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Store-Operated Ca^{2+} Entry in Fibrosis and Tissue Remodeling

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Abstract

Fibrosis is a pathological condition characterized by excessive tissue deposition of extracellular matrix (ECM) components, leading to scarring and impaired function across multiple organ systems. This complex process is mediated by a dynamic interplay between cell types, including myofibroblasts, fibroblasts, immune cells, epithelial cells, and endothelial cells, each contributing distinctively through various signaling pathways. Critical to the regulatory mechanisms involved in fibrosis is store-operated calcium entry (SOCE), a calcium entry pathway into the cytosol active at the endoplasmic reticulum-plasma membrane contact sites and common to all cells. This review addresses the multifactorial nature of fibrosis with a focus on the pivotal roles of different cell types. We highlight the essential functions of myofibroblasts in ECM production, the transformation of fibroblasts, and the participation of immune cells in modulating the fibrotic landscape. We emphasize the contributions of SOCE in these different cell types to fibrosis, by exploring the involvement of SOCE in cellular functions such as proliferation, migration, secretion, and inflammatory responses. The examination of the cellular and molecular mechanisms of fibrosis and the role of SOCE in these mechanisms offers the potential of targeting SOCE as a therapeutic strategy for mitigating or reversing fibrosis.

Keywords

calcium signaling, stromal-interaction molecule (STIM), Orai1, calcium release activated channel (CRAC) (ICRAC), fibrosis, tissue remodeling

Introduction

Calcium (Ca^{2+}) is a universal secondary messenger across numerous signaling cascades. Ca^{2+} plays a critical role in the regulation of almost every eukaryotic cell activity ranging from fertilization to cell fates (Berridge et al., 1998). The various cellular functions regulated by Ca^{2+} include metabolism, gene transcription, immune responses, muscle contraction, cell proliferation, secretion, and programmed cell death (Clapham, 2007; Feske et al., 2012; Hogan and Rao, 2015; Prakriya and Lewis, 2015; Trebak and Kinet, 2019; Benson and Trebak, 2023). Therefore, it is not surprising that any disruption in intracellular Ca^{2+} balance is associated with numerous disorders, including inflammatory, neurological, and metabolic diseases (Shaw and Feske, 2012; Arruda and Hotamisligil, 2015; Zhang and Hu, 2020). There is a huge difference in the Ca^{2+} concentration across the plasma membrane. The resting Ca^{2+} concentration in the cytosol is ~100 nM while the extracellular milieu contains ~1–2 mM. Cells invest a significant amount of energy to maintain this Ca^{2+} concentration gradient. To ensure intracellular Ca^{2+} homeostasis, cells employ a sophisticated network of ion channels, transporters, and exchangers. Cells either expel surplus Ca^{2+} across the plasma membrane (PM) to the extracellular space or transfer it into internal stores, most notably the endoplasmic reticulum (ER), mitochondria (Sukumaran et al., 2021; Yoast et al., 2021; Emrich et al., 2022) and the endolysosomal system(Morgan, 2016; Yuan et al., 2024). The ER represents the most significant reservoir of free intracellular Ca^{2+} within eukaryotic cells,

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with Ca^{2+} concentrations between 100 μM and 1 mM (Bygrave and Benedetti, 1996).

Store-operated calcium entry (SOCE) is the predominant mechanism of Ca^{2+} entry in non-excitable cells (Putney, 1986; Ashby and Tepikin, 2001; Potier and Trebak, 2008; Prakriya and Lewis, 2015; Emrich et al., 2022). SOCE is mediated by five key molecules: the ER-resident Ca^{2+} sensing stromal interaction molecules 1 and 2 (STIM1/2) and the pore forming proteins Orai1/2/3 located in the PM. In non-excitable cells, stimulation of phosphoinositide-specific phospholipase C (PLC)-coupled PM receptors cause the breakdown of the minor membrane lipid, phosphatidylinositol-4,5-bisphosphate (PIP_2) into two second messengers: 1) inositol 1,4,5-triphosphate (IP_3) and 2) diacylglycerol (DAG). The soluble IP_3 binds and activates IP_3 receptors (IP_3Rs) causing Ca^{2+} release from the ER (Berridge et al., 1998; Berridge, 2009; Berridge, 2016). This depletion in ER Ca^{2+} is sensed by the EF-hand domain of STIM proteins, prompting STIM to undergo a structural rearrangement, and aggregate into clusters known as puncta at ER-PM contact sites, where it traps and activates plasma PM Orai channels causing Ca^{2+} influx (Potier and Trebak, 2008; Trebak, 2009; Putney, 2011; Fahrner et al., 2013; Moccia et al., 2014; Zhou et al., 2014; Hogan and Rao, 2015; Prakriya and Lewis, 2015; Trebak and Putney, 2017; Trebak and Kinet, 2019; Yoast et al., 2020a). The current mediating SOCE is termed the Ca^{2+} release-activated Ca^{2+} (CRAC) current, or I_{CRAC} (Lewis and Cahalan, 1989; Hoth and Penner, 1992). While the Ca^{2+} selective CRAC currents mediated by STIM-Orai interactions represent the classical SOCE pathway, other channels mainly members of the transient receptor potential canonical (TRPC) channel subfamily were proposed to mediate, in some specific contexts, nonselective currents called I_{SOC}, which are activated as a consequence of store depletion (Liao et al., 2007; Liu et al., 2007; Kim et al., 2009; Moccia et al., 2023). This review will specifically address the function of CRAC channels in different cell types and tissues of relevance to fibrosis.

