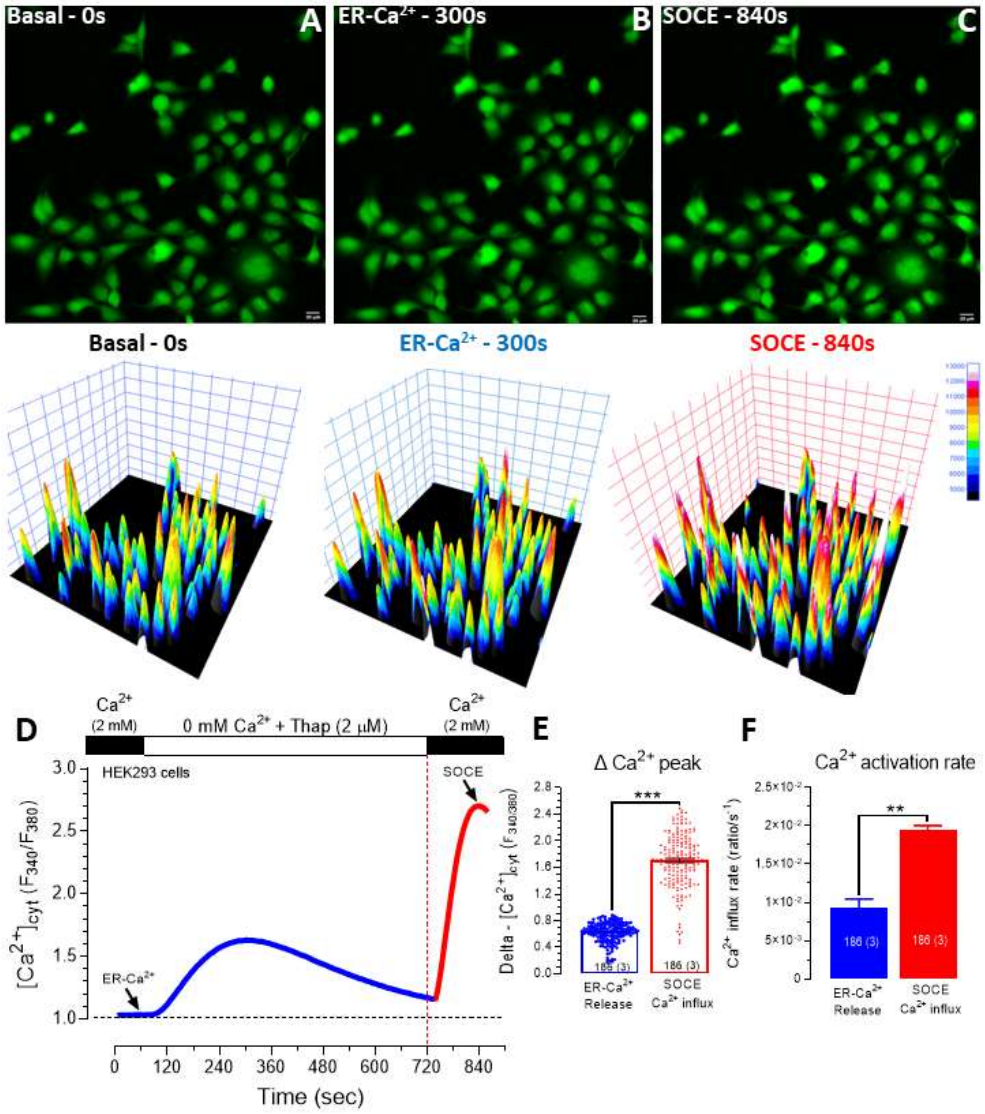

Figure 1: ER-Ca^{2+} release and Ca^{2+} influx mediated by SOCE through ORAI1-3 channels. (A-C), representative fluorescent images of $[Ca^{2+}]_{cyt}$ transients under basal (0s) condition, ER-Ca^{2+} depletion elicited by thapsigargin (Thap, 2 µM, 300s) in Ca^{2+}-free Ringer's solution followed by readdition of 2 mM extracellular Ca^{2+} solution to stimulate the SOCE (840s). Below, the 3-D graphical representation illustrating the basal (0s), ER-Ca^{2+} release (300s), and maximum Ca^{2+} influx via SOCE (840s). **(D)**, original traces of $[Ca^{2+}]_{cyt}$ transients showing ER-Ca^{2+} depletion elicited by Thap, 2 µM, in Ca^{2+}-free Ringer's solution followed by re-addition of 2 mM extracellular Ca^{2+} solution in HEK-293 cells. Quantification of ΔCa^{2+} peak **(E)** and Ca^{2+} influx rate **(F)** parameters under ER-Ca^{2+} release and SOCE. Data represent the mean ± SEM of 186 cells from 3 independent experiments. Data were analyzed by a two-tailed unpaired Student's t-test. $^{**}P < 0.01$ or $^{***}P < 0.001$ vs. respective ER-Ca^{2+} release group.

entry denominated as SOCE. Ca^{2+} influx via SOCE represents the major Ca^{2+} entry pathway into a variety of non-excitable cells [11,13]. From a physiological viewpoint, ORAI1-3 channels are highly selective for Ca^{2+}, being 1000-fold more conductive for Ca^{2+} ions than Na^+ ions [14-16]. However, during experimental or pathological conditions when divalent cations are suppressed from the extracellular solution, ORAI1-3 channels become permeable to monovalent cations as Na^+, cesium (Cs^+), or potassium (K^+) [14,16].

