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Interactions between calcium regulatory pathways and mechanosensitive channels in airways

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Abstract

Introduction: Asthma is a chronic lung disease influenced by environmental and inflammatory triggers and involving complex signaling pathways across resident airway cells such as epithelium, airway smooth muscle, fibroblasts, and immune cells. While our understanding of asthma pathophysiology is continually progressing, there is a growing realization that cellular microdomains play critical roles in mediating signaling relevant to asthma in the context of contractility and remodeling. Mechanosensitive pathways are increasingly recognized as important to microdomain signaling, with Piezo and transient receptor protein (TRP) channels at the plasma membrane considered important for converting mechanical stimuli into cellular behavior. Given their ion channel properties, particularly Ca^{2+} conduction, a question becomes whether and how mechanosensitive channels contribute to Ca^{2+} microdomains in airway cells relevant to asthma.

Areas covered: Mechanosensitive TRP and Piezo channels regulate key Ca^{2+} regulatory proteins such as store operated calcium entry (SOCE) involving STIM and Orai channels, and sarcoendoplasmic (SR) mechanisms such as IP_3 receptor channels (IP_3Rs), and SR Ca^{2+} ATPase (SERCA) that are important in asthma pathophysiology including airway hyperreactivity and remodeling.

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Declaration of interest

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Expert opinion: Physical and/or functional interactions between Ca^{2+} regulatory proteins and mechanosensitive channels such as TRP and Piezo can towards understanding asthma pathophysiology and identifying novel therapeutic approaches.

Keywords

STIM; Orai; Piezo channels; TRPV receptor; Airway smooth muscle; Asthma

1. Introduction

Asthma is one of the most common chronic and non-communicable respiratory disorders affecting as many as 339 million people globally (1). Furthermore, asthma is correlated with a higher risk of other diseases like hypertension, diabetes, obesity, and cancer (2–8). Research has highlighted that a number of environmental and inflammatory factors are involved in asthma pathophysiology, as are different resident cells of the airway along with immune cells, making it difficult to identify single or limited sets of mechanisms that could be targeted towards asthma therapy (9, 10). Regardless, at least one common factor relevant to different airway cells is intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$). Ca^{2+} is an essential second messenger and plays an important role not only normal cellular function but specifically in asthma. For example, increased Ca^{2+} can lead to exaggerated contraction of airway smooth muscle (ASM) cells (11, 12), release of inflammatory mediators (13) and mucus hypersecretion from airway epithelial cells (14) along with increased vascular permeability of endothelial cells (15) overall contributing to airway hyperreactivity, remodeling and inflammation (16). Thus, understanding the mechanisms of Ca^{2+} regulation and dysregulation in airway cells in the context of asthma pathophysiology becomes critical towards development of novel therapies (17–22).

An evolving concept of increasing interest in lung disease pathogenesis is that of mechanobiology, involving the impact of mechanical forces on cellular structure and behavior, and the interaction between intracellular components or that between intracellular and extracellular components in the context of mechanical stimuli. Tschumperlin and Drazen were the first to hypothesize that mechanical stimulation plays a role in airway remodeling (23). In this regard, ASM cells experience substantial mechanical forces in the context of normal breathing and ongoing airway contractions and relaxation. Mechanical stretch can influence the secretory properties of ASM (24, 25). For patients with asthma, who undergo repeated episodes of bronchoconstriction, show pathological airway remodelling such as goblet cell hyperplasia and increased collagen deposition (25), changes in airway structure and airway reactivity alter the mechanical relationships between cells, and the responsiveness of airway cells to mechanical forces. However, the mechanisms by which mechanical forces lead to structural or functional changes, or those that respond to mechanical forces are only recently being understood.

There is increasing recognition that mechanosensitive Piezo and transient receptor potential (TRP) ion channels, which influence entry of cations, particularly Ca^{2+}, in response to mechanical stimuli, are potentially important in airways (26, 27) and might play a role in airway remodeling and airway hyperreactivity in asthma (28, 29). What is less known is how

these plasma membrane channels interact with intracellular pathways to induce structural or functional changes in the airway and whether and how they are detrimental vs. alleviating towards airway physiology (28, 29). We review the current state of knowledge regarding interactions between mechanosensitive ion channels and key Ca^{2+} regulatory proteins that influence both Ca^{2+} homeostasis and airway hyperreactivity and remodeling in the airways, particularly in the context of asthma. Information gleaned from studies to date have the potential to help understand the relevance of mechanosensitive pathways in other lung diseases such as COPD and pulmonary fibrosis that involve altered structure and function of bronchial and parenchymal airways.

2. Ca^{2+} regulatory proteins in asthma

A balance between $[Ca^{2+}]_i$ and extracellular Ca^{2+} is critical to cellular homeostasis and cell survival which involves regulation of Ca^{2+} fluxes across the plasma membrane vs. intracellular regulation of Ca^{2+} availability via several proteins (17, 18). The mechanisms of $[Ca^{2+}]_i$ regulation in airway cells has been recently reviewed (30–40). The sarcoendoplasmic reticulum (SR) is the main intracellular Ca^{2+} store (19, 41, 42). The sarcoendoplasmic reticulum calcium ATPase (SERCA) pumps Ca^{2+} from the cytosol into the SR lumen in an ATP-dependent manner (20) and thus helps to maintain low baseline Ca^{2+} levels. Upon G protein-coupled receptor (GPCR) stimulation by agonists (e.g. acetylcholine and muscarinic receptors; histamine and histaminergic receptors), second messenger cascades involving inositol 1,4,5-trisphosphate (IP_3) or cyclic ADP ribose trigger Ca^{2+} from the SR through IP_3 receptors (IP_3Rs) or ryanodine receptors (RyRs), respectively. Depletion of SR stores under these conditions activates store-operated Ca^{2+} entry (SOCE) (21). SOCE is mediated by stromal interaction molecule (STIM, particularly STIM1) situated on the SR membrane. STIM functions as a luminal Ca^{2+} sensor which is activated by decreased SR Ca^{2+} and translocated into junctions formed between SR and the plasma membrane. Upon binding to the plasma membrane channel Orai1, there is an increase in Ca^{2+} influx. Supporting Ca^{2+} regulatory mechanisms include plasma membrane Ca^{2+} ATPase (PMCA), voltage gated Ca^{2+} channel (VGCC), Na^+/Ca^{2+} exchanger (NCX, $3Na^+$:$1Ca^{2+}$) and non-specific cation channels (22). Here, we explore some of the major Ca^{2+} regulatory pathways in the context of asthma and their potential to interact with mechanosensitive pathways.