Molecular Composition and Function of CRAC Channels

The critical importance of SOCE in physiological functions goes far beyond simply replenishing depleted ER Ca^{2+} stores. SOCE is critical for driving the activation of various gene programs, most notably through isoforms of nuclear factor for activated T cells (NFAT) (Hogan et al., 2003; Oh-hora and Rao, 2009). This critical aspect of signaling to transcription through SOCE was first highlighted by the clinical identification of human patients with inherited loss-of-function (LoF) mutations in either Orai1 or STIM1 (Feske et al., 2006; McCarl et al., 2009; Picard et al., 2009; Lian et al., 2018). These patients first identified in the 1990s, had defective CRAC channel function and suffered a form of severe combined immune deficiency, with muscle hypotonia and ectodermal hyperplasia (Le Deist et al., 1995; Feske et al., 1996; Feske et al. 2001). The molecular identity underpinning CRAC channels were not elucidated until RNAi screens identified STIM1 and Orai1 as the two major molecules mediating SOCE and I_{CRAC} (Liou et al., 2005; Roos et al., 2005; Feske et al., 2006; Vig et al., 2006; Zhang et al., 2006). These original studies catalyzed further investigations utilizing transgenic animal models to explore the roles of CRAC channels in various tissues, organ systems, and disease models (Prakriya and Lewis, 2015; Emrich et al., 2022).

As to be expected, research has primarily focused on STIM1 and Orai1 owing to their critical roles in SOCE and the discovery of patients with LoF mutations in STIM1 and Orai1 (Feske et al., 2006; McCarl et al., 2009; Picard et al., 2009; Lian et al., 2018; Vaeth and Feske, 2018; Silva-Rojas et al., 2020). Indeed, STIM1 and Orai1 are ubiquitously and prominently expressed across various tissues with substantial evidence pointing to their position as the *bona fide* molecular components of SOCE (Williams et al., 2001; Abdullaev et al., 2008; Oh-Hora et al., 2008; Potier et al., 2009; Bisaillon et al., 2010; Feske et al., 2010; Zhang and Trebak, 2011; Spinelli et al., 2012; Motiani et al., 2013; Shinde et al. 2013; Feske, 2019; Luo et al., 2020; Conte et al., 2021; Shawer et al., 2021; Tiffner and Derler, 2021). Nevertheless, recent findings point to the importance of STIM2, Orai2 and Orai3 as critical regulators of SOCE. STIM2 plays a significant role in SOCE across different cell types, including neurons and various cancer cells (Berna-Erro et al., 2009; Bandyopadhyay et al., 2011b; Nelson et al., 2018; Emrich et al., 2019; Benson et al., 2023). Due to differences in the calcium affinity of their EF hand domain, STIM1 is activated by substantial ER calcium depletion and is the primary initiator of SOCE in response to agonist stimulation. However, STIM2 responds to milder ER Ca^{2+} depletion, leading to the reasonable conclusion that STIM2 is active at basal levels to maintain resting ER Ca^{2+} levels. However, recent studies showed that this conclusion is an oversimplification. STIM2 is involved in SOCE across the full range of agonist concentrations and levels of store depletion and is crucial for NFAT activation and transcriptional regulation under physiological agonist-mediated ER Ca^{2+} store depletion. These data indicate that the function of STIM2 goes far beyond mere store replenishment (Emrich et al., 2021b; Ahmad et al., 2022). Furthermore, STIM2 facilitates STIM1 recruitment to ER-PM junctions under conditions of modest ER store depletion, likely serving as a signal amplifier (Brandman et al., 2007; Ong et al., 2015; Subedi et al., 2018).

Studies on Orai2 and Orai3 were initially impeded, partly due to the lack of specific antibodies and the scarcity of specific pharmacological modulators targeting these channel proteins (Emrich et al., 2022). The use of cultured cells