Since the term, TRP was introduced and mammalian TRP channels identified, studies suggested that TRP homologs might represent the molecular components of SOCE and CRAC currents (I_{CRAC}) [17-19]. Most TRP channels are non-selective cation channels widely expressed as cellular sensors with diverse physiological functions, being permeable to both monovalent and divalent cations with Ca^{2+}/Na^+ conductance ranging from 0.01 to 100 [20,21]. The elementary structure of TRP consists of six transmembrane helical domains (TM1-TM6) with a loop between TM5 and TM6 forming the channel pore and N- and C terminal regions located in the cytosol [21,22]. Some of the 28 mammalian members such as the TRPM7 channels contain a catalytic kinase domain and N- and/or C-terminal coiled-coil, responsible for a key role in TRP multimerization and interaction with STIM and ORAI proteins [20]. Recent studies reported that some clustered members from the TRP subfamilies: the TRPC (canonical), TRPV (vanilloid), TRPM (melastatin), TRPP (polycystin), TRPML (mucolipin), TRPA (ankyrin), and TRPN (NOMPC-like) are components of the SOCE [17,23]. However, subsequent reports failed to reproduce these outcomes [17-19]. On the other hand, Rosado's laboratory demonstrated that although TRPC channels did not generate inward Ca^{2+} currents that resemble I_{CRAC}, TRPC1 and other TRPC proteins might play a relevant role in modulating ORAI1 and STIM1 channel functionality [17,19,24]. Additionally, TRPM7 channels potentiate Ca^{2+} influx via SOCE, but its function is fully dependent on the prior activation of the ORAI1 channels [25,26]. Thus, despite this being beyond the scope of the present study, the controversy surrounding the role of TRP channels as part of or mediating SOCE stems from how intertwined these pathways are. In this review, the author aimed at the modulatory crosstalk between Na^+ and Ca^{2+} signaling mediated by TRPM8 channels and SOCE components (ORAI1-3 and STIM1/2), and how these pathways affect other Na^+ and Ca^{2+} ion transmembrane transports.

TRPM8 Channels: Features and Activation

TRPM8 was originally cloned by screening cDNA isolated from trigeminal sensory neurons for their ability to respond to menthol and cold stimuli [27,28], although these channels are widely distributed in different tissues. TRPM8 can be expressed in somatosensory neurons, mucosae, urogenital tract, lung cells, and artery myocytes, which might be related to the allodynia and/or hyperalgesia process [7]. In the last years, the modulation of TRPM8 channels has been considered a prominent approach to develop a novel therapeutic tool for chronic pain and noxious cold sensitization [29]. The significance of these findings and the discovery of the touch-sensitive Piezo1-2 channels [30] won the discoverers D. Julius and A. Patapoutian the 2021 Nobel Prize in Physiology [27,31]. Physiologically, there are two populations of thermal cold-sensitive cells activated in temperature around 12°C, being the largest (≥ 70%) subpopulation sensitive to the TRPM8-ligand, menthol, that is a cold-sensitive compound [20,32,33]. Experimental studies using animals lacking TRPM8 channels revealed a deficient capacity to detect cool temperatures and exhibit a partially defective phenotype although the sensitivity to low temperature (~5 °C) induced cold pain remained intact in these TRPM8 knockout mice [7,34]. These outcomes suggest an important role of TRPM8 in the cold sensation probably associated with activation of other TRP channels and/or ion signaling pathways.

It is well established that TRPM8, a non-selective Ca^{2+}-permeable channel, exhibits multi-gating mechanisms, being activated by innocuous cool to cold temperatures and regulated by crucial molecules such as Ca^{2+} ion and phosphatidylinositol 4,5-bisphosphate (PIP_2) [7]. The C-terminally located PIP_2 sensing domain is one determinant of temperature sensitivity [7,20]. Also, the intracellular Ca^{2+} is required for TRPM8 activation by cooling agonist, icilin, but not by menthol being mediated by residues in S2-3 domains [33,35]. TRPM8 channels are permeable to Na^+ [36] with the ratio permeability between Ca^{2+} and Na^+ ions (PCa/PNa) range between 0.97 to 3.2, with monovalent ions conductance of $Cs^+ > K^+ > Na^+$ [7]. Also, these channels can depolarize the cells and activate voltage-gated Na^+ and Ca^{2+} channels [37], leading to an increase in ions influx. Basal cytosolic Ca^{2+} is required for TRPM8 activation by the cooling agonist, icilin, but not for menthol activity [37]. Cryo-electron microscopy (Cryo-EM) structure studies revealed that the Ca^{2+}-binding site in TRPM8 is conserved within the TRPM subfamily [20,38]. Additionally, the Y745 residue interacts with cooling agonists (icilin and WS-12) and antagonists (AMTB and TC-I 2014), suggesting the key role of Y745 in the ligand-dependent gating of TRPM8 [20,35,37]. Another modulator of TRPM8 channels is the PIP_2 that is required as a cofactor for channel activation by cooling agonists and cold temperatures [7,37,39]. Thus, at high concentrations, PIP_2 itself might be sufficient to activate the TRPM8 channel, whereas depletion of basal PIP_2 levels results in channel desensitization [37,40]. Endogenous ligands including testosterone, artemin, and Pirt (phosphoinositide interacting regulator of TRP) protein have been also proposed as physiological ligands of TRPM8 channels [7,29].

