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Review

Role of Store-Operated Ca^{2+} Entry in the Pulmonary Vascular Remodeling Occurring in Pulmonary Arterial Hypertension

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Abstract: Pulmonary arterial hypertension (PAH) is a severe and multifactorial disease. PAH pathogenesis mostly involves pulmonary arterial endothelial and pulmonary arterial smooth muscle cell (PASMC) dysfunction, leading to alterations in pulmonary arterial tone and distal pulmonary vessel obstruction and remodeling. Unfortunately, current PAH therapies are not curative, and therapeutic approaches mostly target endothelial dysfunction, while PASMC dysfunction is under investigation. In PAH, modifications in intracellular Ca^{2+} homoeostasis could partly explain PASMC dysfunction. One of the most crucial actors regulating Ca^{2+} homeostasis is store-operated Ca^{2+} channels, which mediate store-operated Ca^{2+} entry (SOCE). This review focuses on the main actors of SOCE in human and experimental PASMC, their contribution to PAH pathogenesis, and their therapeutic potential in PAH.

Keywords: PAH; Ca^{2+} signaling; Orai; STIM; TRPC; IP_3R; RyR

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1. Overview of SOCE

In mammals, the modulation of intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) constitutes a signal transduction mechanism for all cell types, regulating a large range of cellular functions, including contraction, proliferation, migration, gene transcription, metabolism, death, and apoptosis [1–3]. Intracellular Ca^{2+} signals are generated by Ca^{2+} release from the internal stores and/or by Ca^{2+} entry from the extracellular compartment through Ca^{2+} channels.

One of the major Ca^{2+} channels located in the plasma membrane (PM) is store-operated Ca^{2+} channels (SOCs), which produce store-operated Ca^{2+} entry (SOCE). The principle of SOCE was first described by Putney in 1986 [4] in non-excitable cells, where he found that extracellular Ca^{2+} influx was coupled to endoplasmic reticulum (ER) Ca^{2+} depletion, and then SOCE could be pumped into the ER by sarcoplasmic/endoplasmic reticulum Ca^{2+-}ATPase (SERCA) to restore ER Ca^{2+} homoeostasis. A few years later, in mast cells, Hoth and Penner provided proof that SOCE is partly mediated by Ca^{2+} currents called Ca^{2+} release-activated Ca^{2+} (CRAC) currents (I_{CRAC}) [5]. I_{CRAC} is a non-voltage-activated Ca^{2+} inward current with strong inward rectification, a positive reverse potential, and a high selectivity for Ca^{2+} ions [5]. I_{CRAC} is regulated through negative feedback that prevents excessive Ca^{2+} influx called Ca^{2+}-dependent inactivation (CDI) [5,6]. CDI is composed of fast CDI and slow CDI.

Over the past several years, evidence from a large variety of cell types has demonstrated the existence of SOCE, and its involvement in cellular processes makes it a potential target for many diseases [7]. For two decades, the molecular identity of SOCs has been unknown. However, the advent of molecular biology techniques has made it possible to identify the molecules responsible for SOCE. In 2005–2006, two major ubiquitous SOCE actors were identified: the stromal interacting molecule (STIM) [8,9] and the Ca^{2+} channel Orai activated by STIM [10]. Additionally, in several cell types, in addition to Orai Ca^{2+} channel activation, STIM molecules activate transient receptor potential canonical channels (TRPCs), which are nonselective cation channels permeable to Ca^{2+}.

1.1. STIM1

The link between ER Ca^{2+} depletion and Ca^{2+} entry was resolved with the discovery of STIM1 [8,9]. STIM1, a single pass transmembrane protein predominantly located in the ER, is able to sense luminal [Ca^{2+}] and activate Orai and TRPC channels.

STIM1 is constituted by a luminal N-terminal part, which notably contains a Ca^{2+}-binding EF hand domain that is able to sense the variation in the ER Ca^{2+} concentration ($[Ca^{2+}]_{ER}$) [11–14] (Figure 1). This EF hand domain forms with the sterile alpha motif (SAM) of the EF–SAM domain, which oligomerizes after ER Ca^{2+} depletion [12,15,16].

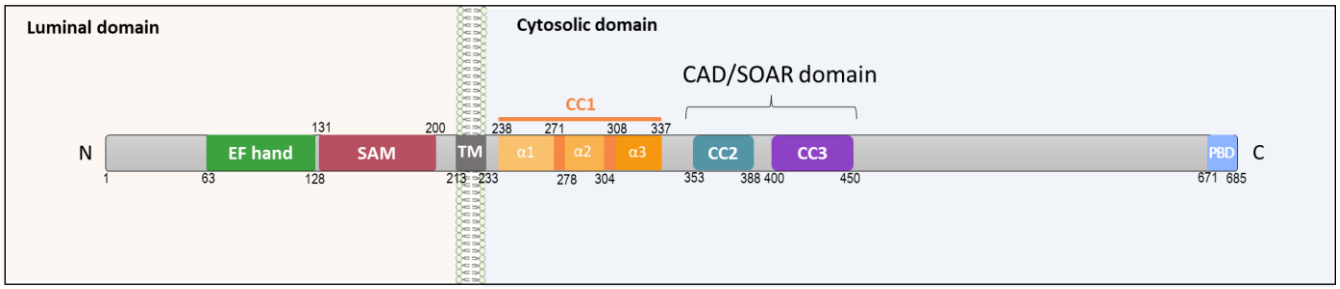

Figure 1. Topology and key domain organization of STIM1. A STIM1 monomer consists of an N-terminal luminal part, a transmembrane domain and a C-terminal cytosolic part. CC, coiled-coil; CAD, CRAC activation domain or SOAR, STIM–Orai activation region; EF hand, helix-loop structural domain; PBD, polybasic domain; SAM, sterile alpha motif; TM, transmembrane domain. Numbers correspond to the location of amino acid.

This luminal part is followed by a transmembrane segment (TM), potentially involved in the conformational change in STIM upon ER Ca^{2+} depletion [17]. The cytosolic part of STIM1 is composed of three coiled-coil parts (CC1, CC2, and CC3) (Figure 1). The structural interplay between these three CC domains is necessary for the elongation of STIM1 during its activation [18–20]. CC2 and CC3 domains are part of the STIM1–Orai1-activating region (SOAR) [21–23], also called CAD for CRAC-activating domain, and are necessary for coupling with Orai1 protein and for Orai1 activation [18,24]. SOAR is followed by a positively charged polylysine domain, which allows STIM1–TRPC electrostatic interaction [25]. The COOH cytosolic part ends in a polybasic domain (PBD), a domain required for the accumulation of STIM1 into puncta at the ER–PM junction by interaction of PBD with negatively charged phospholipids in the PM [22,26,27]. The STIM family is also composed of STIM2, which has high sequence homology with STIM1 with some differences at the N- and C-terminal parts [11]. STIM2 is more sensitive to $[Ca^{2+}]_{ER}$ changes due to its lower affinity for Ca^{2+} and needs a lower level of store depletion than STIM1 for its activation [28,29]. Here, we only described the mechanism of action of SOCE by STIM1 because it is better characterized than STIM2.

Over the years, few additional variants have been found for STIM1 and STIM2. STIM1 long (STIM1L) was described as the product of alternative splicing of exon 11. STIM1L forms permanent clusters that colocalize with Orai1 through an interaction between STIM1L and actin fibers via the additional actin-binding domain (not present in classical STIM1). Most likely, due to its preactivated form STIM1L, it has faster activation than STIM1

associated with rapid activation of SOCE, as demonstrated in skeletal muscle cells [30]. A neuron-specific splice variant called STIM1B was also found, which is specifically localized in the presynaptic ER, explained by a targeting motif added through splice insertion in the cytosolic region of STIM1. STIM1B slowly activates SOCE and reduces Ca^{2+}-dependent inactivation of I_{CRAC} [31]. For STIM2 variants, there are STIM2.1 (or STIM2β) and STIM2.3, considering that the classical STIM2 (known to activate SOCE) is called STIM2.2 or STIM2α. STIM2.1 is known to negatively regulate SOCE, probably through a sequence-specific allosteric interaction with Orai1 [32,33].

