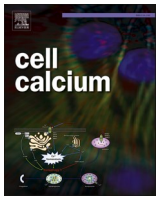
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Store operated Ca^{2+} entry in neural crest cells and their derivatives

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ABSTRACT

Neural crest cells (NCCs) are multipotent stem cells that migrate extensively during embryogenesis and give rise to a broad spectrum of derivatives, including melanocytes, Schwann cells, chromaffin cells, and neurons of the enteric nervous system. NCC proliferation, migration, or differentiation defects lead to a group of disorders collectively known as neurocristopathies. Understanding the signaling pathways that govern NCC behavior is therefore crucial for elucidating the origins of these conditions. Store-Operated Calcium Entry (SOCE) is recognized as the principal calcium influx mechanism in non-excitable cells and regulates key cellular processes such as proliferation, migration, and differentiation. Accumulating evidence indicates a significant role for Ca^{2+} signaling and SOCE in multiple NCC-derived cell types. This review examines current knowledge on Ca^{2+} signaling mediated by SOCE in NCCs and their derivatives, and discusses how dysregulated SOCE signaling may influence the pathogenesis of neurocristopathies.

What is already known

- SOCE is the main Ca^{2+} entry pathway in non-excitable cells.
- SOCE regulates multiple cellular processes.

What this study adds

- The role of SOCE in NCCs and their derivatives has not been synthetized.
- This review aims to provide an overview of the role of SOCE in NCCs lineage.
- Evaluating the potential contribution of SOCE in neurocristopathies.

1. Introduction

Neural crest cells (NCCs) are multipotent stem cells originating from a transient ectodermal structure that forms during neurulation, when neural folds elevate and fuse to generate the neural tube [1–3]. After undergoing epithelial–mesenchymal transition (EMT), NCCs migrate throughout the embryo and colonize cranial [4], trunk [5], vagal/sacral [6,7], and cardiac [8] regions following highly stereotyped trajectories. Their migratory and proliferative character strikingly resembles that of cancer cells [9–11]. NCCs then differentiate into a wide range of derivatives, including melanocytes, Schwann cells, odontoblasts, chromaffin cells, and the enteric nervous system [12]. Because of this remarkable developmental plasticity, several authors have proposed revisiting the classical three-germ-layer paradigm and considering the neural crest as a potential "fourth germ layer" [13,14].

Disruption of NCC proliferation, survival, or migration results in a wide spectrum of disorders collectively termed neurocristopathies [15]. Among the most emblematic are DiGeorge and Hirschsprung's syndromes, which are respectively characterized by cardiac/craniofacial malformations and a lack of enteric ganglia in the distal gut [16]. Over the past decades, major progress has been made in understanding the molecular mechanisms governing NCCs development, leading to the identification of several key regulatory pathways. For example, in Hirschsprung disease, endothelin-3 (ET-3) and glial cell line-derived neurotrophic factor (GDNF) were shown to be essential for NCC colonization of the embryonic gut [17].

Calcium (Ca^{2+}) is a fundamental second messenger used by all eukaryotic cells to regulate essential functions such as fertilization, immunity, contraction, migration, and proliferation [18–20]. It is now well established that Ca^{2+} signaling plays a central role in epithelial–mesenchymal transition (EMT) [21]. In particular, it regulates multiple EMT-associated processes, including integrin signaling [22], extracellular matrix proteolysis [23], and cytoskeletal reorganization

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[24], among others. Thus, Ca^{2+} signaling may be involved in NCCs physiology. Under resting conditions, cytosolic Ca^{2+} levels are about 100 nM, whereas extracellular Ca^{2+} is in the range 1-2 mM [25]. Abnormal increase in cytosolic Ca^{2+} leads to pathophysiological consequences, including cell death, highlighting the importance of maintaining the control on intracellular Ca^{2+} concentration [26]. Activation of signaling pathways induces rapid and tightly controlled changes in cytosolic Ca^{2+} concentrations, gated by a large repertoire of Ca^{2+} channels, transporters, and exchangers located at the plasma membrane and on intracellular organelles such as the endoplasmic reticulum (ER), mitochondria, or lysosomes [27–29].

In excitable cells (i.e. cells that can generate action potential in response to electrical stimulation, such as neurons and muscle cells), the major source for Ca^{2+} influx is mediated by voltage-gated-calcium-channels (VGCCs). In non-excitable cells, the Store-Operated Calcium Entry (SOCE) pathway constitutes the major Ca^{2+} influx [28,30]. Physiologically, upon stimulation of G protein-coupled receptors (GPCR) or receptor tyrosine kinases (RTK), phospholipase C (PLC) generates inositol 1,4,5-trisphosphate (IP3), which activates IP3 receptors (IP3R) and releases Ca^{2+} from the ER [31–33]. Depletion of ER Ca^{2+} stores induces stromal interaction molecule 1 and 2 (STIM1 and STIM2) activation [26,30,34], exposing their SOAR/CAD domain and driving their accumulation at ER–plasma membrane junctions, where they bind and activate Ca^{2+} channels to mediate Ca^{2+} influx [20,35]. ER Ca^{2+} store depletion can activate at least two distinct plasma membrane currents: (i) a highly Ca^{2+}selective inwardly rectifying current mediated by Orai1–3 channels, also known as Calcium Release-Activated Calcium (CRAC) channels, which generates the classical ICRAC current [22,26,27], and (ii) a non-selective cationic current mediated by transient receptor potential canonical (TRPC) channels, commonly referred to as ISOC [36,37]. While several additional proteins, including transient receptor TRPC channels and associated regulatory molecules, may contribute to SOCE depending on the cellular context [38,39], the present review specifically focuses on the Orai1–3 channels and STIM1–2 ER Ca^{2+} sensors that mediate the canonical ICRAC pathway. This choice was made because the available literature concerning NCC-derived lineages predominantly implicates Orai/STIM-dependent signaling, whereas the contribution of alternative SOCE components remains comparatively less characterized in these cell types.