Recently, basic and clinical studies highlighted the TRPM8 channels as a novel pharmacotherapeutic target for the treatment of cancer, neuropathic pain, and inflammation [29,41]. Voltage is a partial activator of TRPM8 channels with low (<1.0) open probability values, decreasing when the temperature rises [36,37]. Electrophysiology data showed that

the half-activation voltage ($V_{0.5}$) saturates at high temperatures, suggesting a lack of strict coupling between TRPM8 voltage and temperature activation [36,37]. Also, TPRM8 channel deactivation at negative voltages and temperature can underestimate the open probability of these channels, showing that temperature affects channel opening through a pathway that does not involve voltage sensor activation [37]. Clinical outcomes have demonstrated that TRPM8 channels are involved in the modulation of cancer hallmarks such as cellular proliferation, survival, and invasion [42], suggesting that TRPM8 channels play contributory roles in tumor growth and metastasis. Several studies revealed that both TRPM8 and SOCE components (ORAI1-3 and STIM1/2) are upregulated in a variety of human neoplastic tissues, cell lines, and solid tumors [41-44]. These findings links TRPM8 and SOCE as well as Na^+ and Ca^{2+} signaling during cancer. Thus, opening a new pathway to the development of the TRPM8 pharmacological modulator and as a prognostic/predictive biomarker and a therapeutic target in cancer treatment.

SOCE and TRPM8 Channels: An Ability to Regulate Different Pathways

The sensory nervous system enables fine coordinated properties of TRP in a heterologous of varied external sensorial stimulus [20]. Although the molecular mechanism underlying their temperature sensitivity remains unclear, the TRP channels are essential to body thermoreceptors [21]. Different subfamilies of TRP channels are requested by regulating a wide temperature oscillation, including the TRPV1-2 in the painful heat, TRPV3-4 in non-painful warmth, and TRPA1 during noxious cold [45]. TRPM8 channels could be modulated by exogenous and endogenous ligands, being the cold-sensitive compounds derived from plants as menthol important TRPM8-ligand [33,35]. These channels also had been named as the cold and menthol receptor 1 (CMR1) being the main detector of cold in humans that is activated during innocuous cool to cold temperatures [7]. They are voltage-sensitive channels and can be activated by changes the membrane potential or depolarization, however, lack the voltage sensor present in the classic voltage-gated ion channels [7,37].

Recent Cryo-EM studies revealed that both Ca^{2+} ion and the phospholipid, PIP_2, have binding sites into transmembrane helical domains, and are required for the properly gating and activation of TRPM8 channels [15,33,37]. As shown in Figure 2 and previously reported [33,35,40], the cold temperature (~14-16°C) and the well-known cooling agents, icilin and menthol, can increase the $[Ca^{2+}]_{cyt}$ levels around 100-800 nM range. Additionally, electrophysiological records reported that menthol triggers inward I_{Na} in trigeminal neurons and HEK-293 cells overexpressing TRPM8 channels [28,46]. Taken together, these outcomes indicate that TRPM8 can uptake Na^+ and Ca^{2+} ions, increasing the Ca^{2+}/Na^+ cytosolic levels at the micromolar range. The permeability ratio between Ca^{2+} and Na^+ ions (PCa/PNa) range between 0.97 to 3.2 [7,32,37]. TRPM8 channels

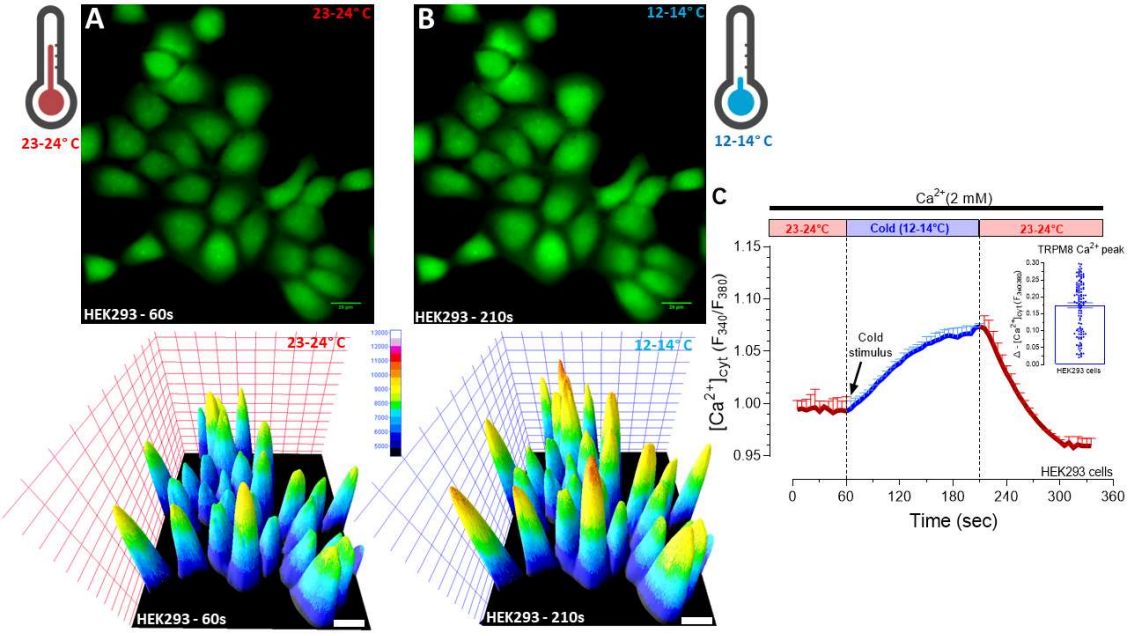

Figure 2: Cold temperature mediated $[Ca^{2+}]_{cyt}$ increase by TRPM8 channels. (A-B), representative fluorescent images of $[Ca^{2+}]_{cyt}$ transients under basal room temperature (23-24°C) condition and after cold (12-14°C) stimulus in 2 mM extracellular Ca^{2+} Ringer's solution followed by readdition of 23-24°C solution. Below, the 3-D graphical representation illustrating the basal room temperature (23-24°C, 60s) and maximum Ca^{2+} influx mediated by cold (12-14°C) stimulus through TRPM8 channels (210s). **(C)**, original traces of $[Ca^{2+}]_{cyt}$ transients showing Ca^{2+} increase elicited by cold (12-14°C) stimulus in HEK-293 cells. Data represent the mean ± SEM of 102 cells from 3 independent experiments.

also can depolarize and activate voltage-gated Na^+ and Ca^{2+} channels [37], leading to more Na^+ and Ca^{2+} influx into the cytosol. This makes the TRPM8 the important molecule that integrates Na^+/Ca^{2+} signaling pathways.