1.2. Orai Channels

In 2006, Feske et al. described the absence of I_{CRAC} on T cells isolated from patients with severe combined immune deficiency (SCID) syndrome [34]. This loss of I_{CRAC} was independent of Ca^{2+} stores or the expression of several genes implicated in the control of Ca^{2+} entry in lymphocytes (*KCNA3*/Kv1.3, *KCNN4*/IKCa1, *TRPC1*, *TRPC3*, *TRPV6*, *STIM1*). By sequencing genomic DNA from SCID patients, they identified loss-of-function mutations in *ORAI1*, identifying Orai1 as an essential archetype of the CRAC current [10]. At the same time, by genome-wide RNA interference screening in Drosophila S2 cells, Zhang et al. confirmed that *olf186-F* (named Orai1) was the main channel of I_{crac} [35], which was subsequently confirmed by further studies [36–38].

The Orai1 channel presents a hexameric structure, as defined by the crystal structure of *Drosphilia melanogaster* Orai [39]. This architecture is formed by six Orai1 subunits coming from three dimers (Figure 2). Each of them contains an assembly of four transmembrane α-helices (TM1-TM4). This arrangement is made around a central point: the ion pore, with the 6 M1 subunits lining the ionic pore. The N- and C-termini are in the cytosol and contain the binding sites for the STIM protein, notably with the extended transmembrane Orai1 N-terminal (ETON) region. The ETON region mediates the interaction with the SOAR of STIM1 [40].

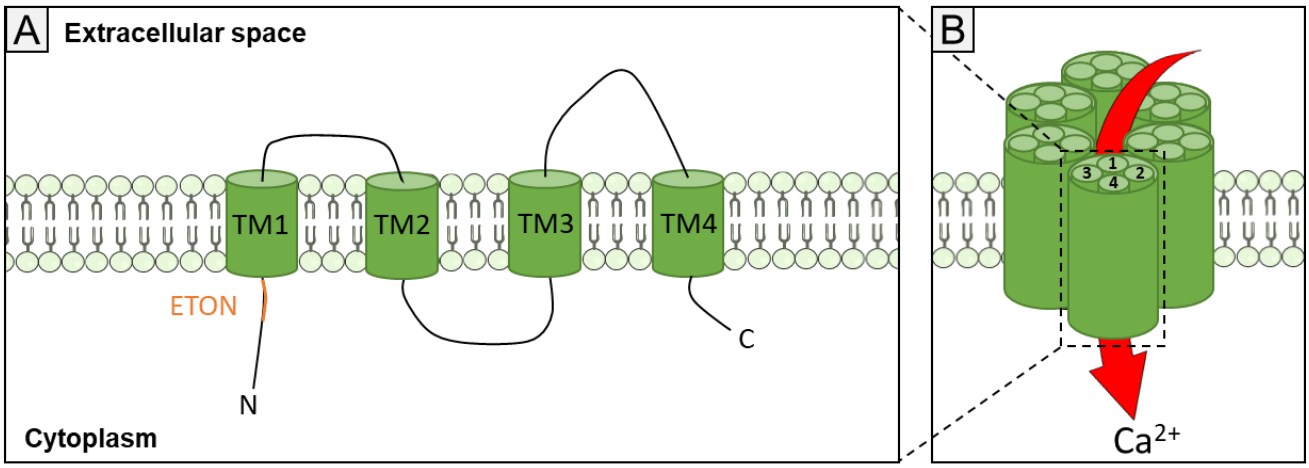

Figure 2. Orai1 topology and key domain for interaction with STIM1. (**A**) The Orai1 monomer consists of an ETON domain in the N-terminal part, four transmembrane domains (TM1-TM4) and a C-terminal domain. ETON, extended transmembrane Orai1 N-terminal. (**B**) Schematic assembly of Orai1 subunits as a hexamer.

The Orai family consists of three members: Orai1, Orai2, and Orai3. All three members are widely expressed in humans [41] and can constitute functional CRAC channels [14,42,43]. Co-expression of STIM1 and Orai2 or Orai3 induced Ca^{2+} currents similar to those of Orai1-induced I_{CRAC}, with small differences in selectivity and inactivation. Regarding selectivity, monovalent cations, such as Na^{+}, permeate better in Orai3 than in Orai1 and Orai2 [44]. Regarding Orai inactivation, Orai2, and especially Orai3, have higher levels of fast CDI, and Orai2 does not have slow CDI [44,45].

In humans, Orai1 has two isoforms: the longer-form Orai1α, of approximately 33 kDa, and the shorter-form Orai1β, of approximately 23 kDa, resulting from an alternative translation initiation site [46]. Both isoforms can support SOCE [47].

1.3. TRPC Channels

TRPC channels are part of the transient receptor potential (TRP) channels, a family of cationic nonselective channels (Ca^{2+}, Na^{+}, K^{+}). This group of channels is subdivided into seven distinct subfamilies according to their sequence homology [48,49]: TRPC (canonical), TRPV (vanilloid), TRPM (melastin), TRPA (ankyrin), TRPP (polycystin), TRPML (mucolipin), and TRPN (*drosophilia* no mechanoreceptor potential C (NOMPC)). Except for TRPM4 and TRPM5, all TRP channels are cationic channels permeable to Ca^{2+} [50]. In the present review, we only focused on TRPC channels because evidence from the literature indicated that TRPC channels are involved in SOCE.

The TRPC family can be divided into four subgroups: TRPC1; TRPC3, -C6, -C7; TRPC4, -C5; and TRPC2, which is a pseudogene in humans [51]. TRPC channels are mostly Ca^{2+}- and Na^{+}-selective, except TRPC2, which is cation-nonselective [52].

Structurally, TRPC channels are relatively analogous [53,54]. They can form heterotetramers or homotetramers. Each TRPC channel consists of at least six transmembrane domains with an ionic pore formed between TM5 and TM6 (Figure 3). On the N-terminal cytosolic domain, there are four to five ankyrin repeats, leading to protein–protein interactions [55,56]. On the C-terminal side, the TRP domain, a well-conserved region in all TRPCs, is essential for channel gating [54], followed by the calmodulin (CaM)/inositol 1,4,5-trisphosphate receptor-binding (CIRB) site, with CaM binding in a Ca^{2+}-dependent manner [51,57,58]. Interestingly, incorrect trafficking of TRPC3 was observed when the CIRB region was deleted [59].

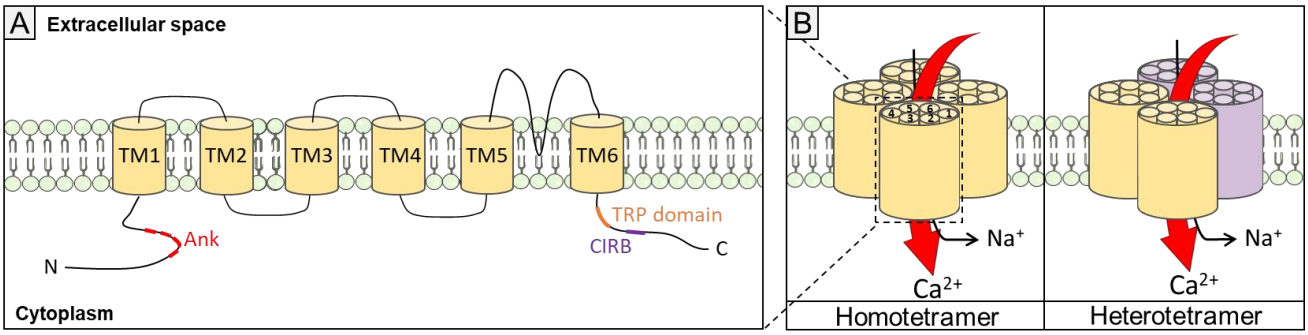

Figure 3. General topology and key domains of TRPC channels. (**A**) The TRPC subunit contains four to five ankyrin-like repeats on the N-terminal side, six transmembrane domains (TM1-TM6), a TRP domain and a CIRB domain on the C-terminal side. Ank, ankyrin-like repeats; CIRB, calmodulin–IP3R binding site. (**B**) Schematic assembly of TRPC subunits as a homotetramer or heterotetramer.