In this review, we first provide an overview of the molecular mechanisms underlying SOCE for readers unfamiliar with this signaling pathway. We then summarize current knowledge regarding the role of SOCE in NCCs and NCC-derived lineages, with particular emphasis on its involvement in fundamental cellular processes such as proliferation, migration, differentiation, survival, and cell death, as well as lineage-specific functions including melanogenesis and dentin formation. Finally, we discuss the potential implications of SOCE dysregulation in neurocristopathies and highlight key unanswered questions and future directions that warrant further investigation.

2. Molecular composition of store-operated-calcium-entry mediated by CRAC channels

ICRAC machinery is composed of 3 highly selective Ca^{2+} channels, Orai1-3 and 2 Ca^{2+} store sensors, STIM1-2 (Fig. 1). Sequence comparison among Orai or STIM isoforms reveal a high degree of homology within the family members [40,41]. Functionally, each Orai channel is capable of supporting SOCE when exogenously co-expressed with STIM1, although their biophysical properties differ [40,41]. Knockout studies of individual and combined Orai isoforms demonstrated that Orai2 and Orai3 can form heteromeric CRAC channels with Orai1. Surprisingly, deletion of Orai2 or Orai3 enhances Orai1-mediated SOCE,

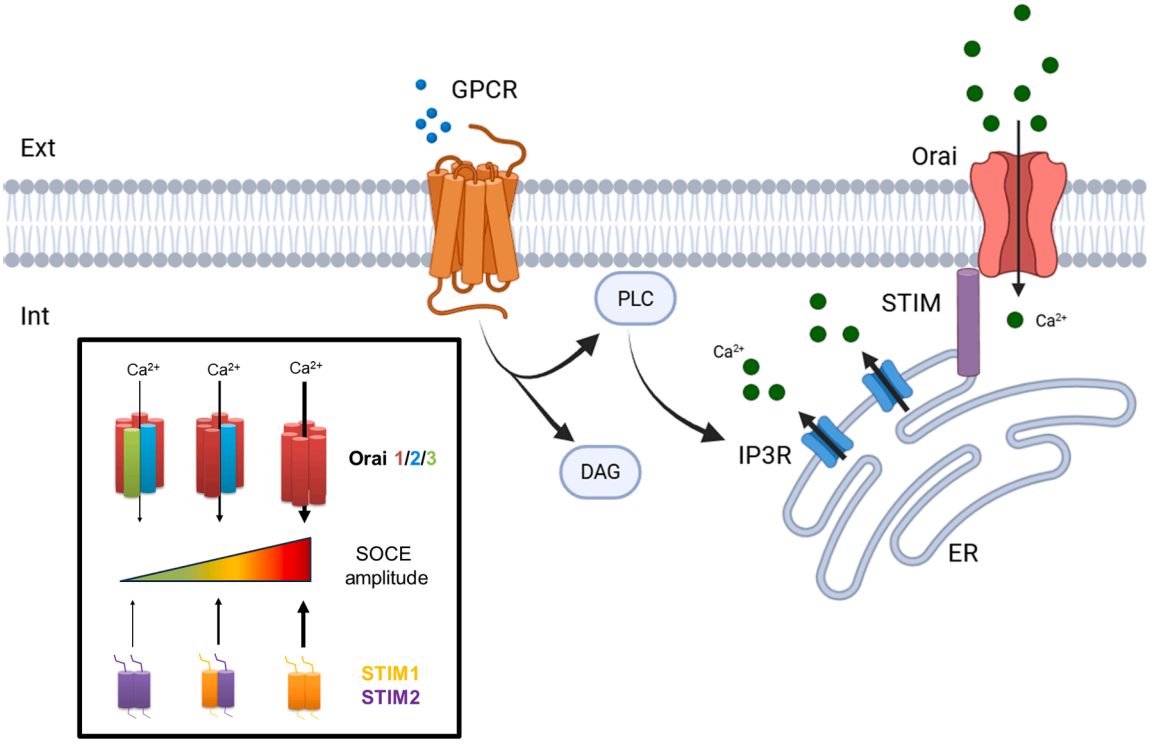


Fig. 1. Store operated calcium entry (modified from Emrich and al., 2021). Activation of G protein coupled receptor (or receptor tyrosin kinase) leads to phospholipase C dependent production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3), which is responsible for IP3 receptor (IP3R) activation and Ca^{2+} release from endoplasmic reticulum (ER) stores. ER store depletion activates stromal interaction molecule 1-2 (STIM1-2), which translocate to ER-plasma membrane junctions where they gate CRAC channels (Orai1/2/3 heterohexamers). In most cells, Orai1 and STIM1 produce the majority of SOCE in response to maximal store depletion, whereas Orai2, Orai3 and STIM2 have less potency. Homo- or heteromeric combinations of Orai and STIM isoforms support the graded diversity of SOCE-mediated Ca^{2+} signaling events in mammals (see insert).