where Orai2 and Orai3 were deleted through CRISPR/Cas9 and primary cells from Orai2 and Orai3 knockout mice showed that Orai2 and Orai3 negatively regulate SOCE, possibly by forming heteromeric channels with Orai1 (Vaeth et al., 2017c; Tsvilovskyy et al., 2018; Eckstein et al., 2019; Yoast et al., 2020b; Emrich et al., 2023). In this regard, the incorporation of Orai2 and Orai3 into a native CRAC channel contributed mostly by Orai1, would serve to fine tune CRAC channel activity by enhancing its graded range of activities to match the diversity of physiological agonist concentrations and levels of ER store depletion (Yoast et al., 2020b; Emrich et al., 2022). Unlike Orai1 and Orai2, Orai3 resists oxidant-mediated inhibition (Bogeski et al., 2010; Ben-Kasus Nissim et al., 2017) and some cancer cells adapt to signal through Orai3 to maintain SOCE activity in hypoxic or oxidant-rich environments (Motiani et al., 2010; Faouzi et al., 2011; Faouzi et al., 2013; Motiani et al., 2013). Orai3 in particular has been reported to play an important role in different disease models and tissue types (Mignen et al., 2008; Motiani et al., 2010; Ay et al., 2013; Thompson et al., 2014; Zhang et al., 2014; Emrich et al., 2021a). Further, Orai3 synergizes with Orai1 for optimal CRAC channel activity necessary for B cell activation and metabolic reprogramming (Emrich et al., 2023). Orai1 expression is elevated while Orai2 expression is diminished in effector T cells compared to their naïve counterparts (Vaeth et al., 2017b). Logically, high expression of Orai2, a negative regulator or CRAC channel activity, in naïve T cells was proposed to prevent unwarranted activation of naïve T cells (Vaeth et al., 2017c). While the precise stoichiometry of Orai isoforms in specific cell types remains to be fully elucidated, it is likely that diverse CRAC channel heteromers adapt to the unique functional needs of each cell type and differentiation states. Obviously, the specific molecular composition of CRAC channels in various cell types is expected to have a unique contribution to Ca^{2+} signaling and to specific cellular functions. This specificity is particularly relevant in the context of fibrosis, a disease characterized by the contribution of several cell types to organ dysfunction. The detailed mechanisms by which different cell types, influenced by specific potential CRAC channel stoichiometries, contribute to the fibrotic process remain unclear. This highlights the need for further understanding of CRAC channel composition and regulation within the fibrotic environment as prerequisite for potential specific targeting of CRAC channels for fibrosis mitigation.

Cellular Mechanisms of Fibrosis

Fibrosis is an exaggerated tissue repair response characterized by the excessive deposition of extracellular matrix (ECM) due to an uncontrolled reaction to wounds and connective tissue damage. This results in scarring, loss of functional parenchymal cells, and organ dysfunction (Wynn, 2008; Weiskirchen et al., 2019). Fibrosis is associated with high morbidity and mortality, and can affect any organ system, including the skin, heart, lung, liver, and kidney. Beyond localized damage, fibrosis can have systemic effects, increasing perfusion resistance and impacting systemic circulation, potentially leading to severe complications like portal hypertension and right-sided heart failure (Li et al., 2018; Wijsenbeek et al., 2022). Moreover, fibrosis is increasingly recognized as a contributor to cancer progression due to chronic inflammation, immune checkpoint upregulation, altered immune cell function, and vascular changes that facilitate tumor development (Dudek et al., 2013; Harimoto et al., 2013; Guidotti et al., 2015; Lurje et al., 2020). The etiology of fibrosis is diverse, ranging from infections, ischemia, and autoimmunity to chronic inflammatory diseases, environmental pollutants, alcohol, and genetic predispositions, including increased MUC5B expression in pulmonary fibrosis, MYH7 mutations in cardiac fibrosis, and Duchesne Muscular Dystrophy (DMD) in skeletal muscle fibrosis (Eming et al., 2014; Allen et al., 2017; Kim et al., 2020; Young et al., 2020). A central theme in fibrosis is tissue damage that triggers repair mechanisms, which, if unchecked, can lead to abnormal fibrotic healing. The wound healing process and the development of fibrotic conditions share overlapping mechanisms. In minor injuries, healing is effective, with a temporary increase in ECM components to restore tissue structure. However, in cases of severe or repeated damage, ECM buildup continues, distorting tissue structure, impairing organ function, potentially leading to organ failure.

The repair process is dynamic, involving multicellular interactions between parenchymal cells, immune cells, and fibroblasts. In this process, an inflammatory response is initially induced, recruiting leukocytes to clear debris, recruit more cellular population and activate the tissue-resident cells that contribute to the profibrotic phenotype. (Ramachandran et al., 2019; Adams et al., 2020; Yang et al., 2021; Xue et al., 2022). As healing progresses, a profibrotic phase marked by persistent inflammation and shifts in immune cell composition begins. This transition moves from an acute inflammatory response to a profile dominated by regulatory and tolerogenic functions, signaling a significant change in the healing and tissue regeneration process. The cell populations driving fibrosis vary depending on the affected organ and the underlying cause of the fibrotic disease. Despite these differences, myofibroblasts remain a hallmark feature of the fibrotic processes (Gyongyosi et al., 2017; Chen et al., 2019; Ackermann et al., 2020; Friedman and Pinzani, 2022). Normally, these myofibroblasts, crucial for ECM production and tissue repair, are eliminated after healing. However, in fibrotic conditions, they persist, leading to continuous ECM production, creating a self-perpetuating cycle of injury, unresolved inflammation, and unchecked fibrogenesis. This cycle exacerbates tissue injury, prolongs myofibroblast activation, and leads to fibrosis and organ failure (Gyongyosi et al., 2017; Chen et al.,

2019; Ackermann et al., 2020; Friedman and Pinzani, 2022). To gain deeper insights into the diverse cell populations involved in fibrosis and their intricate interactions, detailed cellular blueprints of various fibrotic conditions have been meticulously analyzed using single-cell sequencing techniques. Such research has underscored the critical contributions of epithelial cells, endothelial cells, immune cells, and fibroblasts in the development of fibrosis, while also uncovering new cellular players in its progression.