TRPC channels are reported to contribute to both SOCE and receptor-activated Ca^{2+} entry pathways (ROCE). As described below, several studies have demonstrated TRPC channel activation following ER Ca^{2+} depletion.

TRPC1 was first reported to have a role in SOCE from studies using the expression of the splice variant of TRPC1, so-called TRPC1A, in heterologous cell system expression [60] or the expression of a full-length cDNA of human TRPC1 in COS (fibroblast-like cell lines derived from monkey kidney tissue) cells [61]. The role of TRPC1 was confirmed through studies using different approaches (RNA interference, dominant-negative overexpression) in human submandibular gland cell lines [62], endothelial cells [63], human myoblasts and myotubes [64–66], and platelets [67]. Further evidence was provided by studies on *trpc1*$^{-/-}$ mice that showed reduced SOCE in different tissues (salivar gland, pancreatic acinar cells, and aortic endothelial cells) [68–70].

TRPC3 was found to be activated by depletion of Ca^{2+} stores in DT40 chicken B lymphocytes [71]. Selective suppression of TRPC3 protein by small interfering RNA (siRNA) showed TRPC3-mediated SOCE in H19-7 hippocampal neuronal cells [72] and human umbilical vein endothelial cells [73]. When TRPC3 is expressed at low levels in HEK293 cells, the TRPC3 current is inhibited in cells treated with siRNA against STIM1, showing the regulation of TRPC3 by STIM1 [74]. Salivary glands and pancreatic cells isolated from *trpc3*$^{-/-}$ mice and cells treated with a TRPC3 inhibitor exhibit reduced SOCE [75,76]. The regulatory mechanism of TRPC3 appears to be determined by its expression level [71].

TRPC4 has been shown to be activated by Ca^{2+} store depletion in HEK293 cells [74] and *Xenopus laevis* oocytes [77]. Other evidence has been obtained notably by siRNA strategy in human myoblasts and myotubes [64,65], human adrenal cells [78], human corneal endothelial cells [79], human gingival keratinocytes [80], neonatal rat ventricular cardiomyocytes [81] or human and mouse endothelial cells [82]. TRPC4 implication in SOCE has also been shown in neonatal rat ventricular cardiomyocytes by a dominant-negative strategy [81]. In addition, aortic and lung endothelial cells from *trpc4*$^{-/-}$ mice showed reduced SOCE [83,84].

Few studies report the implication of TRPC5 in SOCE, although it was found in smooth muscle cells isolated from rabbit pial arterioles [85] and in neonatal rat ventricular myocytes [81,86].

Regarding TRPC6, several studies have shown that it is also able to drive SOCE. This was shown by siRNA in a leukemic granulocyte cell line [87], antibody inhibition in human platelets [88–90], or overexpression and knockdown by short hairpin RNA (shRNA) in hepatoma cells [91]. On the other hand, in HEK293 cells co-transfected with STIM1 and TRPC6, STIM1 does not influence the TRPC6-induced current [92], except when TRPC6 is expressed at low levels [74].

TRPC7 is not regulated by STIM1 or Orai1, and it was proposed that TRPC7 is activated by a mechanism independent of store depletion [93].

It is also known that some TRPC channels can be directly activated by the phospholipase C (PLC) pathway, notably with the PI(4,5)P2 degradation product diacylglycerol (DAG), by the G protein coupled receptor, protein kinase C (PKC) pathway, or even membrane stretching [73,94,95], resulting in receptor-operated Ca^{2+} entry (ROCE) instead of SOCE.

However, due to their electrophysiological characteristics (Table 1), TRPC channels are not able to produce I_{CRAC}. Indeed, TRPC channels form nonselective Ca^{2+}-permeable channels that do not exhibit the electrophysiological identity of I_{CRAC} (Figure 4A). However, almost all TRPC channels are activated in response to ER–SR Ca^{2+} depletion, with the formation of a nonselective current with a reverse potential close to 0 mV, called I_{SOC} (Figure 4B).

Table 1. TRPC channels properties.

Channel	Selectivity P_{Ca}/P_{Na}	Conductance (pS)	Activation Mechanism	References
TRPC1	1	16	Store depletion, GPCR–PLC pathway, membrane stretching,	[60,95,96]
TRPC2	2.7	42	DAG	[97]
TRPC3	1.6	66	DAG, store depletion, PKC phosphorylation, membrane stretching	[73,94,98–100]
TRPC4	1.1–7.7	42	Store depletion, GPCR–PLC pathway	[101–103]
TRPC5	1.8–9.5	63	Store depletion, GPCR–PLC pathway	[101,103,104]
TRPC6	5	35	DAG, membrane stretching	[77,97,105]
TRPC7	1.9	25–50	DAG, store depletion	[50,94,106]

DAG, diacylglycerol; GPCR, G-protein coupled receptor; P_{Ca}/P_{Na}, permeability ratio between Ca^{2+} and Na^{+}; PKC, protein kinase C; PLC, phospholipase C.

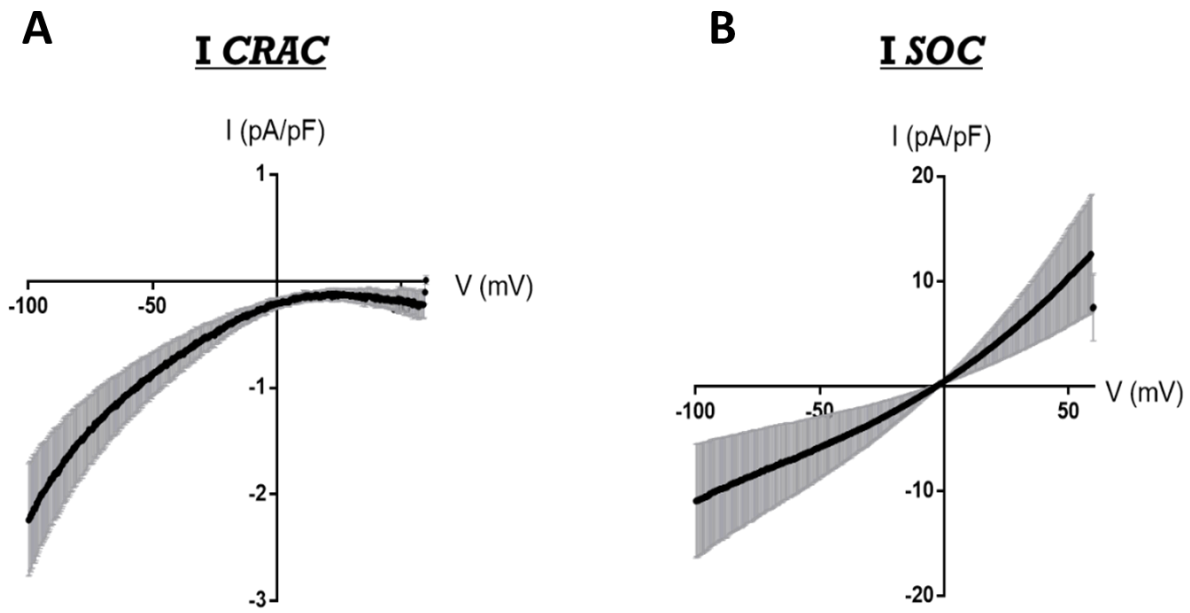

Figure 4. Comparison between ICRAC and ISOC in HEK cells transfected with STIM1 + Orai1. Cells were transfected with Orai1 and STIM1 plasmids 24 h before electrophysiological recordings. (**A**) Representative I_{CRAC} produced by STIM1+Orai1, inward rectifier current with almost no inward potential. In more than 60% of cells displaying I_{CRAC}. (**B**) Representative I_{SOC} produced by mixing STIM1+Orai1 and endogenous TRPC channels (linear current with inward potential close to 0 mV). In almost 40% of cells displaying I_{SOC}. Patch-clamp recordings were performed in whole-cell mode using electrodes of resistance between 2.5–3 MΩ. The pipette solution contained (in mM) 130 caesium methansulfonate, 8 MgCl2, 10 HEPES, 10 BAPTA, and 0.001 thapsigargin, pH 7.2 (CsOH). Extracellular solution contained (in mM): 135 NaCl, 10 CsCl, 4.4 MgCl2, 2.8 KCl, 10 Hepes, 0.5 EDTA, 0.5 EGTA, 10 glucose, and 11 CaCl2, pH 7.4 (NaOH). After measuring the maximal current amplitude, 10 μM Gd^{3+} was added at the end of the recording to block the current and estimate the leak. Currents were recorded during a 1 s ramp of potentials ranging from −130 mV to +85 mV applied with low-pass filtering at 1 kHz.