The modulation between Na^+/Ca^{2+} ion uptake and intracellular cation signaling is finely regulated by transmembrane Na^+/Ca^{2+} exchangers and pumps, and also can be buffered by organelles and cytosolic proteins [47,48]. Electrochemical gradients carry inward Na^+ and Ca^{2+} currents that increase the cytosolic levels of both ions around 1-3 µM for Ca^{2+} and ≥ 40 mM for Na^+ ions, cell-typing dependent [48-50]. Although organelles such as mitochondria and ER buffer these ions, the capacity to store and/or buffer Na^+ and Ca^{2+} is limited due to the intracellular location and saturation of the buffer mechanisms [51,52]. For example, the mitochondria can uptake Ca^{2+} through the mitochondrial Ca^{2+} uniporter (MCU), and also stimulate the Na^+ buffer mediated by NCLX (Na^+-Li^+/Ca^{2+}) exchangers [8,52,53]. By contrast, the ER is the largest Ca^{2+} intracellular organelle, can store Ca^{2+} in a range between 100 to 800 nM [54]. Thus, despite these intracellular buffers being essential for ion homeostasis, the plasma membrane low-affinity Na^+/Ca^{2+} extrusion mechanisms appear to be important players and links between Na^+ and Ca^{2+} signaling and TRPM8 channels.

The Na^+/Ca^{2+} exchanger is a key electrogenic system that directly integrates opposite fluxes of Na^+ and Ca^{2+} across the plasma membrane [50]. These Na^+/Ca^{2+} exchangers are divided in NCX1-3 members encoded by *SLC8A1-3* genes and in the K^+-dependent Na^+/Ca^{2+} exchangers (NCKX1-6) encoded by *SLC24A1-6* being the K^+ ions absolute requirement for Ca^{2+} clearance mediated by NCKX1-6 [55,56]. Both NCX and NCKX have been characterized by singular features that includes: 1) low Ca^{2+} affinity (>1 µM) and high Ca^{2+} capacity (~ 2500 s^{-1}) responsible for the fast Ca^{2+} clearance; 2) NCX extrude 1 Ca^{2+} and uptake 3 Na^+ and NCKX extrude 1 Ca^{2+} and 1 K^+, and uptake 4 Na^+; and 3) increase in cytosolic Na^+ promote its function in the reverse mode in order to clearance excess of Na^+ ions [55,57,58]. These complex feedback functions involve both thermodynamic and kinetic interactions of Na^+ and Ca^{2+} with ion transport and regulatory domains of NCX1-3/NCKX1-6 [55,56,58].

Although the molecular mechanisms responsible for the link between the TRPM8 and SOCE remain unknown, recently emerged some downstream pathways associated with these connections. The potential candidate proteins involved in this crosslink were investigated by *in silico* gene-protein prediction analyses targeting genes responsible for encoded TRPM8, ORAI1-3, STIM1/2, PLCβ, PIP_2, and Na^+/Ca^{2+} exchanger (NCX1-3/NCKX1-6). The *in silico* data revealed a predicted crosslink between these pathways-genes and TRPM8 channels (Figure 3), highlighting possible interconnectivity. TRPM8 activity