supporting the hypothesis that Orai2 and Orai3 may act as negative regulators of Orai1 function [42–45]. However, in some cell types, especially in neurons or in some cancer cells, Orai2 and Orai3 seem to act as positive regulators of SOCE, which suggests a more complex mechanism [46–50]. Because Orai2 and Orai3 display distinct biophysical features compared to Orai1, heteromeric CRAC channels exhibit greater functional diversity and fine-tuning capacity [28,43]. One notable example concerns oxidative stress resistance: Orai3 is uniquely resistant to oxidant-mediated SOCE inhibition. Consequently, heteromeric channels enriched in Orai3 maintain Ca^{2+} influx under hypoxic or oxidant-rich conditions [46–48]. Although the exact stoichiometry and organization of native Orai heteromers remains unresolved, current evidence suggests that subunit composition varies across cell types and physiological states, enabling specialized Ca^{2+} signaling. For instance, in MCF-7, a breast cancer cell line, Orai3, but not Orai1, is the predominant contributor to SOCE [46–48,50].

Regarding the ER Ca^{2+} sensors, most studies initially identified STIM1 as the primary activator of SOCE under native condition [51,52]. For many years, STIM2 was thought to function mainly in maintaining basal ER and cytosolic Ca^{2+} concentrations [53], but recent findings demonstrate that both STIM1 and STIM2 are essential for optimal CRAC channel activation, although their contributions differ depending on the cell type [54]. For instance, STIM2 plays a particularly important role in SOCE from neurons [55] and in colorectal cancer cells [56].

In the next section, we will summarize the data available regarding the contribution of Ca^{2+}, and SOCE in NCCs.

3. Calcium activity in NCCs

Carey & Matsumoto [57] were the first to reveal Ca^{2+} activity in NCCs, using mouse neural tube cultures and Oregon Green Ca^{2+} indicator dye. They identified asynchronous, stochastic Ca^{2+} activity, mostly in single cells, with only rare propagation to neighboring cells. Ca^{2+} activity rose to a maximum after 3-4 days in culture and declined after differentiation to neurons and other NCCs derivatives. Average Ca^{2+} spike frequencies were low (3-5 peaks per hour), probably due to the fact that these investigators monitored Ca^{2+} at room temperature. Ca^{2+} activity was found in both neuron progenitors and differentiated neurons. Ca^{2+} activity was insensitive to ryanodine [58], but could be elicited by thimerosal, which sensitizes the IP3R. Conversely, Ca^{2+} activity decreased when IP3 levels were reduced by the phospholipase C inhibitor U73122 [58] and completely abolished by inhibiting IP3R with 20 mM Mg^{2+}. Cells that did not present Ca^{2+} activity did not differentiate to neurons, and inhibition of Ca^{2+} activity with Mg^{2+} significantly decreased differentiation to neurons [57]. Similarly, inhibition of PI3K, an upstream effector of IP3, with wortmannin, was found to decrease neurogenesis in cultured quail neural tubes [59]. Evrard et al. further found that modulating the protein kinase A and C (PKA/PKC) pathways strongly affected melanocyte vs neuron numbers after 5 days culture [59]. These latter findings would however benefit from further investigation with higher sample numbers. The first *in vivo* demonstration of Ca^{2+} activity in NCCs was performed by electroporating a GCaMP3 vector in the neural tube of chick embryos [60]. These investigators found that trunk NCCs at Hamburger–Hamilton (HH) stages 17–20, corresponding to later stages of chick embryogenesis, exhibited higher Ca^{2+} activity than cranial NCCs at HH stage 11. Ca^{2+} activity was particularly prominent during sympathetic ganglion formation. However, the study was limited by a low imaging frame rate (1 frame every 30 s) [55].

Enteric NCCs cells derive from vagal NCCs and invade the gastrointestinal tract rostro-caudally between stages E10.5-E14.5 in mice to form the enteric nervous system. Ca^{2+} signaling was first revealed in enteric NCCs by Hao and collaborators in 2017, and demonstrated to be sensitive to extracellular ATP signaling via purinergic receptors [61]. The purinergic pathway promotes Ca^{2+} rise in stimulated cells, which could propagate as waves across multiple cells. In a recent study, we have however shown that, as in neural tube derived NCCs [57], the predominant form of Ca^{2+} in enteric NCCs is stochastic and occurs mostly at the single-cell level [62]. Ca^{2+} activity occurs in active cells at a frequency of about 1-cycle per minute, and Ca^{2+} spikes have a width at half maxima of ~10 sec. This activity is insensitive to tetrodotoxin, suggesting a different mechanism than neural action potential [62,63]. Ca^{2+} waves decrease as migration and differentiation of NCCs in the intestine progresses, and is under the control of the ET-B receptor and of its ligand endothelin 3. ET-B activation triggers the opening of Cl^- and T-type Ca^{2+} channels which induces Ca^{2+} influx from the extracellular medium and Ca^{2+} induced Ca^{2+} release via IP3R, but not ryanodine receptors [62]. All three T-types Ca^{2+} channels isoforms (CaV3.1, CaV3.2, CaV3.3) were found to be expressed by enteric neural crest cells (ENCCs). Ca^{2+} activity was found to be necessary for migration by increasing cell contractility, resulting in increased traction force to the extracellular matrix [62]. This research is one of the first to lay down a functional role for Ca^{2+} activity in NCCs and to establish a relationship with the main neurocristopathy affecting the gut, Hirschsprung disease.