2.1. STIM

STIM is one of the major intracellular components and the initiator of SOCE (43). There are two homologous proteins, STIM1 and STIM2, which are multi-domain, single-pass transmembrane proteins residing on the SR membrane and sensing changes in SR luminal Ca^{2+} levels (44, 45), communicating such changes to Orai1 channel proteins in the plasma membrane (46). In the case of STIM1, a 90-kDa protein, located in the SR membrane and plasma membrane with an NH2-terminal luminal low-affinity EF-hand acts as an SR sensor for Ca^{2+} and communication with Orai1 occurs through interaction between the cytosolic COOH-terminal STIM-Orai1 activating region (SOAR) of STIM and the COOH-terminal coiled-coil domain of Orail when Ca^{2+} depletion occurs in the SR (47). STIM proteins sense the Ca^{2+} depletion in the SR, oligomerize, and redistribute into discrete puncta located in junctional SR sites near the plasma membrane and directly interact with Orai1 resulting

in sustained Ca^{2+} entry that allows for refilling of the SR Ca^{2+} stores. Despite the overall high sequence similarity between STIM1 and STIM2 luminal N-terminal domains, STIM2 is only expressed in the SR. This is due to the EF-hand of STIM2 having a lower affinity for Ca^{2+}, which makes STIM2 a weaker activator of Orai1 and results in lower distinct stability and Ca^{2+}-sensitivity (48, 49). As a result, while STIM1 acts as a sensor for SR Ca^{2+} depletion, STIM2 can be activated during sub-maximal reductions in SR Ca^{2+}.

STIM1 has been implicated in the pathogenesis and development of asthma (16, 21). Enhanced expression of STIM1 protein is associated with airway remodeling in asthma (16). One study reported that exposure of mice to the allergen, ovalbumin (OVA) results in increased expression of STIM and Orai1 (50). Hyperplasia of ASM cells is a feature in asthma, and proliferation and migration of ASM cells are promoted by STIM1 and may thus contribute to airway remodeling (51). Knockdown of STIM1 inhibits platelet derived growth factor (PDGF)-induced activation of SOCE and attenuates ASM cell proliferation and migration in OVA challenged mice (50). Interestingly, in a rat model of asthma, aerobic exercise can improve ASM contractile function by downregulating the expression of STIM1, Orai1, and Orai2, blunting excessive SOCE (52). ASM-mediated airway hyperresponsiveness (AHR) and airway remodeling are also significantly blunted in STIM1 knockout mice (21).

We and others have previously shown the importance of ASM Ca^{2+} oscillations in airway contractility and AHR including in human airways (53, 54), where the frequency of Ca^{2+} oscillations determines the extent of ASM contraction (55). Higher airway responsiveness in BALB/c than C57BL/6 mice has been attributed to increased expression of ASM STIM1, which is associated with faster Ca^{2+} oscillations (56). STIM1 is also necessary for house dust mite (HDM)-induced Ca^{2+} oscillations, where STIM1 knockout significantly decreases ASM Ca^{2+} oscillations (21).

Previous studies from our laboratory have also shown that inflammatory triggers on STIM1 aggregates contributes to AHR. The asthma-relevant pro-inflammatory cytokines interleukin (IL)-13 and tumor necrosis factor alpha (TNF-α) increase Ca^{2+} release and SOCE in ASM by upregulating STIM1 and Orai1 (57). Johnson and colleagues found that increased STIM1 expression in ASM can also trigger AHR and remodeling by activation of nuclear factor of activated T cells (NFAT) and secretion of IL-6 (16). BTP2, an efficient inhibitor of SOCE, has been shown to attenuate allergic inflammation induced allergic asthma (52). Beyond ASM, STIM1 protein has been implicated in the activation of mast cells, which are involved in the early phase of asthma pathogenesis (58). Overall, these data underline the role of STIM1 in the pathogenesis of asthma and suggest that inhibition of STIM1 represents a novel therapeutic target.

While STIM2 has similar functional effects to STIM1 in some respects, there is not much known regarding the contributions of STIM2 to airway contractility, AHR, or asthma. Interestingly, one study reported that the expression and function of STIM2 was significantly exaggerated in asthmatic patients (59), but the implications relative to changes in STIM1, or impact on remodeling are unknown. Given the high likelihood that maximal SR depletion does not occur consistently in ASM cells even during substantial contraction, and thus a

sub-maximal reduction of Ca^{2+} is important, the role of STIM2 is likely more important, which can be activated even by mild depletion of SR Ca^{2+} stores and can drive activation of constitutive Ca^{2+} influx (60). Expression of STIM2 has been found to be higher in non-allergic asthmatic children compared to healthy controls following anti-CD3/28 stimulation (61). STIM2 is also expressed in WI-38 fibroblasts and can enhance the percentage of cells showing Ca^{2+} oscillations upon stimulation with agonists that activate G_q (62, 63).

2.2 ORAI

Orai proteins are highly Ca^{2+} selective plasma membrane channels that are regulated by STIM (64). The Orai family consists of three homologs, Orai1, Orai2 and Orai3, which function as thermo-molecular components of the SOCE pathway. Orai expression is associated with airway pathology in asthma, including airway remodeling, inflammation, and bronchoconstriction (65). Orai1 expression is upregulated in ASM from asthmatic mice and in PDGF-mediated ASM cell proliferation, while knockdown of Orai1 attenuates ASM proliferation and SOCE (50, 51). Long-term administration of an Orai1 antagonist (3-fluoropyridine-4-carboxylic acid, FPCA) resulted in bronchodilation in a pig asthma model (66, 67). Orai1 knockdown also significantly inhibited ASM proliferation and chemotactic migration in response to PDGF (50). Beyond ASM, in human bronchial epithelial cells, the allergen house dust mite (HDM) activates STIM1-Orai1-dependent SOCE and drives expression of genes involved in remodeling (50, 68).