1.4. SOCE Mechanism

The activation mechanisms leading to SOCE at the PM by STIM proteins are now better understood: one of the most physiological mechanisms inducing ER–SR Ca^{2+} store depletion is the activation of the PLC via G-protein coupled receptors, with inositol 1,4,5-triphosphate (IP3) generation and IP3 receptor (IP3R) activation [107,108]. In cells with furnished Ca^{2+} stores, STIM1 maintains an inactivated conformation and localizes throughout the ER–SR membrane. In this conformation, STIM1 is able to bind Ca^{2+} with his EF hand–SAM domain. This inactivated conformation of STIM1 prevents spontaneous activation since the CC1 domain is associated with CAD–SOAR [17,109,110].

After ER–SR Ca^{2+} depletion, the luminal side of STIM1 rearranges by oligomerization of the EF–SAM domain [12,15,16] (Figure 5). This association induces the modification of the TM domain, leading to the liberation of CAD–SOAR [20]. This conformational change leads to rapid oligomerization of STIM1 through the CC3 domain and, thus, translocation to the ER–PM junction [18,26,111]. After this oligomerization and translocation, STIM1 forms puncta in this region where Orai is also located. It was shown that one to two STIM1 channels could trap Orai1, but eight STIM1 channels for each Orai1 channel were required to optimally activate these channels [112]. STIM1 interacts and activates with the ETON domain of Orai1 via CAD–SOAR[97]. The Ca^{2+} stores of the ER–SR will then fill up through the activity of the SERCA pump located on the ER–SR membrane. I_{crac} is then regulated through the CDI.

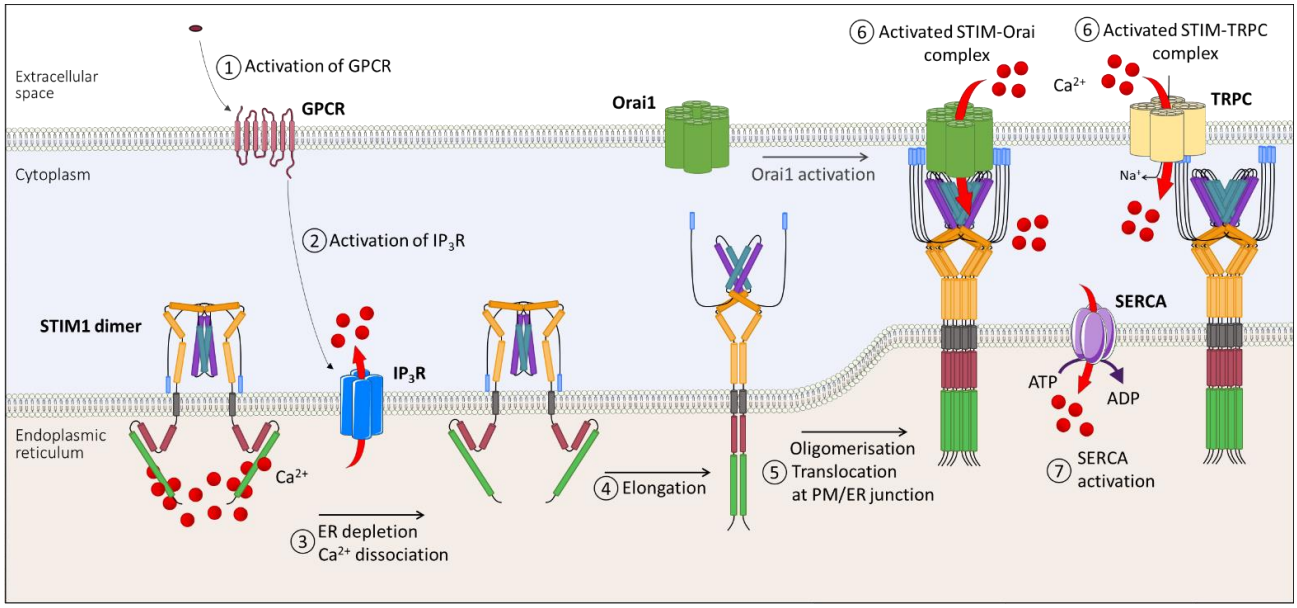

Figure 5. Activation mechanism of store-operated Ca^{2+} channels. Depletion of intraluminal Ca^{2+} concentration triggers Ca^{2+} dissociation of the EF hand of STIM1, allowing elongation and oligomerization of STIM1 at the ER–PM junction. This allows the interaction of STIM1 with Orai1 and/or TRPC channels, allowing Ca^{2+} entry into the cytoplasm. ADP, adenosine diphosphate; ATP, adenosine triphosphate; ER, endoplasmic reticulum; GPCR, G-protein coupled receptor; IP_3R, inositol 1,4,5-trisphosphate receptor; PM, plasma membrane; SERCA, sarcoplasmic/endoplasmic reticulum Ca^{2+-}ATPase; TRPC, transient receptor potential canonical channels.

It has been shown that STIM1 can regulate all TRPC channels, except TRPC7 [74]. STIM1 can bind TRPC1, -C4, and -C5 [74,113] via electrostatic interactions that exist between two positively charged lysins (^{684}KK^{685}) on STIM1 and two negatively charged conserved aspartates (^{639}DD^{640}) on TRPC1 [25]. Such electrostatic interactions also seem to occur with TRPC4 and TRPC5 [114]. Alternatively, STIM1 can regulate TRPC3 and TRPC6 indirectly through heteromultimerisation of TRPC1 with TRPC3 and TRPC4 with TRPC6 [74]. Furthermore, it has been demonstrated that local Ca^{2+} entry via Orai1 channels can regulate plasma membrane recruitment of TRPC1 [115]. TRPC1-containing vesicles can be detected in the region of the subplasma membrane in the immediate vicinity of the ER–PM region where Orai1 and STIM1 aggregate upon Ca^{2+} depletion. Recruitment of TRPC1 for clustering with STIM1 in the ER–PM junction occurs by trafficking via fast recycling endosomes [116]. Despite these studies and putative models, the precise mechanism of TRPC channel contributions in SOCE remains to be elucidated.

In addition to SOCE, activation of PLC-coupled receptors can activate the store-independent Ca^{2+} entry (SICE) pathway. The SICE pathway is performed through arachidonic acid-regulated Ca^{2+}-selective (ARC) [83,117] and leukotriene C_4 (LTC_4)-regulated Ca^{2+} (LRC) [118]. These channels are composed of both Orai1 and Orai3 subunits [119,120] and can be regulated by a pool of STIM1 at the PM [119,121], notably through the interaction of STIM1 with Orai3 [122].