To our knowledge, no data are currently available regarding the molecular composition or physiological function of SOCE in NCCs. In our previous work [62], we did not assess Orai and STIM mRNA or protein expression levels. However, we showed that Gd^{3+}, a known blocker of Orai channels, blocks partially endogenous ET-3-mediated Ca^{2+} oscillations in the mouse intestine at E11.5 [62]. These results may suggest that SOCE participates in ET-3 signaling at this developmental stage, but given the lack of selectivity of Gd^{3+}, these findings should be interpreted cautiously. Our hypothesis is that T-Type Ca^{2+} channels are the predominant channels responsible for Ca^{2+} entry at the plasma membrane during NCCs colonization of mouse intestine, and that SOCE may act as a minor contributor. Further studies will be required to test this hypothesis and to determine the developmental regulation and functional relevance of SOCE in NCCs.

Interestingly, several studies have highlighted the contribution of SOCE in other stem cell types, notably in neural stem cells (NSCs) [64]. These data indicate that SOCE machinery components are expressed in NSCs [65–68], with STIM1 and Orai1 as contributors of SOCE [65,66,69]. Interestingly, in human embryonic NSCs, SOCE is active, but not VGCCs [68], supporting the idea that SOCE plays a crucial role in the fate of human embryonic stem cells. SOCE activation induces nuclear factor of activated T cells (NFAT) nuclear translocation and promotes NSCs proliferation, which can be reduced by Orai1 or STIM1 knockout [66,69,70]. In mouse NSCs, an increase in STIM1 and Orai1 levels is observed during neural differentiation, suggesting a role in the early stages of neural lineage [67]. However, the observation that STIM1, but not Orai1 is required for mouse embryonic SC differentiation into neurons, suggests a mechanism independent of SOCE or requiring Orai2 and/or Orai3 [67]. In ReNcell VM, an immortalized human neural progenitor cell line, neural differentiation is associated with increased spontaneous Ca^{2+} activity and remodeling of SOCE components. During differentiation, Orai1 mRNA and protein expression decrease, whereas STIM1 expression increases. In parallel, Orai2 and Orai3 mRNA levels are upregulated. Interestingly, Orai3 silencing reduces the expression of neural differentiation markers such as MAP2 and GFAP, supporting a role for Orai3 in neural differentiation. However, the study did not directly demonstrate the involvement of Orai3 in SOCE [71]. Also, reduced SOCE promotes early neural differentiation in human neural progenitor cells [61].

Orai1 and STIM1 constitute necessary partners for SOCE in NSCs. A similar pattern may occur in NCCs. Future studies are required to determine the molecular composition of SOCE in NCCs and to establish the respective contributions of Orai1–3 and STIM1–2 to Ca^{2+} entry. Another key challenge will be to define the role of SOCE during the different stages of NCC development. These questions are discussed in greater detail in the “Future Directions” section.

4. Role of store-operated-calcium-entry in NCCs derivatives

Neural crest cells give rise to a remarkably diverse range of derivatives, including, but not limited to, melanocytes, Schwann cells, chromaffin cells, and odontoblasts. Despite this cellular diversity, the role of SOCE has been investigated in only a limited number of NCC-derivatives (Table 1). Furthermore, several studies have linked Orai/STIM signaling to disease-associated processes, including melanoma progression, neuroblastoma cell survival, defects in ectodermal and dental tissues, highlighting the potential importance of SOCE in both normal NCC-derived cell physiology and neurocristopathies (Tables 1 and 2).

In the following sections, we summarize the current knowledge regarding the molecular composition and physiological functions of SOCE in these cells.

4.1. Melanocytes

Melanocytes are skin cells originating from NCCs that migrate and proliferate to colonize the basal epidermal layer during early embryo development. Their main function is to produce melanin pigment to protect tissues from damage caused by ultraviolet radiation. Two major pathways regulate skin pigmentation: adaptive tanning in response to environmental ultraviolet radiation exposure, and baseline melanin production, which determines skin tone [72,73].Transcriptome analyses have shown that Orai1 is the most highly expressed Orai isoform in human melanocytes (Orai1 > Orai3 > Orai2) [74], which is consistent with the expression pattern of Orai channels in most tissues [26,28]. However, STIM2 expression is significantly higher than STIM1 mRNA levels in melanocytes [74]. This is unexpected since STIM1 is usually the predominant STIM isoform in most cell types [26,28]. At the protein level, STIM1 is highly expressed in HEMA-LP, a human melanocyte cell line, while Orai1 is almost not expressed [75]. Several reports have demonstrated the presence of functional SOCE and CRAC current in human melanocytes, with Orai1 accounting for approximately 66% of SOCE [74,75]. To our knowledge, no studies have examined the contribution of Orai2, Orai3, or STIM1 and STIM2 in SOCE from melanocytes. On the functional side, studies have focused on the role of Orai1 in melanocyte physiology. Orai1 silencing using siRNA significantly decreases endothelin-1-induced cell viability and abolishes endothelin-1-induced melanin production [74]. Interestingly, in patients carrying *Orai1* or *STIM1* mutations that result in nonfunctional CRAC current, no pigmentation defects have been reported, and only UV-induced skin damage is impaired [76–79], suggesting that SOCE regulates adaptive tanning rather than basal skin pigmentation.