Increases in $[Ca^{2+}]_i$ resulting from the interaction of STIM and Orai are also involved in the pathogenesis of inflammation in asthma (69, 70). IL-4, a type 2 cytokine, is reduced in T cells of patients with loss-of-function mutations in Orai1 (71). Pretreatment of ASM with IL-4 upregulates the expression of Orai1 and Orai2, promoting ASM contraction, which can be inhibited by aerobic exercise (52). T cell-specific deletion of Orai1 protects mice from HDM-induced allergic airway inflammation, while Orai1 controls the expression of cell cycle regulators and T cell proliferation during allergic airway inflammation (72). Short palate lung and nasal epithelial clone 1 (SPLUNC1), an asthma gene modifier that inhibits Orai1 via its C-terminal α6 region, decreases eosinophilic inflammation in OVA-induced asthma mice and a murine allergic asthma model (73–75). Lung mast cells also express Orai1, wherein shRNA knockdown of Orai1 reduces Ca^{2+} influx (76). Inhibition of SOCE by GSK-7975A and synta-66 suppresses mast cell secretion of IL-5, IL-3 and TNF-α (77). IL-13 regulates airway remodeling in asthma mouse model by regulating Orai1 expression (78). Orai1 inhibition can thus exert broad effects on inflammatory activity and may have therapeutic potential in asthma. Other Orai family members (Orai2 and 3) are also involved in Ca^{2+} regulation in ASM but to a lesser extent than Orai1. Arachidonic acid induced Ca^{2+} oscillations in cultured ASMCs, while unaffected by SOCE inhibitors, are inhibited by knockdown of Orai3 (13, 40). In comparison, knockdown of Orai2 results in only marginal reductions of Ca^{2+} influx (76). Overall, these disparate data underline the importance of different Orai isoforms in airway structure and function in the context of inflammation and asthma.

2.3 IP_3R

IP_3Rs are located on SR and mitochondrial-associated-membranes (79). It is a tetrameric Ca^{2+} release channel consisting of four subunits that binds to IP_3 triggering Ca^{2+} release into the cytosol. The increase in cytosolic Ca^{2+} may regulate cytosolic effectors or uptake by other organelles, while the associated decrease in SR Ca^{2+}, depending on the extent of depletion, activates STIM2 and/or STIM1 and SOCE (80). Cytosolic Ca^{2+} in turn can also regulate the level of IP_3Rs, where higher concentrations of cytosolic Ca^{2+} inhibits IP_3Rs (81).

IP_3R is strongly associated with asthma (52, 82, 83). Both mRNA and protein levels of IP_3R are increased in interleukin-stimulated ASM cells and in HDM-induced asthma models (52). IP_3R levels was also found to be reduced in lipopolysaccharide (LPS) stimulated human bronchial epithelial cells from asthma patients. This reduction was correlated with increased SR Ca^{2+} release (84). In ASM, IP_3R inhibition with 2-APB or Xestospongin C reduces Ca^{2+} oscillation frequency, leading to relaxation (85, 86) while, conversely, IP_3R-dependent Ca^{2+} oscillations and resultant contraction are increased in rat model of asthma (87). Separately, suppressed IP_3R-mediated Ca^{2+} signaling by traniterol, a relaxant of ASM also blunts ASM proliferation (88).

IP_3R has also been linked to airway inflammation in asthma. Activation of IP_3R can trigger release of pro-inflammatory cytokines and chemokines, which attract immune cells to the airways and contribute to development of asthma symptoms (84). Inhibition of IP_3R activity reduces production of pro-inflammatory cytokines in airway epithelial cells (89). Interactions with IP_3R with B-cell lymphoma 2 (Bcl-2), a mitochondrial apoptosis protein, modulates apoptotic pathways in asthma (90, 91). In contrast, B-cell lymphoma-extra-large (Bcl-xL) promotes Ca^{2+} oscillations by increasing sensitization to IP_3R (92, 93).

Studies have also shown that mitochondrial dysfunction is associated with the development of asthma (94, 95). Mitochondria plays a critical role in energy metabolism and are also involved in regulating Ca^{2+} signaling (96). Dysfunctional mitochondria can lead to increased oxidative stress, inflammation, and impaired Ca^{2+} handling, all of which have been implicated in the pathogenesis of asthma (97, 98). IP_3R -mediated Ca^{2+} release from the SR can activate mitochondrial Ca^{2+} uptake, which can further modulate mitochondrial function (99, 100). IP_3R regulates mitochondrial Ca^{2+} concentration, resulting in mitochondrial reactive oxygen species generation and inflammation (101). Here, mitochondria can relay feedback to regulate nearby SR Ca^{2+} channels, thereby maintaining Ca^{2+} homeostasis (102). Carbachol, via IP_3R aggravates mitochondrial disfunction and NLRP3 inflammasome activation (89). IP_3R can also communicate with RyR Ca^{2+} channels and mitochondria to regulate SR Ca^{2+} release, mitochondrial dysfunction, and reactive oxygen species generation (83).

2.4. SERCA

SERCA works to transport cytosolic Ca^{2+} back into the SR (103), and thus contributes to muscle relaxation (104). There are 3 tissue-specific members: SERCA1, SERCA2 and SERCA3 (105). SERCA2 is most highly expressed in smooth muscle (106, 107). In both

asthmatic and healthy ASM cells, inhibition of SERCA2 leads to an increase in $[Ca^{2+}]_i$ levels, which results in enhanced ASM contraction, proliferation, and secretory function (108). Diminished expression of SERCA2 is also correlated with severity of asthma and airway inflammation (104). The ability of SERCA2 to replete SR Ca^{2+} stores is also decreased in asthmatic ASM cells (108). Expression of SERCA2b shows an inverse association with airway tone (104), which is an underlying contributor to airway contractile capacity (109). In addition, AHR is also related to downregulated expression and function of SERCA2b (108).

We have previously shown that inflammatory cytokines such as TNF-α and IL-13 decrease expression of SERCA2 in ASM (110). Brain-derived neurotrophic factor (BDNF), a growth factor associated with asthma that enhances ASM proliferation and contractility (111, 112), also promotes the expression of SERCA, while inhibition of SERCA prevents BDNF enhancement of Ca^{2+} responses to histamine (113).

SERCA expression in immune cells is also relevant to asthma. For example, expression of SERCA shows an inverse association between the ability of human basophils to respond to IgE-dependent stimulation, confirmed by pharmacological inhibitor (thapsigargin) vs. activator (disulfiram) (114). Interestingly bodily symptoms such as muscle weakness and atrophy in asthma is also in part driven by SERCA dysfunction, including decreased expression of SERCA2 (115).