2. SOCE in PAH

2.1. Pulmonary Arterial Hypertension

Pulmonary arterial hypertension (PAH) is a progressive and devastating disorder due to a progressive obstruction of distal pulmonary arteries (PA) (<500 µm in diameter), resulting in an elevation of pulmonary arterial pressure and progressive right heart dysfunction [123]. Recently, PAH was proposed to be defined by a mean pulmonary arterial pressure (mPAP) higher than 20 mmHg (compared to a normal PAPm, a rest of 14 ± 3 mmHg), a pulmonary vascular resistance higher than 3 woods units and a pulmonary arterial wedge pressure lower than 15 mmHg [124,125].

PAH is clinically classified, not according to clinical manifestations but according to etiology. One of the most commonly diagnosed groups is idiopathic PAH (iPAH), which includes patients with no identified causative factor. PAH can also be heritable, induced by drugs and toxins, or associated with other diseases [125]. The classification also includes a subgroup for long-term responders to Ca^{2+} channel blockers, another one for PAH with overt features of venous capillary (pulmonary veno-occlusive disease or pulmonary capillary haemangiomatosis) involvement and a last one for persistent PH of the new-born syndrome [124].

PAH is characterized by an increase in pulmonary vascular resistance explained by endothelial dysfunction, excessive proliferation of pulmonary arterial smooth muscle cell (PASMC) and endothelial cell (PAEC), PA vasoconstriction, and in situ thrombosis [123]. PAEC dysfunction in PAH is mostly targeted by the existing three current therapies. The three main treatments target the prostacyclin pathway with prostacyclin analogues, the endothelin-1 (ET-1) pathway with ET-1 receptor antagonist and the nitric oxide (NO) pathway with PDE5 inhibitors or guanylate cyclase stimulators [126]. However, these treatments cannot cure PAH, and lung transplantation is still necessary for the most severe patients. As the prognosis remains poor with a 5-year survival rate of approximately 60%, there is a need for innovative treatments to target pulmonary vascular remodeling [127,128].

SOCs are ubiquitous, and their role in PAEC dysfunction and right ventricular (RV) failure occurring in PAH should be studied with interest. Indeed, SOCs contribute to systemic PAEC proliferation and migration [73,129] and right ventricular Ca^{2+} handling remodeling in experimental PH models [130,131].

Moreover, PASMC dysfunction is not directly targeted by current PAH therapies. Therefore, we focused this review on the role of SOCE in PASMC dysfunction. PASMC dysfunction is characterized by excessive proliferation, apoptosis resistance, abnormal migration, and vasoconstriction [123,132], which strongly contribute to pulmonary artery remodeling. Since an increase in PASMC $[Ca^{2+}]_i$ is a key trigger of these biological processes, resulting in pulmonary vascular remodeling. SOC modification could act on pulmonary remodeling in PAH and, thus, emerge as a potential additional therapeutic target in PAH.

The understanding of PAH pathogenesis mainly emanates from an experimental model of PAH. Although they do not perfectly reproduce all the clinical parameters of PAH, they are considered PH animal models, mostly performed in rodents, with three main experimental procedures: monocrotaline (MCT), chronic hypoxia (CH), and Sugen 5416 hypoxia (SU/Hx).

2.2. Physiological Implication of SOCE in Control PASMC

The expression of Orai1/2/3 and STIM1/2 was detected in mouse, rat, and human PASMC (hPASMC) [133–135]. In hPASMC, Orai1 and STIM1/2 promotes SOCE [136,137]. In rodent PASMC, Orai1/2/3 and STIM1/2 promote SOCE [134,135,138–140]. Only TRPC1, -C3, -C4, and -C6 were expressed at the mRNA and protein levels in primary hPASMC cultures [141–146], while TRPC1, -C3, -C4, -C5, and -C6 were expressed in rodent PASMC (Table 2).

Table 2. TRPC channels expression in PASMC.

	TRPC1		TRPC3		TRPC4		TRPC5		TRPC6		References
Expression	**mRNA**	**Protein**	**mRNA**	**Protein**	**mRNA**	**Protein**	**mRNA**	**Protein**	**mRNA**	**Protein**	
Human	✓	✓	✓	✓	✓	✓	-	-	✓	✓	[141–146]
Rat	✓	✓	✓	✓	✓	✓	✓	-	✓	✓	[147–150]
Mouse	✓	✓	✓	-	✓	✓	-	-	✓	✓	[133,151–156]

-, no data available.

TRPC1 is overexpressed in proliferative control hPASMC in association with increased SOCE, indicating that TRPC1 contributes to SOCE in control hPASMC [143,157]. In systemic vascular smooth muscle cell (VSMC), caveolin-1 knockdown by siRNA induces a decrease

in TRPC1 expression accompanied by a reduction in SOCE [158]. Furthermore, in mouse PASMC, STIM1 and TRPC1 are functionally coupled and mediate SOCE [159].

The inhibition of TRPC1 by a specific antibody or by the nonselective SOCE inhibitor 2-aminoethyldiphenylbonirate (2-APB) significantly reduced ex vivo neointimal growth in human veins as well as SOCE and proliferation of cultured PASMC. These results highlight the involvement of TRPC1 in vascular remodeling occurring in arteriosclerosis and the protective potential of TRPC1 inhibitors against vascular disease [160].

STIM1 mediates the proliferation of primary human coronary artery SMC [161]. Moreover, the knockdown of STIM1 or Orai1 reduced SOCE and the migration of human saphenous VSMC. Alternatively, the overexpression of the negative form of TRPC5 reduced cell proliferation and cell migration [162]. In addition, an Orai1 blocker, Synta66 (S66), reduced PDGF-evoked human saphenous VSMC migration without a significant change in cell proliferation or viability.

In cultured rat aortic VSMC, Orai1 and STIM1 are overexpressed compared to freshly isolated VSMC, suggesting that these proteins enhance the VSMC proliferative phenotype [163]. STIM1, Orai1, and TRPC1 expression/function are crucial for angiotensin II- or urotensin II-induced rat VSMC proliferation [164,165].

Moreover, PASMCs have two phenotypes: a contractile phenotype, accessible in freshly isolated cells, and a proliferative and migratory phenotype, generally obtained in culture or pathological status. Treatment of rat proliferative PASMC with factors (transforming growth factor β (TGF-β) and heparin), favoring the differentiation of PASMC into a contractile phenotype, enhanced SOCE. Indeed, TGF-β decreased Orai1/2, STIM2, and TRPC6 expression, and heparin decreased Orai1/2/3, STIM1/2, and TRPC6 expression [135].

In rat aortic SMC, STIM1 or Orai1 knockdown reduces SOCE and migration, while the knockdown of Orai2 or STIM2 has no effect on SOCE, proliferation, and migration [163]. In cultured rat aortic SMC, STIM1–Orai1-mediated Ca^{2+} influx plays a key role in platelet-derived growth factor (PDGF)-induced migration, since siRNA knockdown inhibits PDGF-induced migration [166]. Moreover, enhancement of Orai1 function with IA65, a pharmacological activator, results in an increase in rat VSMC migration [167].

These results indicate that Orai1-induced SOCE contributes significantly to in vitro systemic VSMC migration and proliferation. We hypothesize that the SOCE archetype Orai1 could contribute to aberrant PASMC migration and proliferation phenotypes in PAH.

In rat coronary arteries, silencing of Orai1 or STIM1 prevents urotensin-II-induced vasoconstriction [165]. In mouse aortae, VSMC-specific knockout of the *stim1* gene impaired SOCE and reduced the phenylephrine-induced vasoconstrictive response [168]. Moreover, the overexpression of TRPC1 enhances rat PA vasoconstriction [142]. These results indicate that SOCE could contribute to VSMC contraction. Similar to systemic vessels, we hypothesize that SOCs contribute to PA contraction as well as PA vasoconstriction in PAH. However, the contribution of SOCs to the regulation of pulmonary arterial tone has yet to be understudied under physiological conditions and in the physiopathological condition of PAH. In systemic VSMC, SOCE seems to be constituted by STIM–Orai and the TRPC channel complex [169,170]. In addition to their role in SOCE, the Orai–TRPC complex has been demonstrated to also regulate Ca^{2+}-sensitive K^+ channels (KCa), contributing indirectly to the regulation of resting membrane potential. In isolated rat aortic SMC, TRPC1 forms a complex with the large conductance KCa (BK_{Ca}) that promotes Ca^{2+} entry through and then membrane hyperpolarization. This membrane hyperpolarization mediated by TRPC1–BK_{Ca} coupling could prevent excessive contraction of VSMC by reducing agonist-induced membrane depolarization [171].