Table 1
Composition and functions of SOCE in NCCs derivatives.

Cell types	Major SOCE components	Experimental approaches	Physiological functions	References
Melanocytes	Orai1 and STIM1	2-APB, Orai1-KD, Orai1-KO, missense Orai1 mutation, STIM1-KO, STIM2-KO, STIM1 mutation	cell viability, melanin production	[74, 76–79]
Schwann cells	hypothetical role of STIM1	None	Not defined	[82]
Chromaffin cells	Not defined	2-APB	Cell death	[88]
Odontoblasts	STIM1 and Orai1	Synta66, BTP2, La^{3+}, high and low pH, Orai1-KD, STIM1-KO, STIM1-overexpression	proliferation, differentiation, maturation, and mineralization of dentin-forming cells	[95,93, 96]

4.2. Schwann cells

Schwann cells are glial cells derived from NCCs that form the myelin sheath of peripheral nerves. They are also central contributors to peripheral nerve repair, axonal regrowth, and remyelination [80]. By secreting neurotrophic factors and extracellular matrix components, Schwann cells support neuronal survival and the maintenance of axonal networks [81]. Although Schwann cells interact directly with neurons, they are not considered excitable cells and SOCE might thus represent a major Ca^{2+} entry pathway in this cell type. To our knowledge, only a single study has investigated SOCE in Schwann cells [82]. Peripheral myelin protein 22 (PMP22), a protein implicated in Charcot–Marie–Tooth (CMT) disease, interacts with STIM1 in mouse Schwann cells. Overexpression of PMP22 enhances CRAC current. This current is absent in PMP22-deficient cells, supporting the idea that PMP22 is required for SOCE from mouse Schwann cells [82].

4.3. Chromaffin cells

Chromaffin cells are a neuroendocrine cell population located in the adrenal medulla and paraganglia. They originate from NCCs and are responsible for the secretion of catecholamines, including dopamine, adrenaline, and noradrenaline [83–85]. Through these secretory functions, chromaffin cells influence the activity of virtually all organs, regulate metabolic parameters, and participate in stress responses and protective physiological reactions [86]. Long considered incapable of proliferating in adults, chromaffin cells are now recognized as a low-proliferating cell population, raising increasing interest in the mechanisms underlying their postnatal self-renewal [87]. To our knowledge, only one study has investigated the role of SOCE in non-cancerous adrenal medullary chromaffin cells [88]. This work did not address the expression levels of Orai channels or STIM proteins, nor did it provide evidence for their specific contribution to Ca^{2+} entry. However, functional SOCE was present and active in these cells. Chronic intermittent hypoxia was shown to potentiate SOCE activity and cytosolic Ca^{2+} oscillations in chromaffin cells, likely through increased H_2O_2 production, and may thereby promote cytotoxicity [88].

4.4. Odontoblasts

During craniofacial development, ectomesenchymal cells originating from NCCs proliferate and differentiate into odontoblasts. Odontoblasts are tall columnar cells located along the interface between dental and dentin [89], which are responsible for dentinogenesis by promoting dentin extracellular matrix secretion and matrix mineralization [90,91]. In dental pulp stem cells (DPSCs) Orai1 is the most highly expressed Orai channel (Orai1 > Orai2 > Orai3), and its expression increases during odontogenic differentiation [92]. Similarly, STIM1 is more expressed than STIM2 and its expression increases over odontogenic differentiation [92]. Orai1 and Orai2 proteins have been detected in mouse odontoblasts [93], but to our knowledge, no data is currently available regarding the protein levels of Orai3, STIM1, or STIM2. Functionally, CRAC current and SOCE are activated in response to Ca^{2+} store depletion in acutely dissociated rat odontoblasts [94], and conventional SOCE inhibitors, such as Synta66, BTP2, and La^{3+}, effectively inhibit SOCE in rat odontoblasts [95], while basic pH potentiates thapsigargin-induced SOCE, as demonstrated by others in different cellular models [95]. Orai1 or STIM1 knockout abolishes SOCE in DPSC and odontoblasts [92, 96], suggesting functional “classic SOCE”. However, no study has yet investigated the specific contributions of Orai2, or Orai3 channels to SOCE in odontoblasts. Functional studies indicate a key role for Orai1 in cell proliferation and maturation during tooth development [92,93], pointing toward a central involvement of Orai1 in odontoblast physiology. *In vitro*, STIM1 overexpression enhances dentin mineral

Table 2
Composition and functions of SOCE in neurocristopathies.

Disorders	Major SOCE components	Experimental approaches	Physiological functions	References
Melanoma	Orai1 and STIM1 (hypothetical involvement of Orai2/3 and STIM2)	STIM1-KD, Orai1-KD, 2-APB, YM583483, BTP2, IA65, Orai1-overexpression, Orai1-Dominant negative	cell migration, invasion, and metastasis	[75,98–100]
Neuroblastoma	STIM1	2-APB, STIM1-KD	metabolic regulation, cell survival	[112–114]
Pheochromocytoma	STIM1 (hypothetical involvement of Orai1)	SKF-96365, STIM1-KD	cell death	[126,128,129]
Charcot–Marie–Tooth	unknown	none	Disease progression?	[138–141]

deposition, whereas STIM1 knockout decreases mineralization and reduces the expression of mineralization-related differentiation markers [96]. In patients, loss-of-function mutations in Orai1 or STIM1 impair SOCE and result in hypomineralized enamel [96]. Both primary and permanent teeth are affected by Orai1 and STIM1 mutations, suggesting a role for SOCE not only in early tooth development but also in tooth regeneration [96].