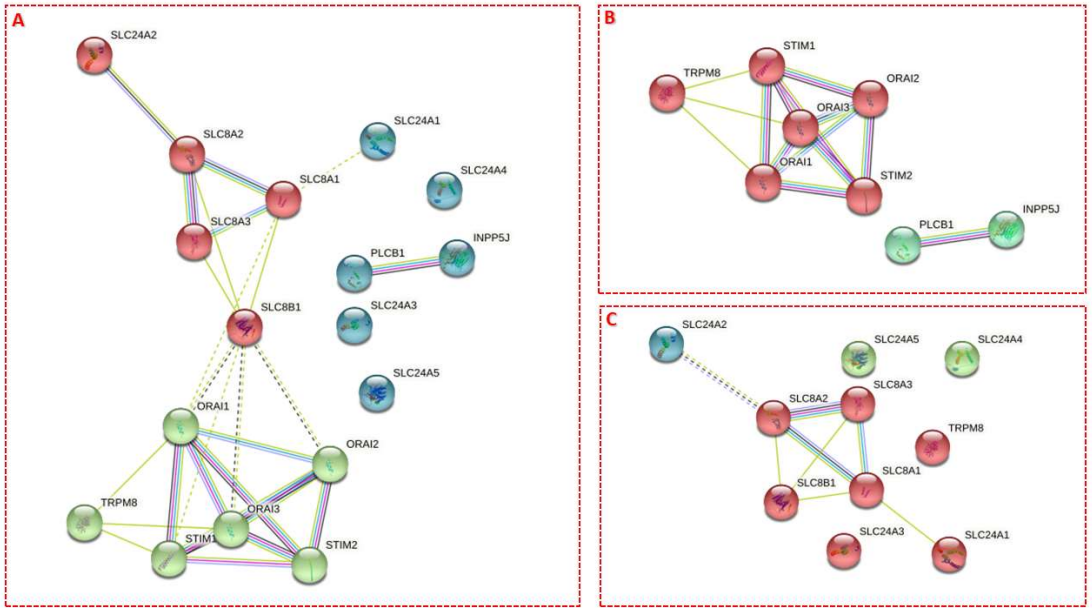

Figure 3: *In silico* analyses predicting crosslink between pathways-genes and TRPM8 channels. (A), STRING analysis using K-means clustering, we found 17 well-known genes encoding proteins responsible for TRPM8 (*TRPM8*), ORAI1-3 (*ORAI1,2,3*), STIM1/2 (*STIM1,2*) , PLCβ (*PLCB1*), PIP_2 (*INPP5J*), and Na^+/Ca^{2+} exchanger, NCX1-3 (*SLC8A1,2,3*) and NCKX1-6 (*SLC4A1,2,3,4,5,6*). **(B)**, 8 genes related to the TRPM8 (*TRPM8*) and SOCE components (*ORAI1,2,3* and *STIM1,2*) and pathways (*PLCB1* and *INPP5J*). **(C)**, 10 genes related to the TRPM8 (*TRPM8*) and Na^+/Ca^{2+} exchanger, NCX1-3 (*SLC8A1,2,3*) and NCKX1-6 (*SLC4A1,2,3,4,5,6*). The line colors evidenced the type of interaction that was established at 1) well-known interactions - light blue is from curated databases and pink from experimentally determined; 2) predicted interactions - light green is from gene neighborhood; 3) violet is related to gene fusions; and 4) dark blue from gene co-occurrence. Enrichment p-value of < 1.10-16. Local clustering coefficient of 0.666 **(A)**, 0.925 **(B)** and 0.501 **(C)**.

can be altered by intracellular Ca^{2+} concentrations and PIP_2 levels, temperature, and pH, whereas endogenous signaling molecules modulate TRPM8-mediated responses to coolness [37]. In pulmonary smooth muscle cells, the TRPM8 agonist icilin caused inhibition of SOCE and a molecular modulation of TRPM8 channels may affect the pulmonary hypertension development related to SOCE activity [59]. Additionally, Zhang demonstrated that both the G protein-coupled receptor (GPCR) $G\alpha_q$-subunit and PIP_2 were able to inhibit TRPM8 channels, and the TRPM8-$G\alpha_q$ binding impaired $G\alpha_q$ coupling and signaling to PLCβ-PIP_2 [60]. In this way, multivariate analysis showed that overexpression of TRPM8, and STIM2 is associated with a lower risk of systemic recurrence after radical prostatectomy [61]. Taken together, these studies suggest that $G\alpha_q$-subunit and PLCβ-PIP_2 generating IP_3 could be a novel insight to further understand the structure-function relationships of TRPM8 and SOCE. Another evidence of modulatory crosstalk between Na^+ and Ca^{2+} signaling mediated by TRPM8 channels, SOCE, and Na^+/Ca^{2+} exchanger is the teeth-related tissues responsible for the mineralization and pain processes [62,63]. Both animals and humans lacking or with loss-of-function mutation of the SOCE components (ORAI1/STIM1) or NCKX4 exchangers result in *Amelogenesis Imperfecta* and deficient enamel formation [10,56,64,65]. Also, the ability of TRPM8 to uptake Na^+ and Ca^{2+} can affect the SOCE and NCKX4 functions, resulting in the disruption of Na^+ and Ca^{2+} signaling during pathological conditions. TRPM8 has also been detected in isolated human odontoblasts and although TRPM8 knockout mice do not lack sensation to noxious cold, they exhibit reduced cold hypersensitivity following nerve injury and inflammation [34,66,67]. Therefore, this evidence makes TRPM8 channels, SOCE, and Na^+/Ca^{2+} exchanger possible key targets molecule integrating Na^+ and Ca^{2+} signaling pathways.

Concluding Remarks

In numerous cell types control their downstream cascades pathways through a transmembrane fine balance between influx and efflux of Ca^{2+} and Na^+ ions [68]. Compared to the Ca^{2+} signaling, the role of Na^+ signaling in the cellular functions emerging now as a prominent target related to channelopathies [50,69,70]. New insights highlight TRPM8 channels as a possible player responsible for the link between Na^+ and Ca^{2+} signaling [2,7,29,50]. Although no direct interaction between TRPM8, SOCE and Na^+/Ca^{2+} exchangers function have been shown, the data reviewed above and the illustrative crosslink on Figure 4 suggest that TRPM8 could be the channel that links Na^+ and Ca^{2+} signaling, providing a novel insight for further understanding of structure-function relationships of these cellular signaling pathways during the ionic influx and efflux. The development of new drugs or repurposing of well-known cooling agonists/antagonists