Myofibroblasts are the primary producers of ECM in fibrosis, while also modulating inflammatory responses and affecting nearby parenchymal cells. While traditionally thought to originate from mesodermal fibroblasts (Sun et al., 2016), Myofibroblasts can arise from various cell types depending on the affected organ. The cellular source of Myofibroblasts and their relative contribution to the total Myofibroblasts pool vary across different tissues and can be affected by differences in the primary site of injury with fibroblasts often serving as the main source (McGowan and Torday, 1997; Lim et al., 2009; Wei et al., 2010; Rehan and Torday, 2012; El Agha et al., 2014; Marangoni et al., 2015; Mastrogiannaki et al., 2016; Torday and Rehan, 2016; El Agha et al., 2017; Sun et al., 2017; Rognoni and Watt, 2018). However, other cell types can also give rise to myofibroblasts. For instance, in the skin, they may originate from subcutaneous adipocytes (Marangoni et al., 2015); in the lungs, from epithelial cells (Sun et al., 2016), mesenchymal stromal cells in the heart (Maione et al., 2022), and in the liver, from hepatic stellate cells (HSCs), pericytes (Kitto and Henderson, 2021) or from mesothelial cells undergoing a mesothelial-mesenchymal transition during liver fibrosis (Li et al., 2013). Single-cell sequencing has shown that myofibroblasts display distinct gene expression profiles with dynamic changes in fibrosis across various organs (Tabib et al., 2018; Farbehi et al., 2019). Regardless of their origin, activated Myofibroblasts across different organs often exhibit a contractile phenotype marked by α-smooth muscle actin (α-SMA) expression (Younesi et al., 2021). The heterogeneity of myofibroblasts, coupled with their acquired resistance to apoptosis as the disease progresses, makes them challenging to target (Hinz and Lagares, 2020; Kato et al., 2020). Therefore, emerging strategies aim to indirectly inhibit myofibroblasts by targeting their precursors to reduce the overall Myofibroblasts population. The different Myofibroblasts precursors during fibrosis will be discussed in some detail in the sections below. Another approach involves preserving or modulating the activity of other parenchymal and leukocyte components involved in tissue remodeling to break the cycle of tissue damage, unresolved inflammation, and uncontrolled fibrogenesis.

SOCE has been reported to regulate multiple biological processes necessary for tissue remodeling, fibroblasts activation and differentiation into myofibroblasts, cell proliferation, secretion, migration, and transcriptional as well as metabolic modulation (Chen et al., 2010; Capiod, 2011; Pinto et al., 2015; Prakriya and Lewis, 2015; Xie et al., 2016; Feng et al., 2019; Shapovalov et al., 2021). The following sections will provide an overview of the primary cell types implicated in fibrotic conditions and, when known, the role of SOCE in regulating their functions (Ramachandran et al., 2019; Adams et al., 2020; Yang et al., 2021; Xue et al., 2022).

Fibroblasts

Fibroblasts are critical for the maintenance and repair of connective tissues. Fibroblasts play a vital role in wound healing, normal tissue development, growth, regeneration, and repair (Kakkar and Lee, 2010). The differentiation of fibroblasts into the hyperproliferative, matrix-producing and contractile myofibroblasts, is a key cellular event in many fibrotic conditions (Gibb et al., 2020). Although multiple cell types can serve as a progenitor for myofibroblasts, fibroblasts remain the classical precursor and a major contributor to the myofibroblasts pool in multiple fibrotic diseases.

Ca^{2+} plays a crucial role in fibroblast activation and differentiation into myofibroblasts. Multiple studies have demonstrated that both voltage- and non-voltage-gated ion channels modulate intracellular ion levels and cellular activity, contributing to fibroblast differentiation, proliferation, contraction, and secretory function (Chen et al., 2019; Xing et al., 2023). Evidence supporting the role of Ca^{2+} includes studies demonstrating that a sustained increase in cytosolic Ca^{2+} is a crucial factor in transforming inactive fibroblasts into myofibroblasts. This transformation is driven by profibrotic agents such as TGF-β, AngII, PDGF, histamine, and Endothelin-1, all known to bind specific receptors and activate robust intracellular Ca^{2+}-dependent signaling (Alevizopoulos et al., 1997; Ostrom et al., 2003; Furuya et al., 2005; Mukherjee et al., 2012; Mukherjee et al., 2013; Zhou et al., 2014; Stempien-Otero et al., 2016; Kondo et al., 2018; Li et al., 2019). The Ca^{2+} channels proposed to play a role in this process include transient receptor potential (TRP) channels, Piezo1, CRAC channels, voltage-gated Ca^{2+} channels, in addition to sodium and potassium channels. These channels have been shown to regulate cytosolic Ca^{2+} concentrations in myocardial fibroblasts (Du et al., 2010; Davis et al., 2012; Harada et al., 2012; Adapala et al., 2013; Thodeti et al., 2013; Rahaman et al., 2014; Chen et al., 2019; Gibb et al., 2020; Gibb et al., 2020). Earlier research has primarily focused on TRP channels, specifically TRPV4, TRPC6, and TRPM7, in fibroblasts differentiation (Du et al., 2010; Davis et al., 2012; Harada et al., 2012; Adapala et al., 2013; Thodeti et al., 2013; Rahaman et al., 2014; Chen et al., 2019). Recently, however, other ion channels have gained recognition as significant regulators of fibrosis in fibroblasts. These studies are beyond the scope of this review. Herein, we will focus on the role of CRAC channels and SOCE in regulating fibrosis.