4.5. Other cell types

We are not aware of any data regarding the expression or function of SOCE machinery in conotruncal cardiac cells, pharyngeal arch cells, facial dermal fibroblasts, cranial chondrocytes, osteoblasts, enteric glial and ENCCs. Considering the homogeneous responses observed in the different cell types analyzed in the previous sections (Table 1), it is highly plausible that Orai1 and STIM1 constitute the main SOCE components in these cell populations as well. However, further experimental investigations will be required to determine the physiological roles of SOCE machinery in these cells, which could provide valuable insights into embryonic development and neurocristopathies.

5. Contribution of SOCE in neurocristopathies

In the following sections, we will summarize the current knowledge regarding the contribution of SOCE to neurocristopathies. It is important to emphasize that most available studies focus on NCC-derived cancers (Table 2), as SOCE has emerged as a relevant anticancer target.

5.1. Melanoma

Melanoma is a highly metastatic cancer of melanocyte lineage and can serve as a relevant model to study the evolution of pro-migratory pathways originating from melanocytes. Over the last decades, the incidence of melanoma has progressively increased, making it one of the most common cancers worldwide [97]. Several reports have described alterations of SOCE machinery in melanoma cells, with a possible contribution to melanoma metastasis and proliferation [75,98,99]. In patients with melanoma, fibroblast growth factor 2 (FGF2) expression, a known promoter of cell migration, positively correlates with STIM1 and Orai1 expression [99]. *In vitro*, FGF2 significantly increases Orai1 mRNA levels in MUM2B melanoma cells [99]. Umemura et *al.*, showed at the transcriptional and protein levels, an increase in STIM1, in invasive melanoma cells compared to non-invasive cells [75]. By contrast, Orai1 and Orai3 protein levels do not appear to be significantly altered in pro-metastatic melanoma [75], suggesting a complex and context-dependent modulation of the SOCE machinery during melanoma metastasis. Little is known about the precise molecular composition of SOCE in melanoma cells. In the same study, the authors reported that knockdown of Orai1 or STIM1 decreases SOCE by approximately 50% in metastatic melanoma cells. However, the knockdown decreases Orai1 and STIM1 protein by around 50%, which may imply that either Orai1 and STIM1 are sufficient to promote SOCE in those cells, or that Orai2 and Orai3 may participate too [75]. It is unclear whether the amplitude of SOCE correlates with metastatic potential [75,100]: one report described higher SOCE amplitude in metastatic melanoma cells compared to non-metastatic cells [75], while another found lower SOCE and CRAC current amplitude in highly invasive melanoma lines relative to non-invasive cells [100]. This discrepancy may be due to the differing cell line sets used in these two studies. If so, it would highlight the possible heterogeneity of melanoma cells, and therefore the challenge to identify the underlying mechanisms that regulate the pathophysiology of this disease. These discrepancies also extend to functional studies examining the role of SOCE in migration and invasion [75,98–100]. SOCE inhibition and STIM1 or Orai1 silencing impair cell migration *in vitro* and metastasis *in vivo* [75,99]. In contrast, UV exposure significantly reduces SOCE in melanoma cells, but resulted in increased cell migration [98]; pharmacological inhibition of SOCE by BTP2 enhanced melanoma cell invasion, and increasing SOCE with IA65 reduced invasion capacity [98].

5.2. Neuroblastoma

Neuroblastoma is a solid tumor that arises in the sympathetic nervous system and that is mostly localized in the adrenal gland [101]. It originates from NCCs, with high transcriptome homology with chromaffin cells and adrenal neuroblasts [102,103]. Neuroblastoma constitutes 7-8% of childhood malignancies and corresponds to approximately 15% of pediatric cancer deaths [104]. Approximately 40% of the patients are younger than 1 year at diagnosis [105]. Because of the heterogeneity of neuroblastoma, intensive work focused on cellular pathways responsible for disease progression, in order to identify future therapeutic targets. Among them, calcium signaling has been involved in neuroblastoma progression [106]. SOCE machinery transcripts and proteins have been detected in neuroblastoma cells [107–109]. The expression level of SOCE components appears to correlate with clinical prognosis and immune activity in neuroblastoma patients, suggesting their potential value as biomarkers [110]. Despite these observations, the precise functional composition of SOCE in neuroblastoma remains largely unknown, and additional studies are needed to define the respective contributions of Orai channels and STIM proteins in this cancer type. Currently, only a limited number of studies have examined SOCE activation in neuroblastoma. Cannabinoid receptor (CB1R) stimulation and extracellular Ca^{2+} activation of the Calcium-Sensing Receptor (CaSR) both trigger SOCE in neuroblastoma cells; however, the signaling pathways involved and the physiological consequences are not yet elucidated [111]. In SH-SY5Y cells, muscarinic acetylcholine receptor (mAChR) activation induces a STIM1-dependent SOCE response that enhances glucose uptake, indicating a plausible role of SOCE in metabolic regulation [112,113]. This involvement in metabolism aligns with observations in other cell types [28]. SOCE also appears to contribute to neuroblastoma cell survival. In particular, SOCE activation improves cell viability in cells exposed to cadmium [114], supporting the broader idea that SOCE participates in pro-survival pathways, as documented in several other cancers [115,116].