2.5. Caveolin

The relevance of caveolins and caveolar proteins lies in their ability to integrate plasma membrane signals and modulate the interactions of plasma membrane proteins with intracellular components. There are three caveolin family members: Caveolin-1 (Cav-1), Cav-2, and Cav-3 (116). Cav-2 is co-expressed with Cav-1 in multiple cell types including epithelial and ASM cells, while Cav-3 is expressed mainly in cardiac and skeletal muscle cells. Cav-1 is most related to asthma (117). Cav-1 is a 178-amino acid hairpin structural protein with a hydrophobic transmembrane domain (118). Caveolae harbor Ca^{2+} regulatory proteins including receptors for bronchoconstrictor agonists and SOCE proteins such as Orai1. Thus Cav-1 is required for the association of STIM1 with Orai1, and suppression of Cav-1 reduces the expression of Orail1 but not STIM1 (119). Functionally, Cav-1 has been shown to regulate ASM $[Ca^{2+}]_i$ by modulating SOCE, thereby regulating cell contraction (119). By virtue of harboring agonist receptors, disruption of caveolae using siRNA attenuates $[Ca^{2+}]_i$ responses to agonists such as histamine, acetylcholine, and bradykinin (120). Thus Cav-1 plays a critical role in ASM cell function, and thus the assumption would be that increased Cav-1 is associated with increased ASM contractility. However, this is not consistently the case. For example, Cav-1 plays an important role in airway inflammation by mediated the effect of TNF-α and IL-13 on enhanced $[Ca^{2+}]_i$ in ASM (121). Cav-1 expression in ASM induced by OVA is also correlated to the degree of airway obstruction and hyperresponsiveness (122, 123). However, patients with asthma have lower Cav-1 expression, and this decrease is associated with enhanced expression of extracellular matrix (ECM) proteins (collagen, tenascin and periostin deposition) (123, 124). A drug

caveolin scaffolding domain (CSD) that restores Cav-1 function in Cav-1-deficient cells is protective in ASM (125).

The role of Cav-1 in epithelium is also protective for the most part. IL-4 is required for allergen induced mucus production and airway inflammation (126, 127). Cav-1 plays an important role in mucus in asthmatics (128). Blocking Cav-1 prevents Ca^{2+} influx and MUC5AC synthesis induced by IL-4 in bronchial epithelial cells (129). However, Cav-1 deficient mice show increased thickness of subepithelial collagen layer and develop asthma-like responses to OVA (31, 130). In addition, silencing GATA6 increases Cav-1 and reduces inflammation and mucus production in asthmatic mouse model (128). Cav-1 expression acts to stabilize E-cadherin and β-catenin at adherens junctions to maintain epithelial barrier function (131). Suppression of Cav-1 results in delocalization of E-cadherin and barrier dysfunction in 16HBE epithelial cells (131). Cav-1 knockout mice exhibit activation of TGF-β, mediating subepithelial airway fibrosis (132). Overall, the preponderance of data suggest Cav-1 plays a protective role in asthma.

2.6. NCX

NCX is a bidirectional transporter using the electrochemical gradient driven by Na^+ to respond to elevated $[Ca^{2+}]_i$ and contribute to Ca^{2+} extrusion (133). NCX is encoded by three genes: NCX1, NCX2, and NCX3 (134). The expression, function, and regulation of NCX differ across tissues and species. Only NCX1 has been detected in ASM so far. While largely known for Ca^{2+} extrusion, under extreme conditions, NCX works in reverse mode (NCX_{REV}), and promotes Ca^{2+} influx with Na^+ efflux, resulting in increased Ca^{2+} and enhancing contraction. NCX operating in reverse mode is involved in ASM contraction (135) and is thought to contribute to asthma and AHR (136, 137), via mechanisms involving neurokinin receptors (138). Inflammatory cytokines TNF-α and IL-13 increase the expression of NCX protein further enhancing Ca^{2+} fluxes (139). NCX also contributes to ASM cell proliferation and migration, by preventing excessive mitochondrial Ca^{2+} overload and supporting the entry of Ca^{2+} through SOCE pathways. NCX also activates Ca^{2+}/calmodulin-dependent kinase II, leading to transcriptional and reprogramming. Furthermore, a model of asthma involving NCX knockout in smooth muscle exhibits reduced airway remodeling, AHR and airway fibrosis (140). Overall, these limited studies suggest a detrimental role of NCX in asthma.

3. Mechanosensitive Ion Channels

3.1. Piezo channels

Mechanosensitive pathways transmit mechanical signals into electrochemical signals essential for cellular function (141). Relevance of mechanosensitive pathways lie in their potential ability to influence both airway contractility and remodeling (142). In this regard, there is substantial interest in the role of the more recently identified Piezo channels, Piezo 1 (Fam38a) and Piezo 2 (Fam38b), that are sensitive to various forms of mechanical stimuli including stretch, compression, and shear (143–146). Recent studies have shown that Piezo channels play critical roles in regulating physiological and pathological functions across different cell types and organs (147). Piezo channels are expressed in lung, bladder, skin,

and neurons and are involved in a range of functions such as regulating RBC volume, organ development, cell proliferation, and migration (148–150). Their interaction with the plasma membrane, and/or ECM components as well intracellular signaling proteins make Piezo channels appealing in terms of understanding their potential importance in airway function and asthma. Mechanical forces exerted on the cytoskeleton and ECM causes the opening of the Piezo1 channel, leading to the influx of extracellular Ca^{2+} and transducing mechanical signals into electrical and chemical signals in the cell (Figure 1). Piezo channel mediation of cellular functions through plasma membrane and/or ECM interactions is evident in multiple cell types. For example, dendritic cell activation via changes in stiffness is mediated through Piezo (149). Piezo channels are involved in macrophage polarization (150). Piezo1 modulates matrix degradation in vascular smooth muscle cells (97). In the absence of ECM proteins, Piezo1 is not sensitive to mechanical forces (151).

In the lung, Piezo1 is expressed in pulmonary endothelial cells (152), ASM (153) and alveolar epithelial cells (154), although the data are limited often to gene expression or protein without localization. In rat ASM, Piezo1 activation by the specific agonist Yoda1 decreases cell stiffness and traction force, disrupting stress fibers and cell migration (153). Our previous study found that Piezo1 and Piezo2 are expressed in human fetal ASM cells, where activation of Piezo1 by agonist Yoda or stretch causes significant $[Ca^{2+}]_i$ responses and increased ECM production (155, 156). Piezo2 has been found in neurons that are responsive to mechanical forces including those in the lung (157–159). In a preliminary study, Piezo2 staining was localized in bronchial epithelial cells, macrophages, and smooth muscle cells (160). How Piezo1 and Piezo2 in lungs interact in the context of airway structure and function or in asthma has not been extensively investigated. Piezo1 in bronchial epithelial cells is higher in asthmatic mice (26). Impairment of airway epithelial function and disordered tight junction expression relevant to asthma (161) may be tied to Piezo1 (26). Piezo1 is activated by auto-positive end-expiratory alveolar pressure, resulting in an increase in $[Ca^{2+}]_i$ and aggravates the degradation of tight junction in a Piezo1 dependent manner (26).