Lung Fibroblasts. Bendiks and colleagues examined the mechanisms of store refilling after ER Ca^{2+} depletion in murine lung fibroblasts. Using TRPC1/6 and STIM1/2-deficient murine lung fibroblasts, they showed that SOCE decreases upon STIM1/2 knockout but not with TRPC1/6 deficiency. Leveraging primary murine lung fibroblasts from STIM1/2-floxed mice, they induced STIM1/2 knockout *ex vivo*, revealing a reduction in cellular functions such as proliferation, migration, and the nuclear localization of the transcription factor, NFAT. These findings underscore the pivotal role of STIM1/2-mediated SOCE in fibroblast activation and its downstream functional consequences (Oh-Hora et al., 2008; Bendiks et al., 2020).

Recent studies suggested the involvement of SOCE in mediating histamine-induced Ca^{2+} signaling in lung fibroblasts, and triggering fibroblast proliferation, contraction, migration, and collagen production. Ca^{2+} imaging in WI-38 human fetal lung fibroblasts showed that SOCE is required for sustaining histamine-evoked Ca^{2+} transients. These oscillations were inhibited by 10 μM of the trivalent cations La^{3+} and Gd^{3+} (Jordana et al., 1988; Garbuzenko et al., 2004; Kunzmann et al., 2007; Kohyama et al., 2010; Veerappan et al., 2013). PCR analysis revealed prevalent expression of STIM2 and Orai3 in WI-38 human fetal lung fibroblasts (Berra-Romani et al., 2022). Yu and colleagues explored the role of Orai channels in lung fibrosis using a bleomycin-induced rat model and proposed that enhanced Orai1/Orai3 interactions form a store-independent Orai1/Orai3 channel that drives fibroblast proliferation and ECM production during lung fibrosis. Their *ex vivo* experiments with primary lung fibroblasts treated with TGF-β1 showed a concentration-dependent increase in Orai3 and collagen I expression. Notably, knockdown of Orai3 or Orai1 led to reduced TGF-β1-induced fibroblast proliferation, α-SMA expression, ECM production, and activation of both NFAT1 and Calpain/ERK signaling pathways, along with decreased glycolysis levels (Yu et al., 2022a). Guzmán-Silva et al. explored the significance of SOCE in mediating the response of human lung fibroblasts to chemical stimuli. They discovered that beractant, a natural lung surfactant, not only promoted an anti-fibrogenic response but also induced apoptosis in normal human lung fibroblasts. The action of beractant was mediated through beractant-dependent increase in intracellular Ca^{2+} levels through ER Ca^{2+} release and SOCE. Importantly, inhibition of Ca^{2+} mobilization effectively blocked the anti-fibrogenic and pro-apoptotic effects of beractant (Guzman-Silva et al., 2015). These studies align with the common dual theme of Ca^{2+} signaling, whereby physiological levels of SOCE drive fibrogenic programs while excessive SOCE activation (as induced by beractant) acts as anti-fibrogenic through activation of apoptosis (Benson and Trebak, 2023).

Cardiac Fibroblasts. Ross et al. investigated the specific effects of SOCE on collagen secretion in human ventricular fibroblasts from heart failure patients compared to those from healthy controls. Their findings showed a significant increase in Ca^{2+} influx via SOCE in the heart failure group, which was closely associated with elevated collagen secretion and increased expression and co-localization of Orai1 and STIM1. Importantly, their study showed that the SOCE inhibitor YM58483 significantly reduced collagen secretion in these fibroblasts (Ross et al., 2017). Čendula et al. examined the changes in mRNA expression of STIM and Orai isoforms in human cardiac fibroblast cultures activated by cardiovascular stress mimetics, phenylephrine and isoprenaline. This activation resulted in an upregulation of Orai2 and STIM2 mRNA expression, suggesting that SOCE might be enhanced (Cendula et al., 2021).

Angiotensin II (Ang II) is a profibrotic hormone that plays a central role in driving fibrosis across various conditions by upregulating SMAD2 and enhancing TGFβ1 production, which facilitates the transformation of fibroblasts into collagen-secreting myofibroblasts (Li et al., 1997; Mezzano et al., 2001; Rosenkranz et al., 2002; Watanabe et al., 2005). In cardiac fibroblasts specifically, Ang II notably increases the expression of STIM1 and Orai1. The increase in fibrosis-associated proteins such as fibronectin, connective tissue growth factor, and α-SMA, triggered by Ang II, can be significantly reduced through the inhibition of SOCE using SKF-96365 or by silencing STIM1 and Orai1. Silencing Orai1 not only diminished these fibrotic markers but also impeded the translocation of NFATc4 and the phosphorylation of Smad2 and Smad3 (Zhang et al., 2016a).

Other Fibroblasts. Activated pancreatic stellate cells, which function analogously to fibroblasts in other tissues, play a crucial role in the development of fibrosis within the pancreas. One study by Radoslavova et al. showed that knockdown of Orai1 in activated pancreatic stellate cells leads to a reduction in cell proliferation, TGFβ1 production and activation of AKT. The authors proposed the existence of a TGFβ1-induced autocrine feedback loop in these cells that promotes Orai1 upregulation and AKT activation to enhance proliferation (Radoslavova et al., 2021).Wu et al. highlights the critical role of SOCE in the activation and differentiation of fibroblasts in systemic sclerosis, a key factor in the disease's pathogenesis. Enhanced SOCE activity was observed in systemic sclerosis fibroblasts, directly correlating with the progression of systemic fibrosis. The application of non-specific inhibitors of SOCE, including 2APB, SKF96365, and indomethacin, reduced fibrosis markers and facilitated the dedifferentiation of these fibroblasts. This study noted that exogenous factors such as gelatin-1 and human albumin further influenced fibroblast differentiation through increased SOCE activity (Wu et al., 2019).