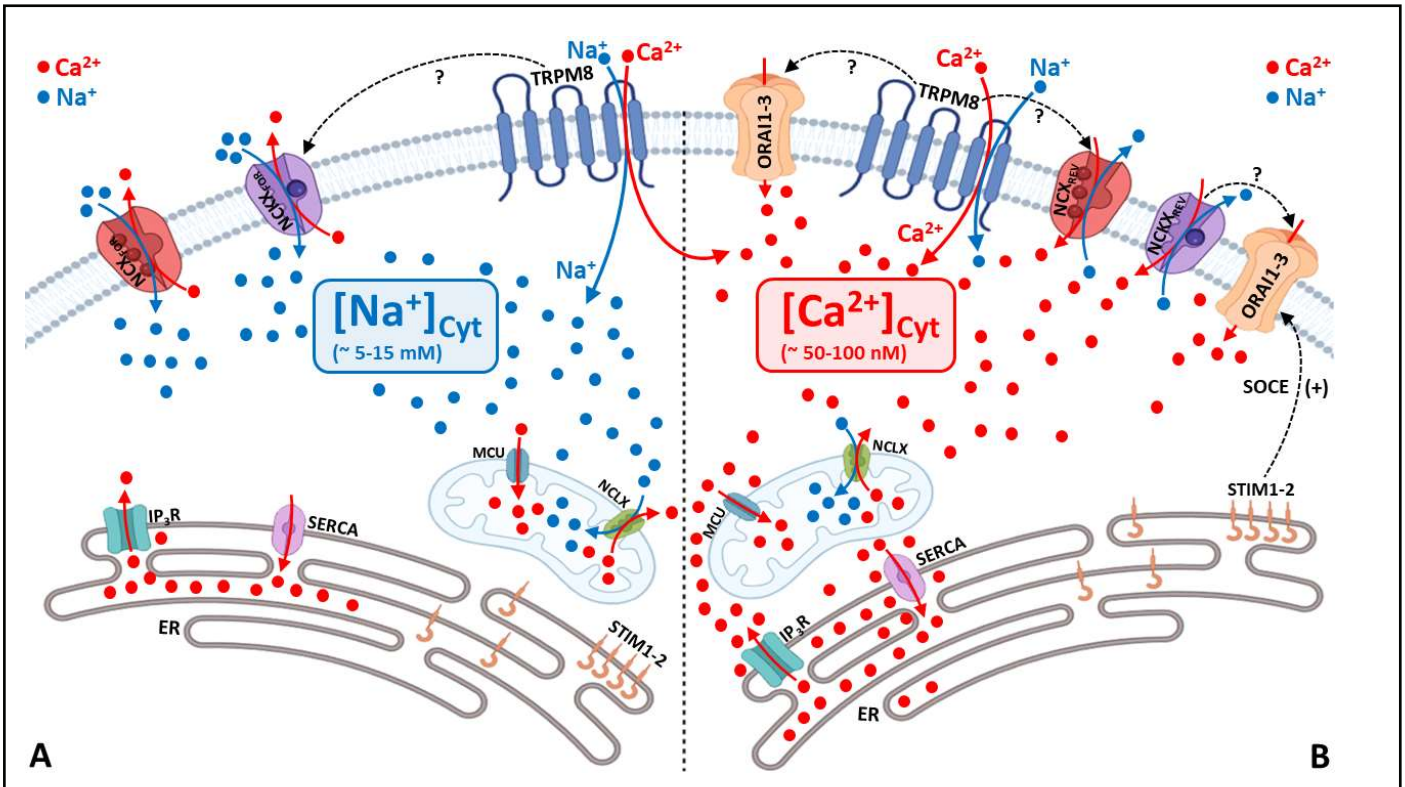

Figure 4: Schematic illustration showing Na^+ and Ca^{2+} signaling and the possible crosslink between TRPM8, SOCE, and Na^+/Ca^{2+} exchangers. TRPM8 uptake Na^+ (blue dots) and Ca^{2+} (red dots) ions increasing the cytosolic levels of both ions and changing the Na^+ (**A panel**, left) and Ca^{2+} (**B panel**, right) signaling, possibly linked to Na^+/Ca^{2+} exchangers (NCX/NCKX/NCLX) and SOCE (ORAI1-3) functions.

has been challenged by the pharmacological profile of these compounds, being the TRPM8 channels a new target to be explored in the future.

References

1. Salari V, Naeij H, Shafiee A. Quantum Interference and Selectivity through Biological Ion Channels. Sci Rep. 2017;7:41625.

2. Armstrong CM, Hollingworth S. Na(+) and K(+) channels: history and structure. Biophys J. 2021;120(5):756-63.

3. Penner R, Neher E. The role of calcium in stimulus-secretion coupling in excitable and non-excitable cells. J Exp Biol. 1988;139:329-45.

4. Biales B, Dichter M, Tischler A. Electrical excitability of cultured adrenal chromaffin cells. J Physiol. 1976;262(3):743-53.

5. Brandt BL, Hagiwara S, Kidokoro Y, Miyazaki S. Action potentials in the rat chromaffin cell and effects of acetylcholine. J Physiol. 1976;263(3):417-39.

6. Garcia AG, Garcia-De-Diego AM, Gandia L, Borges R, Garcia-Sancho J. Calcium signaling and exocytosis in adrenal chromaffin cells. Physiol Rev. 2006;86(4):1093-131.

7. González-Muñiz R, Bonache MA, Martín-Escura C, Gómez-Monterrey I. Recent Progress in TRPM8 Modulation: An Update. Int J Mol Sci. 2019;20(11).

8. Bootman MD. Calcium signaling. Cold Spring Harb Perspect Biol. 2012;4(7):a011171.

9. Doherty AH, Ghalambor CK, Donahue SW. Evolutionary physiology of bone: bone metabolism in changing environments. Physiology (Bethesda). 2015;30(1):17-29.

10. Eckstein M, Vaeth M, Aulestia FJ, Costiniti V, Kassam SN, Bromage TG, et al. Differential regulation of Ca(2+) influx by ORAI channels mediates enamel mineralization. Sci Signal. 2019;12(578).

11. Lopez JJ, Jardin I, Albarrán L, Sanchez-Collado J, Cantonero C, Salido GM, et al. Molecular Basis and Regulation of Store-Operated Calcium Entry. Adv Exp Med Biol. 2020;1131:445-69.

12. Yeung PS, Yamashita M, Prakriya M. Molecular basis of allosteric Orai1 channel activation by STIM1. J Physiol. 2020;598(9):1707-23.

13. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. Nature. 2006;441(7090):179-85.

14. Alansary D, Kilch T, Holzmann C, Peinelt C, Hoth M, Lis A. Patch-clamp measurement of ICRAC and ORAI channel activity. Cold Spring Harb Protoc. 2014;2014(6):602-7.

15. Hou X, Outhwaite IR, Pedi L, Long SB. Cryo-EM structure of the calcium release-activated calcium channel Orai in an open conformation. Elife. 2020;9.