3.2. TRP channels

TRP proteins are a group of relatively non-specific cationic channels located mainly on the plasma membrane (162). TRP proteins contains an intracellular-N and C-termini, 6 membrane-spanning helices, and a presumed pore-forming loop (163). These channels respond to various heterogeneous stimuli, including physical stimuli (mechanical force and temperature), endogenous and exogenous chemical mediators, depletion of Ca^{2+} stores in SR and free cytosolic Ca^{2+}. Seven subfamilies have been identified: TRPA, TRPC, TRPV, TRPM, TRPP, TRPML and TRPN. The expression and function of all these families have not been uniformly explored in the airway or lung disease. Nonetheless, TRPC and TRPV channels appear to be most relevant, including for mechanotransduction.

TRPC channels have been more highly explored in the airway in the context of Ca^{2+} regulation but are also relevant to mechanosensation as discussed further below. TRPC channels can be activated by IP_3 and inactivated by calmodulin under conditions of high intracellular Ca^{2+}. TRPC can also serve in a store operated activation role like STIM1-

Orai1. TRPC channels can also be activated downstream of mechanosensitive GPCRs signaling through phospholipase C. Deformation of the plasma membrane can also activate TRPCs. Here, TRPC1, TRPC5, and TRPC6 are thought to be mechanosensitive. TRPC1 mechanosensitivity has been shown in a variety of cell types including ganglionic neurons (164), cardiac cells (165), and bronchial epithelial cells (29, 166). Furthermore, TRPC1 and TRPC5 can heterodimerize (167) and remain mechanosensitive, while such properties may change when complexing with TRPC4 which is not mechanosensitive (168, 169). TRPC5 can be activated by membrane stretching or osmotic pressure changes (170, 171). TRPC5 is localized to the apical membrane of airway epithelial cells is important for mechanotransduction changes with osmotic pressure (172). TRPC6 is mechanosensitive in arterial smooth muscle cells in response to intravascular pressure (173), but is also expressed in other tissues where its role is less known. TRPC3 is a key molecular component of nonselective cation channels found in ASM cells, which is important in regulating resting membrane potential and $[Ca^{2+}]_i$ in ASM cells, as well as membrane depolarization and hyperresponsive in OVA-sensitized/-challenged cells (174). In guinea pig ASM cells, TRPC3 is important for maintaining $[Ca^{2+}]_i$ basal levels and preserving smooth muscle basal tone. Blocking TRPC3 with 2-aminoethoxydipheny1(2-APB) and Pyr3 significantly decreases baseline $[Ca^{2+}]_i$ (175). Expression of TRPC3 is also enhanced in ASM cells of sensitized mice, resulting in elevation of baseline $[Ca^{2+}]_i$, potentially contributing to the development of AHR relevant to asthma (174). TRPC3 can been activated by IP_3 resulting in Ca^{2+} influx, in addition to conversely opening IP_3Rs to induce Ca^{2+} release from intracellular Ca^{2+} stores (176). While there is evidence for TRPC3 in regulation of $[Ca^{2+}]_i$ in the airways (177), it is important to emphasize that links to mechanosensitivity as not yet known.

The TRPV family (TRPV1-TRPV6) is a group of polymodal channels that sense thermal, acidic, mechanical stress, and osmotic stimuli and can be activated by endogenous ligands (178). TRPV1 to TRPV4 are non-selective cation channels that exhibit a preference for Ca^{2+} influx over Na^+, TRPV5 and TRPV6 are selective channels that specifically permit Ca^{2+} (28). Under the TRPV family, TRPV1, TRPV2 and TRPV4 are considered relevant to development and exacerbation of asthma (179).

TRPV1 increases airway inflammation (180–182), AHR (183), mucus production (184), ASM contraction, cough, and airway remodeling (185, 186), all potentially relevant to asthma. Capsazepine, a TRPV1 antagonist inhibits AHR, airway remodeling and airway inflammation in mice (186) and prevents bronchoconstriction in guinea pig ASM (187), similar to SB-705498 and PF-04065463 (188). Both endogenous and exogenous TRPV1 agonists (ROS and bradykinin) can induced cough in response to tissue inflammation in asthma (189).The antagonist HC-030031 reduces cough response (146), while GDC-0334a, an orally bioavailable TRPV1 antagonist, inhibits allergic airway inflammation (190). Airway infiltration of leukocytes, IL-13, IL-5, IL-4, IL-13 and TNF-α are reduced in TRPV1 deleted mice (186, 191, 192). In addition, TRPV1 gene mutation was closely related to bronchial asthma in children and provide a new treatment and prognosis of children with bronchial asthma.

TRPV2 has been found to be a potential new biomarker for diagnosis of childhood asthma with typical IgE levels (28, 180, 193) using peripheral lymphocytes which show upregulation of TRPV2 (180). Blockade of TRPV2 with SKF-96365 decreases secretion of inflammatory cytokines (TNF-α, IL-13 and IL-17A) (194). A traditional Chinese prescription, San-ao decoction used to treat asthma, reduced the expression of TRPV2 in the lungs of OVA-induced asthmatic mice, and diminished the levels of IL-4 and IL-10 in BALF (195). TRPV4 is expressed in airway epithelial cells and ASM cells. Activation of TRPV4 by warm temperatures, osmotic, and mechanical stimuli induces proliferation of ASM (196, 197), allergic inflammation (198), and airway remodeling (199), TRPV4 has been implicated in non-atopic asthma, where stimulation of TRPV4 increases $[Ca^{2+}]_i$ and releases ATP, which activates P2X4 receptors on mast cells, and further evokes the release of leukotrienes thus promoting ASM contraction (179). TRPV4 can also function as an osmolarity sensor in airways when stimulated by hypotonic solutions (196). GSK222069 and GSK2337429A, antagonists of TRPV4, attenuate lung inflammation by reducing neutrophils, macrophages and associated cytokines (200). TRPV4 contributes to Ca^{2+} regulation by forming a complex with NCX and with IP_3R with downstream effects on airway tone as shown in mice (201). TRPV4 can also modulate ASM contraction in exercise and with inspiration of humid air in the context of hypoosmotic stimulus (202). In a murine model of HDM-induced asthma, activation of TRPV4/Rho/MRTF-A signal pathway results in increased remodeling and ECM deposition (203).

Ambient temperature is another factor that may trigger asthma. TRPs are sensitive to temperature, where TRPV1 is heat-sensitive while TRPM8 channels are cold-sensitive. Cold air stimulus induced airway inflammatory and remodeling by increasing TRPM8 expression while knockdown TRPM8 attenuates this response (204). TRPV1 responds to thermal stimuli exceeding 42˚C (205). TRPM8 and TRPA1 are decreased in ASM of the rat asthma model, while activation of TRPM8 and TRPA1 inhibits ASM proliferation (206).