Epithelial Cells

Epithelial and endothelial cells play crucial roles in the progression of fibrosis, significantly influencing tissue remodeling and the fibrotic response across various organs. These cells are not only critical for initiation of inflammation and

activation of fibroblasts but also affect the recruitment of immune cells. Epithelial and endothelial cells serve as vital sources of myofibroblasts through processes known as epithelial-mesenchymal transition (EMT) and endothelial-mesenchymal transition (EndoMT). Epithelial cells play a crucial role in maintaining the stability of organs. However, when these cells undergo injury-induced apoptosis, it disrupts the structural integrity of tissues, leads to ineffective repair mechanisms, and activates fibroblasts—all essential elements in the development of fibrosis (Parimon et al., 2020; Carraro et al., 2021). Notably, in conditions with an epithelial origin of fibrosis, epithelial cells are major contributors to the myofibroblast population through EMT (Ng et al., 1998; Iwano et al., 2002; Woo et al. 2004; Willis et al., 2006; Park et al., 2007; Liu, 2010; Micallef et al., 2012; He et al., 2013; Distler et al., 2019; Yao et al., 2019).

SOCE plays a critical role in regulating essential functions of epithelial cells, such as proliferation, permeability, secretion, and remodeling, which are vital for maintaining their health and integrity (Liu et al., 2019; Uwada et al., 2019). SOCE also plays a key role in inflammation, epithelial barrier function, and induction of EMT, all of which are pivotal in the pathogenesis and progression of fibrosis (Jairaman and Prakriya, 2024). The transformation of epithelial cells into myofibroblasts is largely driven by the TGF-β1/Smad signaling pathway, a fundamental regulator of fibrosis (Roberts et al., 2006; Meng et al., 2015). This pathway promotes the transcription of target genes that contribute to ECM production and induces the trans-differentiation of epithelial cells into a more mesenchymal phenotype. (Hills and Squires, 2011; Meng et al., 2015). This transition is characterized by the loss of E-cadherin and the upregulation of myofibroblast markers such as α-smooth muscle actin and vimentin, significantly enriching the myofibroblast pool in fibrotic diseases (Liu, 2004). Interestingly, research has shown that TGF-β1 enhances SOCE, particularly noted in A549 cells, an epithelial-derived cell line. Ca^{2+} influx through SOCE appears to be a crucial mediator in the EMT process, as demonstrated by studies where modulation of internal Ca^{2+} levels with agents like thapsigargin or the cytosolic Ca^{2+} chelator BAPTA-AM significantly influence the TGF-β1-induced EMT via the Smad signaling pathway (Wu et al., 2017). These findings suggest that the EMT process triggered by TGF-β1 is intricately linked to Ca^{2+} signaling.

The role of SOCE in epithelial inflammation and cellular damage is particularly evident in gastrointestinal health, where inhibition of SOCE in intestinal epithelial cells is emerging as a promising strategy for managing the disruption of epithelial barrier function (Uwada et al., 2019; Glauben et al., 2022). A study by Liang et al. showed that STIM1 expression is increased in intestinal tissues from inflammatory bowel disease (IBD) patients. They showed that mice lacking STIM1 specifically in intestinal epithelium have increased goblet cell survival, reduced epithelial damage under inflammatory stress and protected intestinal epithelium. This was attributed to the inhibition of SOCE, presumably reducing ER stress and production of inflammatory cytokines by T cells (Liang et al., 2022). Balghi et al. showed that pathogenic mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) gene result in increased activity of Orai1 channels and elevated SOCE in human airway epithelial cells. This aberration leads to enhanced secretion of IL-8, exacerbating inflammation—a process typically regulated by the CFTR-dependent modulation of the Orai1/STIM1 complex (Balghi et al., 2011).

Mai et al. studied Orai1 in renal fibrogenesis using both *in vitro* models of human proximal tubule epithelial cells (HK2) and *in vivo* models, specifically a high-fat diet in ApoE knockout mice and unilateral ureteral obstruction in C57/BL6 mice (Mai et al., 2016). These studies found increased expression of Orai1 in kidney tissues from these disease models. Similarly, kidney biopsies from patients with fibrotic nephropathy exhibited elevated Orai1 levels compared to those with minimal disease, establishing a clear link between Orai1 expression and human kidney fibrosis. Crucially, knockdown of Orai1 reduced TGF-β1-induced Ca^{2+} influx and phosphorylation of Smad2/3, which halted the EMT process, as documented by reduced expression of key fibrotic markers such as fibronectin and α-SMA. Specific inhibition of calcineurin (with FK506) but not the inhibition of CaMKII (with KN93), significantly reduced the phosphorylation of smad2/3 and lowered the expression of mesenchymal markers. However, contradictory findings have emerged regarding the role of Orai1 and SOCE in fibrotic processes across different cell types. While Orai1 appears to promote fibrosis in proximal tubular epithelial cells, its function in mesangial cells suggests a protective role against fibrosis, as SOCE has been shown to negatively regulate TGF-β1/Smad3 signaling and ECM production in these cells (Wu et al., 2015, Chaudhari et al., 2017). One potential reason for this controversy lies in the differing contributions of these cell types to kidney fibrosis at various stages. Mesangial cells are more involved in the early stages of diabetic nephropathy, contributing to mesangial expansion, whereas proximal tubular epithelial cells play a significant role in the later stages, characterized by interstitial fibrosis. The varying impact of Orai1 in these cell types and stages underscores the complexity of its role in renal fibrosis and highlights the need for further research to clarify these cell-specific effects.