2.3. Physiopathological Implication of SOCE in PAH PASMC

Several studies found an increase in SOCE in hPASMC isolated from iPAH patients, resulting in an increase in $[Ca^{2+}]_i$ [157,172]. Control hPASMC exposed to hypoxia (3% O_2 for 72 h) saw an increase in $[Ca^{2+}]_i$ associated with an increase in Orai1/2, STIM1/2, and TRPC6 protein levels [173]. The knockdown of HIF-1α in rat PASMC or HIF-1α deficiency

in mice (*hif-1α*$^{-/-}$) reduced the overexpression of Orai2 induced by hypoxia exposure (10% O_2, 21 days for mice or 4% O_2, 60 h for rat PASMC) [134]. As the increased expression of HIF-1α plays a key role in the pathogenesis of PAH [174–176], we hypothesized that HIF-1α overexpression in PAH promotes an increase in SOCE in iPAH PASMC.

An increase in STIM2 protein levels has been demonstrated in iPAH hPASMC compared with control PASMCs, while the STIM1 protein level remained unchanged. Using a siRNA strategy, they also found that the knockdown of STIM2 reduces SOCE and proliferation of iPAH hPASMC without any effect on control hPASMC [136]. In an additional study, they demonstrated that the transition of rat PASMCs from a contractile to proliferative phenotype was associated with enhanced SOCE due to increased expression of Orai2, STIM2, and TRPC6 [135]. Moreover, they demonstrated that nicotinamide phosphoribosyl transferase promotes pulmonary vascular remodeling in PAH and experimental PH, partly due to an overexpression of Orai2 and STIM2 protein levels leading to an increase in SOCE and in hPASMC proliferation [177].

SOCE increased in rat distal PASMCs exposed ex vivo to acute hypoxia (4% O_2) compared to rat proximal PASMC, in association with an increased expression of TRPC1 and STIM1 [178]. Another study also found increased expression of STIM1 in the distal PA of experimental PH in rats exposed to hypobaric chronic hypoxia CH (for 21 days) [140]. Additionally, in rat PASMC, it was demonstrated that the knockdown of STIM1 inhibited hypoxia-induced nuclear factor of activated T-cells (NFAT) cytoplasmic 3 (NFATc3) nuclear translocation and, thus, excessive PASMC proliferation [140]. In contrast to these studies, STIM1 expression was unchanged in rat distal PA and PASMC exposed to CH (10% O_2 for 21 days) [134]. In this study, the authors found increased expression of Orai1/2, while Orai3 remained stable. It was also reported in mouse PASMC exposed to acute hypoxia (95% N_2 and 5% CO_2) that there was an increase in TRPC1, Orai1, and STIM1 interaction to mediate increased SOCE [151].

STIM1 and Orai1 expression and function were increased in aortas from spontaneously hypertensive rats [179]. In an experimental obstructive sleep apnea model induced in rats by chronic intermittent hypoxia (CIH) (5% inspired O_2 for 20 s, followed by 280 s of room air, 12 times per hour for 8 h a day for 14 to 28 days), Castillo-Galán et al. showed the increased protein expression of Orai1, STIM1, and TRPC1, -C4, -C6 in the lungs of CIH rats [180]. Treatment of these rats with 2-APB decreased right ventricular systolic pressure (RVSP) and pulmonary vessel remodeling, which increased following CIH exposure [181].

In control hPASMC, platelet-derived growth factor (PDGF) application stimulated STIM1 and Orai1 overexpression through the AKT/mTOR signaling pathway, which led to an increase in SOCE [137]. As it is well recognized that PDGF is overproduced in PAH [182–184], this overproduction could explain why SOCE increased in iPAH hPASMC.

In experimental PH induced by CH exposure in mice, *trpc1*$^{-/-}$ + *trpc6*$^{-/-}$ double knockout protected mice against PH. In this experimental PH model, the deletion of *trpc1* and *trpc6* prevented pulmonary vessel remodeling after CH [152], demonstrating that TRPC1 and TRPC6 are essential for the development of PH under CH exposure in mice. In addition, Sun et al. showed that, in a CH-induced PH murine model (11% O_2 for 28 days), intratracheal in vivo administration of siRNA against TRPC1 attenuates pulmonary and RV arterial remodeling, with a significant reduction in right ventricular systolic pressure [185]. In vivo TRPC1-siRNA delivery also counteracts the increase in inflammatory biomarkers (TNF-α and MMP-9) in the lung and apoptotic biomarkers in the RV myocardium that was observed in a murine model of CH-induced PAH.

In PH rats induced by CH exposure, TRPC1 and -C6 expression was increased in isolated PA, which was accompanied by an increase in SOCE. In addition, nonselective pharmacological inhibition of SOCE by lanthanum (La^{3+}) and SKF-96365 normalizes elevated $[Ca^{2+}]_i$ in PASMC and vascular tone in PAs of CH–PH rats [145].

Another study found that TRPC1 mRNA levels were increased in murine PASMC under hypoxia exposure (1% O_2 for 72 h). In this study, hypoxia exposure enhanced the proliferation of PASMC, which was reduced by the knockdown of TRPC1 (siRNA approach).

The proliferation of PASMC isolated from *trpc1*$^{-/-}$ mice was also reduced compared to the proliferation of PASMC isolated from *trpc1*$^{+/+}$ mice. Furthermore, *trpc1*$^{-/-}$ mice developed partial protection against PH in response to CH compared to *trpc1*$^{+/+}$ mice exposed to CH. Both *trpc1*$^{+/+}$ and *trpc1*$^{-/-}$ mice exposed to CH present similar RV hypertrophy, while pulmonary vascular remodeling is attenuated in *trpc1*$^{-/-}$ mice [153].

Increased TRPC1 and TRPC4 mRNA expression and protein levels in PAs isolated from MCT-PH rats were also found to be associated with increased SOCE and PA vasoconstriction [186].

Additionally, an increase in the expression of TRPC3 was described in iPAH hPASMC, which could partly explain the exacerbated SOCE in iPAH hPASMC[173].

Using *trpc4*$^{-/-}$ rats exposed to the sugen–hypoxia protocol (single subcutaneous injection of 20 mg/kg SU5416 followed by 10% O_2 for 3 weeks), Alzoubi et al. found a reduction in the occlusion of small PA and plexiform lesions in *trpc4*$^{-/-}$ rats compared with wild-type (WT) rats. However, *trpc4*$^{-/-}$ rats have similar hemodynamic parameters to WT rats, but TRPC4 deficiency provided a significant survival benefit, with preservation of cardiac output [187].

Regarding the role of TRPC6 in PAH, single nucleotide polymorphisms (SNPs) were found in the promoter of the *TRPC6* gene in a few iPAH patients, facilitating the expression of the TRPC6 protein and increasing its function in iPAH [188,189]. Therefore, this SNP could predispose individuals who have this mutation to develop PAH.

TRPC6 expression (mRNA and protein) was found to be increased in lung and hPASMC from PAH patients, and the knockdown of TRPC6 by siRNA reduced the hyperproliferative phenotype of PAH hPASMC [146]. The role of TRPC6 was also predicted in PASMCs from Milan hypertensive strain (MHS) rats, a genetic model of systemic hypertension. Increased expression of TRPC6, SERCA2, and Na^+/Ca^{2+} exchanger-1 (NCX1) was reported to likely contribute to the abnormal Ca^{2+} homoeostasis and subsequent vasoconstriction and increase blood pressure observed in MHS rats [190].