4. Crosstalk between mechanosensitive channels and Ca^{2+} regulatory proteins

Given that a number of Ca^{2+} regulatory pathways exist within the plasma membrane or either physically or functionally interact with it, it would be reasonable to assume that mechanosensitive channels also within the plasma membrane could potentially modulate Ca^{2+} in a number of ways. Such crosstalk between mechanosensitive channels and Ca^{2+} regulatory proteins was recently summarized in the context of cardiovascular health and disease (207) demonstrating the importance of many of the plasma membrane intracellular pathways that are also relevant to the airways. However, there are also clear differences in the expression and functionality of these pathways in the cardiovascular vs. pulmonary systems. Yet there is only scattered and newly emerging information relevant to the role of mechanosensitivity in the airways. Understanding these interactions in the context of airway structure and function and airway diseases holds potential for identification of novel disease mechanisms as well as potential targets for intervention.

4.1. Piezo and Ca^{2+} regulatory proteins

Given the relative novelty of Piezo channels, there is obviously little known regarding their interactions with intracellular Ca^{2+} proteins. Recently, SERCA2 has been found to interact with Piezo1 channels via a 14-residue intracellular linker region at PM-ER junction to regulate cellular mechanotransduction processes. Mutating this linker reduces this interaction between Piezo1 and SERCA2 and abolishes SERCA2-mediated inhibition of mechanosensitive currents (208). Piezo1 interactions with SERCA2 are thought to modulate Piezo1-induced Ca^{2+} entry in the context of stretch (208). Whether such effects are relevant for example to ASM cells is unknown. Eisenhoffer et al. found that Piezo 1 dependent Ca^{2+} influx appears to activate two opposing processes in epithelial cells dependent on where and how Piezo1 is activated. Piezo1 accumulates in the plasma membrane to activate epithelial cell division in regions with sparse epithelial cells, while Piezo1 localizes in cytoplasm in cell dense regions allowing cell extrusion to maintain cell number at a stable homeostatic level (209).

Piezo1 also appears to modulate SR Ca^{2+} release dynamics via IP_3R_2 at least in the cardiovascular system (210). The release dynamics downstream of Piezo1 are independent of the initial increase in SR lumen Ca^{2+} under sheer stress, but deletion of IP_3R_2 by siRNA reduces the rate constant of SR Ca^{2+} decay without affecting rate constant of SR Ca^{2+} increase (210). Thus, IP_3R_2 appears important for release of SR Ca^{2+} by activation of Piezo1 (210). The Piezo1 activator Yoda1 increases generation of cAMP, prevented by inhibition of soluble adenylate cyclase (210) and thus Piezo1 induced rapid mobilization of intracellular Ca^{2+} into the SR followed by SR Ca^{2+} release is thought to involve both sAC-cAMP and IP_3R_2 (210). However, it is important to note that while IP_3R_2 is expressed in the CV system, its expression and function in airways seems less clear. In fact, ASM is more likely to express IP_3R_1 and IP_3R_3 (176), but there is currently no information on the interactions between Piezo1 and these isoforms.

4.2. TRPs and Ca^{2+} regulatory proteins

In differentiated, normal bronchial epithelial cells which express TRPM4 and all isoforms of NCX, suppression of these proteins blunts MUC5AC and mucus secretion (211). In goblet cells, TRPM5 links to $NCX_{Rev,}$ such that the NCX inhibitor KB-R9743 significantly reduces mucus secretion (212).

TRPC channels can also function in STIM1-dependent and STIM1-independent modes (213). Cav-1 helps to retain TRPC1 within STIM1 punctiform domains after storage depletion. This enables the interaction of TRPC1 with STIM1, facilitating TRPC1-mediated SOCE. At baseline, Cav-1 binding to the N-terminal region of TRPC1 keeps the channel in an inactive state (214). STIM1 replaces Cav-1 for binding to TRPC1 to activate this channel. Cav-1 re-binds to TRPC1 following refilling of SR Ca^{2+} stores (214, 215). Knockdown of Cav-1 results in dislocation of TRPC1, preventing STIM1 from gating the channel (214). Cav-$1^{-/-}$ mice exhibit disruption of TRPC1 localization in endothelial cells (216). Thus, Cav-1 acts as a scaffold for inactive TRPC1 and facilitates activation of TRPC1 by STIM1.

TRPC1 colocalizes and interacts with STIM1 after storage depletion, in contrast, refilling of SR-Ca^{2+} stores results in dissociation of STIM1 from TRPC1 and functional inactivation of TRPC1 (217, 218). These interactions involve aspartate residues in TRPC1 with polybasic domain of STIM1 (219). The ERM (ezrin/radixin/moesin) domain of STIM1 mediates the selective binding of STIM1 to TRPC1, 2 and 4, helping with the gating of TRPC1 (220). In human ASM, TRPC channels form complexes with STIM1 and Orai1, and this complex regulates Ca^{2+} influx (221). Orai1 also plays a key role in TRPC1 activation by store depletion. Orai1-mediated Ca^{2+} entry triggers recruitment of TRPC1 into the plasma membrane where it is activated by STIM1 (222, 223).

IP_3R is not only a link between the plasma membrane and Ca^{2+} but also a sensor of the degree of filling the store. The Ca^{2+}-binding site for IP_3R is located in lumen (224). When Ca^{2+} dissociates from it, triggering exposure of a cytosolic signal-transfer domain, TRP-based Ca^{2+} entry channels are activated by IP_3R (225, 226). 2-APB which inhibits SOCE also inhibits IP_3Rs, SERCA, and TRP channels. TRPC1 links to the IP_3 receptor in the context of regulating Ca^{2+} filling status of the SR (219). TRPP2 can strongly interact with IP_3R by binding to positively charged amino acids in the N-terminal ligand-binding domain of IP_3R, and increase local cytosolic Ca^{2+}, enhancing smooth muscle contraction (227). In addition, TRPP2 would inhibit the binding of IP_3 to IP_3R due to a conformational change of N-terminal ligand-binding domain of IP_3R. However, at higher dose of IP_3, this inhibition will be overcome (228, 229). These data indicate that TRP proteins are integral parts of agonist and store depletion activated Ca^{2+} entry channels and that these channels are regulated directly by IP_3Rs.

The interaction between TRP channels and SERCA in ASM is essential for regulating Ca^{2+} homeostasis and preventing excessive smooth muscle contraction (230). Sustained activation of TRP channels with excessive Ca^{2+} influx and smooth muscle hypercontractility contributes to airway hyperresponsiveness (231). Activation of TRPC7 and TRPC3 channels is blocked by the SERCA pump inhibitor thapsigargin (232) and thus prevents sustained TRP activation. Activation of TRPV4 channels in ASM can lead to an increase in Ca^{2+} uptake by SERCA, suggesting that SERCA plays a role in regulating the activation of TRP channels in this tissue (231, 233).