Zhang et al. showed that increased expression of STIM1 in lupus nephritis (LN), a systemic autoimmune disease that is associated with exacerbated fibrosis and renal dysfunction. Specifically, elevated STIM1 levels were found to correlate with increased levels of fibronectin, α-SMA, urine protein, blood urea nitrogen, and serum creatinine—markers indicative of worsening fibrosis. Furthermore, exposure to lipopolysaccharide (LPS) augmented STIM1 expression as well as fibronectin and α-SMA in mouse renal tubular epithelial cells. This coincided with a decrease

in E-cadherin, signaling a shift towards EMT and subsequent fibrosis. Critically, STIM1 silencing attenuated these effects (Zhang et al., 2020).

Collectively, these studies indicate that SOCE plays a role in epithelial cell functions, including inflammation, barrier function, and cellular transitions such as EMT, all of which are pivotal in the pathogenesis and progression of fibrosis. Given that epithelial cells can transform into myofibroblasts—the primary builders of the fibrotic matrix that are notoriously resistant to apoptosis—targeting SOCE presents a promising avenue. In principle, SOCE inhibition could prevent the transformation of epithelial cells into myofibroblasts, thereby indirectly inhibiting myofibroblasts activity. This approach would curb the unchecked proliferation and activity of myofibroblasts but also inhibit the sustained inflammation and remodeling that characterize the fibrotic diseases.

Endothelial Cells

Endothelial cells play a critical role in the progression of fibrotic tissue remodeling, primarily through their involvement in angiogenesis, tissue remodeling, and the production of reactive oxygen species (ROS). These cells are central to the formation of new blood vessels supporting their growth and persistence (Lee et al., 2021). In addition to promoting angiogenesis, endothelial cells contribute to tissue remodeling and injury through ROS, which cause cellular damage and inflammation, further exacerbating fibrosis (Pardo et al., 2016; Bartneck et al., 2019; Sutti et al., 2019). Consequently, sustained inflammation leads to the recruitment of additional immune cells via a feedback loop that self-amplifies this effect (Lurje et al., 2023). The role of SOCE in blood vessels including endothelial cells dysfunction and vascular smooth muscle cell dedifferentiation is thoroughly discussed elsewhere (Trebak, 2009; Moccia et al., 2014; Zhou et al., 2014; Johnson and Trebak, 2019; Lu et al., 2022; Moccia et al., 2023). Here, we will focus on how SOCE impacts particular endothelial cell functions that are pivotal in fibrosis development. Specifically, endothelial SOCE is expected to modulate fibrogenesis through proliferation, angiogenesis, ROS production, vascular inflammation and remodeling, mesenchymal transition and change in endothelial barrier function. Together, these actions would facilitate the growth of the myofibroblast pool at injury sites, exacerbating fibrosis.

Abdullaev and colleagues were first to show that SOCE and I_{CRAC} in endothelial cells is mediated by STIM1 and Orai1 proteins, rather than by the previously thought TRPC channels. Disruption of STIM1 or Orai1 impairs SOCE, resulting in cell cycle arrest and decreased endothelial cell proliferation underscoring the essential role of SOCE in endothelial cell biology (Abdullaev et al., 2008). Subsequent studies showed that SOCE is indispensable for endothelial cell proliferation and activation, as knockdown of Orai1 and SARAF (SOCE-associated regulatory factor) severely hindered endothelial proliferation and migration (Chen et al., 2011; Li et al., 2011; Galeano-Otero et al., 2021). Angiogenesis plays a critical role in tissue repair and fibrotic remodeling after injury, as it enhances blood flow to meet increased metabolic demands and draws additional cells to the injury site, exacerbating tissue damage and disrupting ROS homeostasis (Lee et al., 2021). The angiogenic process is largely driven by factors such as vascular endothelial growth factor (VEGF), which initiates signaling pathways that elevate intracellular Ca^{2+} levels through SOCE (Abdullaev et al., 2008). Recent studies have underscored the pivotal role of SOCE in angiogenesis across various models. Specifically, knockdown of Orai1 in human umbilical vein endothelial cells (HUVEC) disrupts the VEGF-induced intracellular Ca^{2+} rise and adversely affects HUVEC tube formation, proliferation, and migration (Galeano-Otero et al., 2022).Yu et al. proposed that Orai1 plays a significant role in vascular inflammation by regulating the expression of adhesion molecules in endothelial cells and influencing interactions with immune cells. Alterations in Orai1 levels—decreasing or increasing—correspondingly reduce or exacerbate inflammation and tissue damage triggered by TNF-α. The Orai1-Ca^{2+}-calcineurin-NFATc4 signaling axis is central for endothelial activation, suggesting that endothelial Orai1 could be a target for anti-inflammatory therapies (Yu et al., 2018). Additionally, a number of studies suggested that SOCE further contributes to this inflammatory process by maintaining Ca^{2+} levels within endothelial cells, crucial for managing oxidative stress response in the fibrotic environment (Oike et al., 1994; Vaca and Kunze, 1994; Blatter, 2017; Savage et al., 2019). STIM1 was shown as required for agonist-induced disruption of endothelial barrier function through mechanisms that do not rely on Ca^{2+} signaling and are independent of Orai1(Shinde et al., 2013). This SOCE-independent function of STIM1 might play a pivotal role in endothelial barrier integrity within the fibrotic environment (Antigny et al., 2011; Li et al., 2011; Shinde et al., 2013; Lu et al., 2022).