Recently, Jain et al. demonstrated that oral gavage with TRPC6 blocker BI-749237 reduced the development of PH induced by CH exposure in mice [191], suggesting that TRPC6 could be a potential target in PAH.

The majority of patients with heritable PAH have mutations in bone morphogenetic protein type 2 receptor (*BMPR2*) gene [192,193]. Reduction in BMPR-II signaling is a hallmark of PAH [194–196]. BMPR2 is activated by BMP ligands, including BMP2 and BMP4 [197]. BMP2 is protective against CH-induced PH, while BMP4 contributes to the development of PH [198]. BMP2 application in rat distal PASMCs induced a decrease in TRPC1, -C4, and -C6 expression (mRNA and protein levels), and therefore a reduction in SOCE, a reduction in basal $[Ca^{2+}]_i$, and a reduction in PASMC proliferation and migration [199]. Moreover, BMP4 application promotes pulmonary vascular remodeling in CH-PH mice, and *bmp4*$^{+/-}$ mice exposed to CH were protected against the development of PH [198]. In rat distal PASMC, in contrast to BMP2 application, BMP4 application increases the expression of TRPC1, -C4, and -C6 (mRNA and protein levels); increases SOCE and $[Ca^{2+}]_i$; enhances PASMC proliferation and migration; and protects PASMC mice from apoptosis [154,155].

The resistance to apoptosis of hPASMC is also a hallmark of PAH. Currently, there are no studies on PAH hPASMC linking apoptosis resistance to SOCE. However, several studies have shown the role of Orai in the regulation of apoptosis in other cell types and diseases. For example, reduced Orai1 and STIM1 activity increases apoptosis of pancreatic cancer cells, and the in vivo silencing of Orai1 in mice protects macrophages from apoptosis [200,201]. On the other hand, it was demonstrated in human lymphoma B cell lines that pharmacological inhibition or silencing of Orai1 leads to an enhancement of apoptosis [202]. Thus, the contribution of SOCE and SOCs to the regulation of apoptosis resistance in iPAH PASMC needs to be further investigated.

The involvement of SOCs in hypoxic pulmonary vasoconstriction was also documented in rats using nonselective pharmacological approaches [203,204]. The real con-

tribution of SOCs to the regulation of pulmonary arterial tone needs to be investigated using more selective pharmacology or genetic tools. The physiopathological implications of SOCs in PAH PASMC are summarized in Table 3.

Table 3. Changes in SOC expression (mRNA and protein) and function in PASMC from PAH and from experimental models of PH.

	mRN	Prote	SOCE	hPASMC	Rodents Models	Consequences	References
STIM1	-	↑	-	Hypoxia		Increased proliferation of rat PASMC Increased NFATc3 nuclear translocation	[140,173]
	↑	↑	-		Rat CH Distal PA		
STIM2	-	↑	↑	PAH		Increased proliferation of iPAH hPASMC	[136,173]
	-	↑	-	Hypoxia			
Orai1	-	↑	-	Hypoxia			[134,173]
	↑	↑	↑		Rat CH PA Rat CH PASMC		
Orai2	-	↑	-	Hypoxia			[134,173]
	↑	↑	↑		Rat CH PA Rat CH PASMC		
TRPC1	↑	↑	↑		Rat CH/MCT PA Rat CH PASMC	Reduced CH-induced PH phenotype and PASMC proliferation in *trpc1*$^{-/-}$ mice Pharmacological inhibition normalized vascular tone in PAs of CH-induced PH rats Increased murine PASMC proliferation	[145,152,153,185,186]
	↑	-	-		Mouse PASMC exposed to hypoxia		
TRPC3	↑	↑	↑	PAH			[173]
TRPC4	↑	↑	↑		Rat SU/Hx PA Rat SU/Hx PASMC	*trpc4* gene deletion reduces PH	[186,187]
TRPC6	↑	↑	-	PAH		*hPASMC* proliferation *trpc6* gene deletion reduces CH-induced PH in mice Pharmacological inhibition normalized vascular tone in PAs of CH-induced PH rats	[145,146,152,173]
	-	↑	-	Hypoxia			
	↑	↑	↑		Rat CH PA and PASMC		
SOCE	-	-	↑	PAH		Increased STIM1–Orai1–TRPC1 interaction in hypoxic mouse PASMC	[151,157,172]
	-	-	↑		Mouse PASMC exposed to hypoxia		

The upwards pointing arrow shows an increase; -, no available information.

Since SOCE contribute to the regulation of SR Ca^{2+} content and since SOCE is increased in PAH hPASMC, we can hypothesize that SOCE-induced increase in SR Ca^{2+} content result in an increase in the activity SR Ca^{2+} channels such as IP_3R and ryanodine receptors (RyR). VSMC including PASMC exhibit three different RyR isoforms (RyR_1, RyR_2, and RyR_3) and three different IP_3R isoforms (IP_3R_1, IP_3R_2, and IP_3R_3) which could contribute to the regulation of PASMC functions. It has been demonstrated that $IP_3R_2^{-/-}$ mice developed more severe PH than WT mice under CH-exposure [205]. Using isolated PASMC, Shibata et al. found that SOCE is strongly increased in $IP_3R_2^{-/-}$ PASMC in normoxic condition as well as in the CH condition. The authors demonstrated that IP_3R_2 negatively regulated SOCE in mouse PASMC, indicating the presence of IP_3R_2 to protect against the development of experimental PH by regulating SOCE [205]. The contribution of the IP_3R channel has not been studied in the aberrant phenotypes of PAH PASMC (proliferation, resistance to apoptosis, migration, contraction). IP_3R was previously found to be functionally coupled with TRPC by a direct binding with the N-terminus of the IP_3R and the C-terminal CIRB motif of the TRPC subtypes [57,206]. This direct binding with IP_3R and TRPC has been demonstrated for all IP_3R isoforms and all TRPC subtypes [58,207]. However, the mechanism by which IP_3R isoforms regulate of TRPC function has not been yet demonstrated in PASMC from PAH patients.

In *ryr*$_2^{-/-}$mice, it has been demonstrated that an RyR_2-mediated Ca^{2+} release contributes to pathological ROS generation induced by CH exposure [208]. SMC-specific *ryr*$_2^{-/-}$ mice have similar PAP in response to hypoxia compared to WT; however, RyR_2 was suggested to have a role in the sustained phase of hypoxic pulmonary vasoconstriction [209]. In PASMC isolated from CH-PH and MCT-PH rats, important changes in the cellular localization of RyR isoforms and Ca^{2+} stores have been demonstrated, contributing to the pathogenesis of experimental PH [210]. The expression of TRPV4 and RyR_2 proteins increased in isolated PA from CH-PH rats. In this study, the authors demonstrated that RyR_2 regulated TRPV4 function in PASMC from CH-PH rats, contributing to excessive PA constriction [211].

3. Targeted SOCE in PAH: A Novel Therapeutic Option?

In PAH, the only ion channels targeted in the clinic are L-type voltage-gated Ca^{2+} channels. However, L-type voltage-gated Ca^{2+} channel blockers (nifedipine, diltiazem, or amlodipine) are only effective for less than 10% of PAH patients, named "the responder", and defined by a fall of 10–40 mmHg in PAPm during inhalation of NO. Voltage-gated Ca^{2+} channel blockers act on the reduction in excessive pulmonary arterial vasoconstriction [212,213].

As SOCs constitute another important source of Ca^{2+} mostly involved in pulmonary artery remodeling, and L-type voltage-dependent Ca^{2+} channels are mainly involved in pulmonary artery vasoconstriction, targeting SOCs may be the next challenge to overcome PAH phenotypes. Indeed, PAH hPASMC are characterized by excessive proliferation, excessive migration, and vasoconstrictive phenotypes resulting from Ca^{2+} homoeostasis remodeling (particularly due to SOC activities).