5.3. Pheochromocytoma

Pheochromocytoma is a rare neuroendocrine tumor originating from chromaffin cells of the adrenal medulla and is characterized by excessive production and secretion of catecholamines [117]. Most patients carry

germline or somatic mutations that categorize tumors into three major molecular clusters based on their genetic signatures [118]. Tumors from cluster 1 (pseudohypoxia pathway related tumors) show a very high metastatic risk, whereas those from cluster 2 (kinase signaling pathways related tumors) are associated with a much lower metastatic risk [118–120]. Cluster 3 (Wnt signaling pathway related tumors) tumors display aggressive features and a high probability of metastasis [121–123]. Current therapeutic options do not provide a definitive cure, and five-year survival in metastatic cases remains around 60% [124, 125]. High protein expression of STIM1, STIM2, and Orai1 has been observed in PC12 pheochromocytoma cells [126]. Co-immunoprecipitation experiments further demonstrated a physical interaction between STIM1 and Orai1 following thapsigargin treatment, indicating plausible "classical" SOCE mechanism in this cell line [126]. Functional studies show that STIM1 silencing reduces SOCE by approximately 66% in PC12 cells [127]. Currently, the respective contributions of Orai isoforms and STIM2 to SOCE in pheochromocytoma remain unknown and require further investigation. Several studies implicate SOCE in Ca^{2+}-overload–induced cell death in pheochromocytoma. Pharmacological inhibition of SOCE with SKF-96365, a non-specific SOCE blocker, protects PC12 cells from the neurotoxin MPP^{+}-induced toxicity [128,129]. Similarly, family with sequence similarity 3 (FAM3A) overexpression decreases SOCE and confers resistance to glutamate-induced apoptosis [126]. In addition, 6-hydroxydopamine (6-OHDA) triggers ROS-mediated toxicity through a STIM1- and Orai1-dependent mechanism [130].

5.4. Charcot-Marie-Tooth (CMT)

Charcot-Marie-Tooth (CMT) constitutes the most prevalent category of inherited neuropathy and neuromuscular disorder with a prevalence of 1:2500 [131]. It is defined by the demyelination and/or length-dependent axonal degeneration of the motor or sensory peripheral nerves [132]. Clinical symptoms arise usually in early adulthood, although it varies considerably between patients [132,133]. The advancing neurodegeneration causes progressive weakness and wasting of the distal limb muscles leading to motor impairment, sensory loss and skeletal deformities of the hands and feet [134,135]. There is a wide variety of genes associated with CMT, reflecting the heterogeneity of the disease [136]. Among them, *PMP22, GJB1, MPZ and MFN2* are mutated in more than 90% of CMT cases [137]. No studies have investigated the expression of SOCE machinery components in the context of CMT syndrome, and only a few reports have examined SOCE itself in relation to this disorder. Even if the molecular composition of SOCE in CMT-deficient neurons remains unknown, mutations in Ganglioside-Induced Differentiation-Associated Protein 1 (GDAP1), a protein involved in mitochondrial trafficking and implicated in several forms of CMT, have been shown to significantly reduce SOCE in multiple studies [138–141]. The prevailing hypothesis is that reduced mitochondrial presence within plasma membrane SOCE nanodomains decreases the ability of mitochondria to buffer Ca^{2+} entering through CRAC channels, thereby enhancing slow Ca^{2+}-dependent inactivation. These findings suggest that reduced SOCE may contribute to CMT progression, potentially by altering neuronal metabolism [139]. By contrast, PMP22, which is overexpressed in CMT enhances CRAC current in Schwann cells [82]. Further work is required to clarify the role of SOCE in CMT and to assess the therapeutic potential of pharmacological strategies aimed at enhancing SOCE.

6. Future directions

Despite increasing evidence supporting the importance of Ca^{2+} signaling in NCC-derived cells, major gaps remain regarding the precise contribution of SOCE during NCC development and in neurocristopathies. To date, no study has directly characterized the molecular composition or physiological role of SOCE in NCCs themselves. One of the major priorities for the field will therefore be to determine whether NCCs express SOCE machinery component and if it relies predominantly on Orai1/STIM1 or whether alternative SOCE components, including Orai2, Orai3, STIM2, or additional regulatory proteins, contribute to Ca^{2+} influx depending on developmental stage or lineage specification. Recent advances in genetically encoded Ca^{2+} indicators and high-resolution live imaging now provide powerful opportunities to study Ca^{2+} dynamics *in vivo* during embryogenesis. Combining these approaches with conditional knockout mouse models, lineage tracing strategies, and single-cell transcriptomic analyses should allow the identification of SOCE-dependent signaling programs during embryo development.