5. Expert opinion

Ca^{2+} signaling plays an important role in airway structure and function and in the airway hyperreactivity and remodeling characteristic of asthma. Here, beyond the many pathways that regulate Ca^{2+} in cells such as epithelium and ASM, there is increasing recognition that interactions with mechanosensitive pathways can modulate Ca^{2+} regulation and thus increase the complexity of how Ca^{2+} contributes to airway physiology. Thus, in the context of ultimately treating asthma, there remains much to understand regarding the interplay between mechanical forces and Ca^{2+} regulation. Here, an important aspect is to determine whether such interplay leads to enhancement of features of asthma such as AHR (in particular, given the importance of Ca^{2+} in contractility) or even remodeling in the long term, vs. any alleviating effects when Piezo or TRP channels are activated. Certainly Piezo and TRPs interact with a number of mechanisms that increase $[Ca^{2+}]_i$ such as STIM1,

STIM2, Orai1 and IP_3Rs and in that sense there are multiple pathways via which mechanical stimulation can lead to increased $[Ca^{2+}]_i$ and contractility of smooth muscle, and even have Ca^{2+} mediated stimulatory effects in other cell types such as epithelium (towards mucus production) and immune cells (towards inflammation). On the other hand, mechanosensitive channels can also interact with NCX and SERCA that could reduce $[Ca^{2+}]_i$ under normal circumstances, although it is difficult to predict whether the channels would blunt these regulatory mechanisms towards increasing $[Ca^{2+}]_i$ or whether they would enhance their function and thus reduce $[Ca^{2+}]_i$. Beyond Ca^{2+} and contractility, it is also increasingly apparent that mechanical forces can modulate epithelial barrier function, mucus production, ECM production, and airway remodeling, many of which may also be Ca^{2+} dependent. Responses to mechanical forces could also include production of inflammatory and growth factors, themselves Ca^{2+} dependent. Thus, understanding the role of mechanosensitive pathways such as Piezo and TRP channels becomes important, especially given emerging data in the cardiovascular system for crosstalk between these mechanisms and the Ca^{2+} regulatory pathways. Even here, there remain significant gaps in our knowledge of the interactive mechanisms at play, particularly for Piezo channels. This review summarized current understanding, albeit limited, of crosstalk between mechanosensitive channels and Ca^{2+} regulatory pathways in asthma, given the more direct links between this airway disease and Ca^{2+} in the context of AHR and even remodeling. However, it is likely that Piezo and TRP channels also play a role in other lung diseases such as COPD and pulmonary fibrosis (155, 156). Even here, the data are only emerging in that such mechanosensitive channels are expressed in other lung areas, and show altered responses to mechanical forces, and contribute in particular to fibrosis. However, what is not known is whether there are any interactions with Ca^{2+} regulatory pathways as we summarize here. Future studies will need to consider further investigation of mechanical forces in the airway and other parts of the lung, to better understanding how these pathways interface with Ca^{2+}, contractility, and remodeling towards creating novel interventions for asthma and perhaps beyond (Figure 2).

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Article highlights

1. In the context of diseases such as asthma, regulation of intracellular Ca2+ has several downstream effects towards airway contractility and even remodeling (proliferation and fibrosis).
2. There is increasing recognition for the role of mechanosensitive pathways in airway cell structure and function, with particular interest in Piezo and transient receptor protein (TRP) channels that are permeant to Ca2+.
3. A number of pathways regulate Ca2+ in airway cells, including Ca2+ release via IP3 receptors and reuptake via Ca2+ ATPase in the sarcoendoplasmic reticulum, and Ca2+ influx pathways that respond to depletion of Ca2+ stores, involving STIM proteins and Orai channels. Additional pathways such as sodium-calcium exchange and caveolins provide further modulation.
4. Piezo and TRP channels physically or functionally interact with Ca2+ regulatory pathways, typically enhancing their function.
5. Crosstalk between mechanosensitive Piezo or TRP channels and Ca2+ regulatory pathways in the lung in the context of asthma is only now being recognized and provides an opportunity to identify novel targets to address airway hyperreactivity and remodeling.