16. Yoast RE, Emrich SM, Zhang X, Xin P, Johnson MT, Fike AJ, et al. The native ORAI channel trio underlies the diversity of Ca(2+) signaling events. Nat Commun. 2020;11(1):2444.

17. Lopez JJ, Jardin I, Sanchez-Collado J, Salido GM, Smani T, Rosado JA. TRPC Channels in the SOCE Scenario. Cells. 2020;9(1).

18. Bavencoffe A, Zhu MX, Tian JB. New Aspects of the Contribution of ER to SOCE Regulation: TRPC Proteins as a Link Between Plasma Membrane Ion Transport and Intracellular Ca(2+) Stores. Adv Exp Med Biol. 2017;993:239-55.

19. Berna-Erro A, Jardín I, Smani T, Rosado JA. Regulation of Platelet Function by Orai, STIM and TRP. Adv Exp Med Biol. 2016;898:157-81.

20. Huang Y, Fliegert R, Guse AH, Lü W, Du J. A structural overview of the ion channels of the TRPM family. Cell Calcium. 2020;85:102111.

21. Nilius B, Owsianik G. The transient receptor potential family of ion channels. Genome Biol. 2011;12(3):218.

22. Santoni G, Morelli MB, Marinelli O, Nabissi M, Santoni M, Amantini C. Calcium Signaling and the Regulation of Chemosensitivity in Cancer Cells: Role of the Transient Receptor Potential Channels. Adv Exp Med Biol. 2020;1131:505-17.

23. Zitt C, Halaszovich CR, Lückhoff A. The TRP family of cation channels: probing and advancing the concepts on receptor-activated calcium entry. Prog Neurobiol. 2002;66(4):243-64.

24. Lopez JJ, Albarran L, Gómez LJ, Smani T, Salido GM, Rosado JA. Molecular modulators of store-operated calcium entry. Biochim Biophys Acta. 2016;1863(8):2037-43.

25. Souza Bomfim GH, Costiniti V, Li Y, Idaghdour Y, Lacruz RS. TRPM7 activation potentiates SOCE in enamel cells but requires ORAI. Cell Calcium. 2020;87:102187.

26. Faouzi M, Kilch T, Horgen FD, Fleig A, Penner R. The TRPM7 channel kinase regulates store-operated calcium entry. J Physiol. 2017;595(10):3165-80.

27. McKemy DD, Neuhausser WM, Julius D. Identification of a cold receptor reveals a general role for TRP channels in thermosensation. Nature. 2002;416(6876):52-8.

28. Peier AM, Moqrich A, Hergarden AC, Reeve AJ, Andersson DA, Story GM, et al. A TRP channel that senses cold stimuli and menthol. Cell. 2002;108(5):705-15.

29. Liu Y, Mikrani R, He Y, Faran Ashraf Baig MM, Abbas M, Naveed M, et al. TRPM8 channels: A review of distribution and clinical role. Eur J Pharmacol. 2020;882:173312.

30. Coste B, Xiao B, Santos JS, Syeda R, Grandl J, Spencer KS, et al. Piezo proteins are pore-forming subunits of mechanically activated channels. Nature. 2012;483(7388):176-81.

31. Bautista DM, Siemens J, Glazer JM, Tsuruda PR, Basbaum AI, Stucky CL, et al. The menthol receptor TRPM8 is the principal detector of environmental cold. Nature. 2007;448(7150):204-8.

32. Voets T, Owsianik G, Nilius B. TRPM8. Handb Exp Pharmacol. 2007(179):329-44.

33. Yin Y, Lee SY. Current View of Ligand and Lipid Recognition by the Menthol Receptor TRPM8. Trends Biochem Sci. 2020;45(9):806-19.

34. Colburn RW, Lubin ML, Stone DJ, Jr., Wang Y, Lawrence D, D'Andrea MR, et al. Attenuated cold sensitivity in TRPM8 null mice. Neuron. 2007;54(3):379-86.

35. Yin Y, Le SC, Hsu AL, Borgnia MJ, Yang H, Lee SY. Structural basis of cooling agent and lipid sensing by the cold-activated TRPM8 channel. Science. 2019;363(6430).

36. Steinberg X, Lespay-Rebolledo C, Brauchi S. A structural view of ligand-dependent activation in thermoTRP channels. Front Physiol. 2014;5:171.

37. Diver MM, Cheng Y, Julius D. Structural insights into TRPM8 inhibition and desensitization. Science. 2019;365(6460):1434-40.

38. Winkler PA, Huang Y, Sun W, Du J, Lü W. Electron cryo-microscopy structure of a human TRPM4 channel. Nature. 2017;552(7684):200-4.

39. Journigan VB, Zaveri NT. TRPM8 ion channel ligands for new therapeutic applications and as probes to study menthol pharmacology. Life Sci. 2013;92(8-9):425-37.

40. Daniels RL, Takashima Y, McKemy DD. Activity of the neuronal cold sensor TRPM8 is regulated by phospholipase C via the phospholipid phosphoinositol 4,5-bisphosphate. J Biol Chem. 2009;284(3):1570-82.

41. Liu Z, Wu H, Wei Z, Wang X, Shen P, Wang S, et al. TRPM8: a potential target for cancer treatment. J Cancer Res Clin Oncol. 2016;142(9):1871-81.

42. Yee NS. Roles of TRPM8 Ion Channels in Cancer: Proliferation, Survival, and Invasion. Cancers (Basel). 2015;7(4):2134-46.

43. Xie J, Pan H, Yao J, Zhou Y, Han W. SOCE and cancer: Recent progress and new perspectives. Int J Cancer. 2016;138(9):2067-77.