Another important challenge will be to define if SOCE participates in the distinct phases of NCC biology, including epithelial-to-mesenchymal transition (EMT), migration, proliferation, and lineage differentiation. Given the established roles of SOCE in cytoskeletal remodeling, cell migration, transcriptional regulation, and cell proliferation, it is reasonable to hypothesize that SOCE contributes to multiple aspects of NCC physiology. However, direct evidence supporting such a role is currently lacking. Interestingly, genetic ablation of Orai1 or STIM1 in mice often results in perinatal lethality, although the precise cause of death remains unclear [142]. Defective skeletal muscle development has been proposed as a contributing factor [143]. In contrast, viable mice and patients carrying loss-of-function mutations in ORAI1 or STIM1 display a relatively restricted spectrum of phenotypes, including severe immunodeficiency [144], myopathy [143], thrombocytopenia [145], and ectodermal dysplasia [77]. Considering the widespread expression of SOCE machinery across tissues, it is striking that disruption of ORAI1/STIM1 signaling does not produce a broader range of developmental abnormalities. This observation suggests either that SOCE is dispensable in certain cell types under physiological conditions, or that alternative store-operated and/or non-store-operated Ca^{2+} entry pathways can compensate for the loss of canonical ORAI1/STIM1-mediated SOCE [142]. Whether NCCs and NCC derivatives rely on such compensatory mechanisms remains unknown and represents an important question for future investigation.

Future studies should focus on defining the molecular composition and physiological functions of SOCE across the diverse range of NCC derivatives. Although Orai1 and STIM1 appear to constitute the predominant SOCE machinery in melanocytes, astrocytes, odontoblasts, and possibly other NCC derivatives, the respective contributions of Orai2, Orai3, and STIM2 remain largely unexplored. A systematic characterization of SOCE component expression at both the transcriptomic and proteomic levels, combined with electrophysiological and Ca^{2+} imaging approaches, will be required to determine whether distinct NCC derivatives rely on common or cell-specific SOCE complexes. Beyond the identification of SOCE components, future work should investigate the downstream signaling pathways controlled by SOCE in NCC-derived cells. Current evidence suggests roles for SOCE in cell survival, proliferation, migration, pigmentation, dentin mineralization and cell differentiation (Table 1). However, the molecular mechanisms linking SOCE to these processes remain poorly understood. Identifying the signaling networks activated downstream of SOCE, including transcriptional, metabolic, and cytoskeletal pathways, will be essential to understand how SOCE contributes to the specialized functions of NCC derivatives. Another major challenge will be to characterize SOCE in NCC-derived cell populations that remain almost completely unexplored, including conotruncal cardiac cells, pharyngeal arch derivatives, facial dermal fibroblasts, cranial chondrocytes and osteoblasts, and enteric glial cells. Given the broad conservation of SOCE signaling observed in other NCC-derived lineages, it is plausible that similar mechanisms operate in these cells. Determining whether SOCE regulates their development, differentiation, and physiological functions could provide important insights into the cellular basis of neurocristopathies.

Another promising direction concerns the relationship between

SOCE and neurocristopathies. Current evidence mainly focuses on NCC-derived cancers such as melanoma, neuroblastoma, and pheochromocytoma, whereas the contribution of SOCE to developmental neurocristopathies remains largely unexplored (Table 2). Investigating SOCE signaling in disorders such as Charcot–Marie–Tooth disease, Hirschsprung disease or craniofacial malformations, could provide new mechanistic insights into disease pathogenesis and identify novel therapeutic targets. Finally, the growing development of pharmacological modulators targeting SOCE raises important translational perspectives. Several Orai channels inhibitors are currently under preclinical or clinical evaluation in inflammatory diseases and cancer (clinical trial numbers: NCT00006486, NCT00005045, NCT00003869, NCT00019461, NCT00019019, NCT00004146, NCT03401190, NCT02958982, NCT03119467). Better characterization of SOCE function in NCC derivatives may therefore open new therapeutic opportunities not only for NCC-derived cancers but also for congenital neurocristopathies and regenerative medicine applications.

7. Conclusion

During the last decades, SOCE has emerged as a key Ca^{2+} signaling pathway in diverse cell types, yet its contribution during embryogenesis, particularly in the NCCs, remains poorly defined. Here, we summarized the current knowledge regarding the contribution of SOCE in NCCs and its derivatives. Although no direct data currently exist regarding SOCE in NCCs themselves, studies performed in neural stem cells and NCC-derivatives strongly suggest that SOCE is likely to participate in early NCC proliferation, viability, and lineage specification. In NCC-derivatives, SOCE appears to exert cell type-specific functions, including melanin production and dentin mineralization, highlighting its functional versatility. At the molecular level, most studies have focused on Orai1 and STIM1, which are likely to be the predominant mediators of SOCE in NCC-derived cells, consistent with their roles in other systems. However, the potential contribution of Orai2, Orai3 and STIM2 remain underexplored, and the precise composition of SOCE in NCC and their derivatives has not yet been clearly defined.

In the context of neurocristopathies, the involvement of SOCE is still insufficiently characterized. Existing data are largely limited to NCC-derived cancers, such as melanoma, neuroblastoma and pheochromocytoma, in which SOCE regulates cell proliferation, cell death and metastasis. Additional studies are needed to thoroughly characterize the participation of SOCE and the Ca^{2+} signaling network in neurocristopathies, especially during embryogenesis. Thus, identifying the molecular composition, dynamics, and functions of SOCE in NCCs themselves represents one of the next critical steps to understand both NCCs biology, and the involvement of Ca^{2+} signaling in neurocristopathies.

CRediT authorship contribution statement

Olivier Romito: Writing – review & editing, Conceptualization. **Nicolas R. Chevalier:** Writing – review & editing, Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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