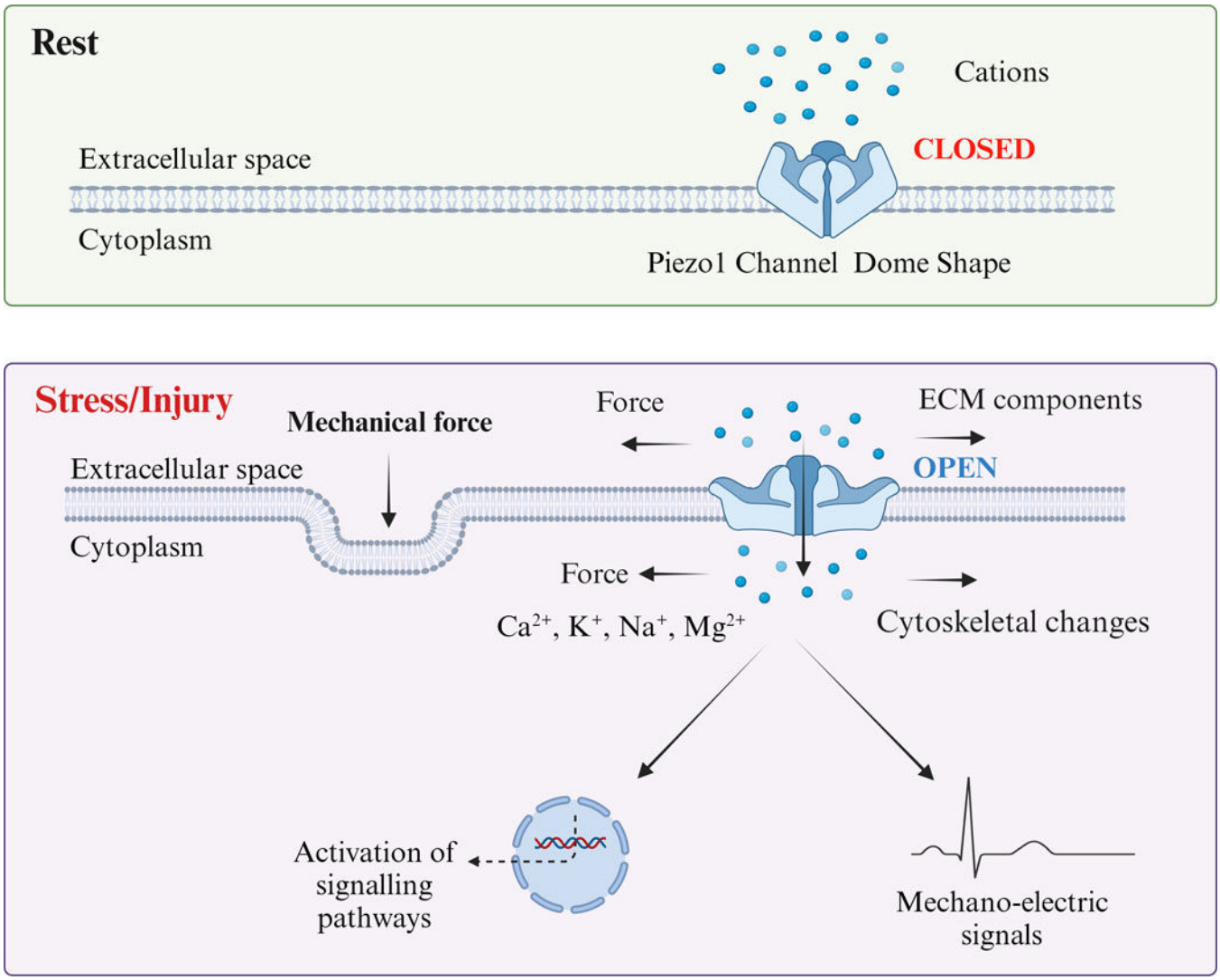

Figure 1.

Schematic diagram of Piezo1 Channel activation by mechanical force. The Piezo1 channel is a trimeric structure located in the plasma membrane. The mechanical force exerted on the cytoskeleton and extracellular matrix (ECM) causes the opening of the Piezo1 channel, leading to the influx of extracellular Ca^{2+} and transducing mechanical signals into electrical and chemical signals in the cell.

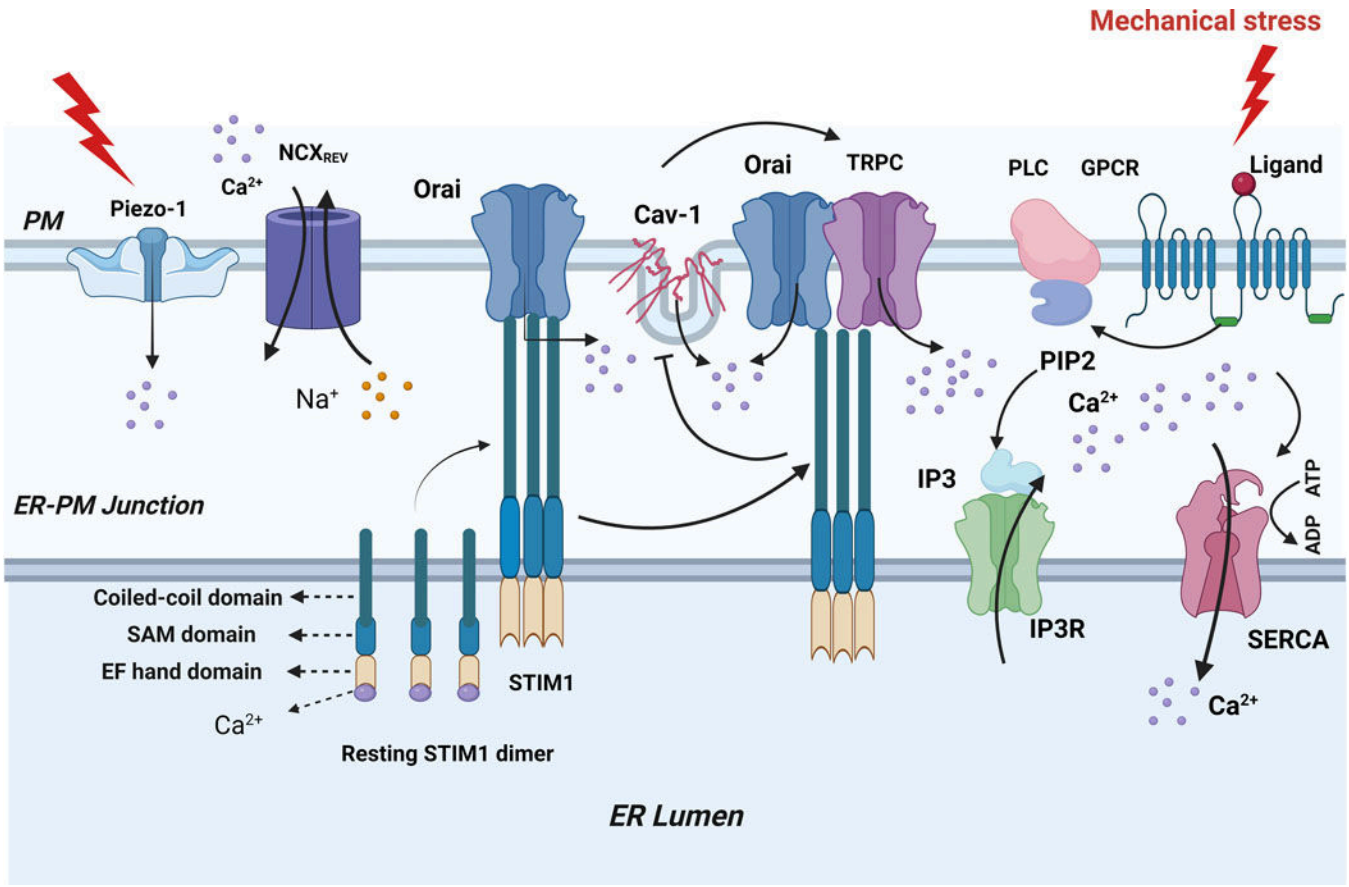

Figure 2.

Crosstalk between mechanical and calcium regulatory channels in the airway. Mechanical overstretch induces Piezo1 channels to open, which causes endoplasmic reticulum (ER) pressure to facilitate Ca^{2+} release and ER store depletion, As stores deplete, Ca^{2+} dissociates from the luminal EF-hand domain of STIM1 proteins, which in turn causes STIM1 oligomerize and translocate to ER-plasma membrane junction and activate Ca^{2+} release-Ca^{2+} (CRAC) channels formed by Orai protein causing Ca^{2+} influx, this is also trigger the recruitment of TRP and activated by STIM1, TRP, STIM1 and Orail form complex to regulates Ca^{2+} influx, this complex suppress the bind of Cav-1 to TRP, but loss of effect after refill of ER-Ca^{2+} stores. In addition, mechanical overstretch stimulate G-protein coupled receptors (GPCR) associated with phospholipase-C(PLC) produces IP_3. IP_3 binds to IP_3R to facilitate Ca^{2+} release and ER store depletion.