Drugs acting directly and selectively on different SOCs could be attractive for improving PASMC remodeling in the context of PAH. As represented in Table 4, several compounds are available to differentially inhibit almost all SOCs.

Table 4. SOCs inhibitors used as research tool.

Compound	Mode of Action	IC50	Side Effects	References
Orai1 Inhibitor				
YM-58483 (BTP2 or Pyr2)	-	10–590 nM	Inhibits TRPC3 and -C6 (IC50: 0.3 µM) Activates TRPM4 channels (EC50: 8 nM) Inhibit Orai2 and Orai3 at 10 µM	[214–219]
GSK7975A and GSK-5503A	Potentially allosteric effect on the selectivity filter of Orai	4 µM	Orai2 and Orai3 at 10 µM, L-type Ca^{2+} (IC50: 8 µM), and TRPV6 channels	[219,220]
Synta-66	Binds TM1 and TM3 helices and the extracellular loop segments	26 nM-3 µM	Potentiate Orai2 at 10 µM	[219,221–224]
JPIII	-	244 nM	-	[225]
Gd^{3+} or La^{3+}	Binds extracellular loop of Orai1	200 nM	Inhibit Orai2/3	[219,226]
AnCoA4	Binds the C-terminus of Orai1	880 nM	-	[227]
5J-4	-	10 µM	-	[228]
STIM1 Inhibitor				
ML-9	Inhibit STIM1 puncta formation	10 µM	Inhibit Myosin light chain kinase	[229]
TRPC3 Inhibitor				
Pyr3	Direct binding	0.7 µM	-	[230]
Pyr10	-	0.72 µM	-	[218]
TRPC4 Inhibitor				
ML-204	-	1–3 µM	Inhibit TRPC5 and weakly TRPC6	[231]
HC-070	Direct binding	9.3 nM	Inhibit TRPC4 (IC50:46 nM) and TRPC3 (IC50: 1 µM)	[232,233]
HC-608 (Pico145)	-	0.35 nM	Inhibit TRPC5 (IC50: 1.3 nM), TRPC1-4 complex (IC50: 0.03 nM) and TRPC1-5 complex (IC50: 0.2 nM)	[234]
TRPC5 Inhibitor				
AC1903	-	13.6 µM	Inhibit TRPC4 (IC50 > 100 µM)	[235]
GFB-8438	Direct binding	0.18 µM	Inhibit TRPC4 (IC50: 0.29 µM)	[236,237]
TRPC6 Inhibitor				
SAR7334	-	9.5 nM	Inhibit TRPC3 (IC50: 282 nM) and TRPC7 (IC50: 226 nM)	[238]
SKF-96365	-	10 µM	-	[239]
GSK2833503	-	3 nM	Inhibit TRPC3 (IC50: 21 nM)	[240,241]
BI 749327	-	19 nM	-	[242]
SH045	-	7.9 nM	Inhibit TRPC3 (IC50: 282 nM) and TRPC7 (IC50: 226 nM)	[243]
AM-1473	Direct binding	0.22 nM	-	[244]

Inhibitors are classified according to their smallest IC50. EC50, half maximal effective concentration; IC50, half maximal inhibitory concentration; -, no data available.

Concerning inhibitors of Orai1, there is a well-known family of pyrazole derivatives, with the widely used BTP2 (YM-58483) [214–218] and GSK compounds (GSK7975A and GSK-5503A) [220], acting on the selectivity filter of Orai1, Synta-66, which binds directly to Orai1 [221–224] and its suitable in vivo analogue JPIII [225]. The lanthanide family (Gd^{3+} or La^{3+}) has been known as an Orai blocker for many years [219,226]. The less-used AnCoA4 [227] and 5J4 [228] also exist. ML-9 is used to inhibit STIM1 puncta formation [229]. Since 2006 and the identification of Orai1 as the archetype of SOCE, Orai1 has been a potential target in several pathological processes, including psoriasis, pancreatitis, asthma, and COVID-19 pneumonia.

Auxora (or CM2489), an Orai1 channel inhibitor, was tested in a clinical trial to treat moderate to severe plaque psoriasis. However, it showed only a limited clinical effect but was safe and well tolerated by patients. The compound CM2489 had some chemical improvements and design to treat acute pancreatitis. The preclinical trials were successful in mice, and the phase I clinical trials were successful, allowing entry into phase II with a good safety profile and improvement in patient outcomes [245,246]. In addition, a clinical study, although limited by its design, has been conducted for the treatment of severe or critical COVID-19 pneumonia with this compound [247]. Another Orai1 inhibitor (RP3128) has reached clinical trials (Phase I/IIa) for asthma [248]. Finally, a last candidate, the Orai1 inhibitor PRCL-02, has achieved a phase IIa clinical trial for the treatment of moderate to severe chronic plaque psoriasis [249].

Concerning TRPC channel inhibitors used in experimental research, very few of them are selective because of the structural similarity between all TRPC channels. Xanthine-based inhibitors are known to inhibit TRPC1, -C5 and -C6 at nanomolar concentrations [232]. Among the xanthine-based inhibitors, HC-608 (also called Pico145), described to be one of the most potent inhibitors of TRPC1, -C4, and -C5 [234], and HC-070, is widely used to inhibit TRPC4 and -C5 [233]. The benzamidiole ML-204 is used for TRPC4 [231] and AC1903 for TRPC5 [235], but they both also inhibit TRPC4 and -C5. Alternatively, GFB-8438, produced from pyridazinone 1 (Pyr1), is a potent TRPC4 and TRPC4/C5 inhibitor [236,237]. Pyr3 and Pyr10 are known to inhibit TRPC3 [230]. Another sub micromolar potent inhibitor of TRPC3 and -C6 is GSK2833503, which is known to be more than 100-fold more selective against TRPC3 and TRPC6 than other Ca^{2+} channels [240,241]. The BI 749327 inhibitor was developed to specifically inhibit TRPC6. It is an orally bioavailable inhibitor that does not inhibit TRPC5 or other TRP channels [242]. The (+)-larixol derivative SH045 is also used to inhibit TRPC6, with good selectivity [243]. TRPC6 can also be inhibited by a nanomolar inhibitor and orally bioavailable SAR7334 [238] or by its analogue AM-1473 [244].

Some studies are ongoing, such as the TRPC5 channel inhibitor GFB887, tested in Phase I on healthy volunteers, and now in Phase II for patients with diabetic nephropathy or with focal segmental glomerulosclerosis [250]. However, research on TRPC inhibitors is at an early stage but should be accelerated by recent cryo-EM structure discovery.

As described in this part, the selectivity of these molecules is not enough to discriminate each of the TRPC isoforms. In vitro, these inhibitors may be used at specific concentrations to ensure selectivity, but in vivo the use of these molecules is challenging due to their lack of selectivity. Additionally, the mechanism of action or channel specificity remains unclear for some of these pharmacological agents. Moreover, some compounds are not stable in vivo, which prevents their use in preclinical or clinical research. Progress in the identification of SOCs involved in the pathogenesis of PAH is essential to develop specific therapeutic tools. The recent advance in the determination of cryo-EM structures of TRPC channels with sufficient resolution to allow the identification of specific bounding site of small molecules [251,252] should help to develop more potent selective inhibitors or activators, since the need of selective molecules is crucial for the development of innovative therapy in various diseases, including PAH. Despite important progress in the selectivity of the molecules described in this review, the development of more selective pharmacological tools to selectively inhibit each SOC isoform could facilitate the emergence of innovative therapies concerning multiple diseases, including PAH.

4. Conclusions

PAH represents a major human and social burden because this orphan disease is associated with a poor prognosis, affects children and young adults, and has no cure treatment except lung transplantation for eligible patients. The data presented in the present review support evidence of the involvement of SOCs in the pathogenesis of PAH, and each of these channels could be considered a potential new therapeutic target for PAH. Nevertheless, these channels are ubiquitous. Consequently, specific pharmacological tools towards a target organ should be carefully considered in preclinical experiments to identify eventual side effects.

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