44. Schild A, Bhardwaj R, Wenger N, Tscherrig D, Kandasamy P, Dernič J, et al. Synthesis and Pharmacological Characterization of 2-Aminoethyl Diphenylborinate (2-APB) Derivatives for Inhibition of Store-Operated Calcium Entry (SOCE) in MDA-MB-231 Breast Cancer Cells. Int J Mol Sci. 2020;21(16).

45. Moran MM. TRP Channels as Potential Drug Targets. Annu Rev Pharmacol Toxicol. 2018;58:309-30.

46. Malkia A, Pertusa M, Fernández-Ballester G, Ferrer-Montiel A, Viana F. Differential role of the menthol-binding residue Y745 in the antagonism of thermally gated TRPM8 channels. Mol Pain. 2009;5:62.

47. Prins D, Michalak M. Organellar calcium buffers. Cold Spring Harb Perspect Biol. 2011;3(3).

48. Gilabert JA. Cytoplasmic Calcium Buffering: An Integrative Crosstalk. Adv Exp Med Biol. 2020;1131:163-82.

49. Carbone E, Borges R, Eiden LE, Garcia AG, Hernandez-Cruz A. Chromaffin Cells of the Adrenal Medulla: Physiology, Pharmacology, and Disease. Compr Physiol. 2019;9(4):1443-502.

50. Verkhratsky A, Trebak M, Perocchi F, Khananshvili D, Sekler I. Crosslink between calcium and sodium signalling. Exp Physiol. 2018;103(2):157-69.

51. Wahl M, Sleight RG, Gruenstein E. Association of cytoplasmic free Ca2+ gradients with subcellular organelles. J Cell Physiol. 1992;150(3):593-609.

52. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. Nat Rev Mol Cell Biol. 2012;13(9):566-78.

53. Berridge MJ. Calcium microdomains: organization and function. Cell Calcium. 2006;40(5-6):405-12.

54. Krebs J, Agellon LB, Michalak M. Ca(2+) homeostasis and endoplasmic reticulum (ER) stress: An integrated view of calcium signaling. Biochem Biophys Res Commun. 2015;460(1):114-21.

55. Khananshvili D. Basic and editing mechanisms underlying ion transport and regulation in NCX variants. Cell Calcium. 2020;85:102131.

56. Jalloul AH, Szerencsei RT, Rogasevskaia TP, Schnetkamp PPM. Structure-function relationships of K(+)-dependent Na(+)/Ca(2+) exchangers (NCKX). Cell Calcium. 2020;86:102153.

57. Giladi M, Tal I, Khananshvili D. Structural Features of Ion Transport and Allosteric Regulation in Sodium-Calcium Exchanger (NCX) Proteins. Front Physiol. 2016;7:30.

58. Altimimi HF, Schnetkamp PP. Na+/Ca2+-K+ exchangers (NCKX): functional properties and physiological roles. Channels (Austin). 2007;1(2):62-9.

59. Mu YP, Lin DC, Zheng SY, Jiao HX, Sham JSK, Lin MJ. Transient Receptor Potential Melastatin-8 Activation Induces Relaxation of Pulmonary Artery by Inhibition of Store-Operated Calcium Entry in Normoxic and Chronic Hypoxic Pulmonary Hypertensive Rats. J Pharmacol Exp Ther. 2018;365(3):544-55.

60. Zhang X. Direct Gα(q) Gating Is the Sole Mechanism for TRPM8 Inhibition Caused by Bradykinin Receptor Activation. Cell Rep. 2019;27(12):3672-83.e4.

61. Perrouin-Verbe MA, Schoentgen N, Talagas M, Garlantezec R, Uguen A, Doucet L, et al. Overexpression of certain transient receptor potential and Orai channels in prostate cancer is associated with decreased risk of systemic recurrence after radical prostatectomy. Prostate. 2019;79(16):1793-804.

62. Eckstein M, Aulestia FJ, Nurbaeva MK, Lacruz RS. Altered Ca(2+) signaling in enamelopathies. Biochim Biophys Acta Mol Cell Res. 2018;1865(11 Pt B):1778-85.

63. Hossain MZ, Bakri MM, Yahya F, Ando H, Unno S, Kitagawa J. The Role of Transient Receptor Potential (TRP) Channels in the Transduction of Dental Pain. Int J Mol Sci. 2019;20(3).

64. Eckstein M, Vaeth M, Fornai C, Vinu M, Bromage TG, Nurbaeva MK, et al. Store-operated Ca(2+) entry controls ameloblast cell function and enamel development. JCI Insight. 2017;2(6):e91166.

65. Robertson SYT, Wen X, Yin K, Chen J, Smith CE, Paine ML. Multiple Calcium Export Exchangers and Pumps Are a Prominent Feature of Enamel Organ Cells. Front Physiol. 2017;8:336.

66. Tazawa K, Ikeda H, Kawashima N, Okiji T. Transient receptor potential melastatin (TRPM) 8 is expressed in freshly isolated native human odontoblasts. Arch Oral Biol. 2017;75:55-61.

67. Tsumura M, Sobhan U, Sato M, Shimada M, Nishiyama A, Kawaguchi A, et al. Functional expression of TRPM8 and TRPA1 channels in rat odontoblasts. PLoS One. 2013;8(12):e82233.

68. Berridge MJ, Bootman MD, Roderick HL. Calcium signalling: dynamics, homeostasis and remodelling. Nat Rev Mol Cell Biol. 2003;4(7):517-29.

69. Moreau A, Gosselin-Badaroudine P, Chahine M. Biophysics, pathophysiology, and pharmacology of ion channel gating pores. Front Pharmacol. 2014;5:53.

70. Annunziato L, Secondo A, Pignataro G, Scorziello A, Molinaro P. New perspectives for selective NCX activators in neurodegenerative diseases. Cell Calcium. 2020;87:102170.