Immune Cells

Dysregulated immune function during tissue healing can lead to fibrosis causing excessive tissue repair and scarring. Proper tissue regeneration depends on two critical regulatory mechanisms: (1) the initiation of activation signals that promote healing; (2) the maintenance of inhibitory, tolerogenic signals whose absence can lead to uncontrolled activation and consequently, excessive healing and fibrosis. The activation phase of tissue healing is divided into two key stages. An initial pro-inflammatory phase that jumpstarts the healing process, followed by a profibrotic phase where fibroblasts proliferate and deposit extracellular matrix, often resulting in scar formation. Each phase is marked by a

distinct cellular milieu tailored to either combat the initial injury or rebuild tissue structure. For instance, during the pro-inflammatory phase, cytokine-mediated inflammation activates T cells and recruits neutrophils and macrophages to clear debris and facilitate the transition to the profibrotic tissue repair phase. This transition involves a shift in immune cell composition from acute inflammatory phenotypes towards profibrotic ones, notably the polarization of macrophages towards a pro-fibrotic "M2-like" phenotype and a shift in T-cells towards Th17 and Th2 responses with their associated profibrotic cytokine profiles (Travis and Sheppard, 2014; Distler et al., 2019; Guillot and Tacke, 2019). When this delicate balance is disrupted by persistent inflammation or an exaggerated fibrotic response, pathological fibrosis can ensue, resulting in permanent scarring. The importance of SOCE in immune function is clearly demonstrated in clinical settings, as evidenced by patients with loss-of-function mutations in STIM1 and Orai1. These mutations abrogate CRAC channel activity and lead to severe combined immunodeficiency (SCID), characterized by a significant reduction in lymphocyte activation, proliferation, and cytokine production, leading to a complex condition marked by impaired immunity to pathogens, autoimmunity, and other non-immunological complications (Partiseti et al., 1994; Le Deist et al., 1995; Feske et al., 1996; Feske et al., 2006; Feske, 2007; McCarl et al., 2009; Picard et al., 2009; Fuchs et al., 2012; Klemann et al., 2017; Lian et al., 2018; Clemens and Lowell, 2019; Trebak and Kinet, 2019; Kahlfuss et al., 2020; Vaeth et al., 2020). The role of SOCE in regulating the immune cell milieu specifically within the fibrotic microenvironment remains essentially unknown. Therefore, below we will extrapolate from the established roles of SOCE in the immune system to explore its potential influence in modulating immune responses in the fibrotic microenvironment.

Adaptive Immunity. When epithelial or endothelial cells are damaged, they release pro-inflammatory substances that initiate the recruitment, activation and maturation of T cells within the fibrotic environment. Naive $CD4^+$ T cells can differentiate into various mature $CD4^+$ T helper cell types, including Th1, Th2, Th17, Tfh (follicular helper), and Treg (regulatory), each characterized by a unique cytokine profile with varying impacts on inflammation and fibrosis. In addition to $CD4^+$ T cells, cytotoxic $CD8^+$ T cells are also recruited to the site of injury to assist in clearing debris. Normally, these cellular subsets work in harmony to achieve the sweet spot by inducing inflammation, which is considered the first step in tissue repair, and promote the fibrotic phase while achieving immune tolerance to prevent exaggerated and deleterious immune responses. However, it is believed that skewed immune activation results in biases towards excessive fibrotic states. Studies suggest that the absence of mature T cells can mitigate fibrosis post-injury, emphasizing their crucial role in fibrosis. (Bank, 2016). Here, we will delve into the specific contributions of each T cell subtype in promoting inflammation, fibrosis, or tolerogenic responses, all of which are crucial stages of fibrosis (Wynn and Ramalingam, 2012; Distler et al., 2019). When relevant, we will also explore the reported role of SOCE in regulating these functions, highlighting how SOCE within each T cell subtype might impact on the fibrotic process.

Th1 Cells. Th1 cells are an integral part of the inflammatory process, which is essential in the early phase of tissue repair, mainly through IFN-γ and TNF-α production. During the inflammatory phase, Th1 cells aid tissue repair by producing IFN-γ to enhance inflammation. However, the role of Th1 cells in fibrosis is complex and highly context-dependent, illustrated by varying effects across different models of fibrosis. In some cases, pro-inflammatory cytokines such as IFN-γ and IL-1β are associated with increased presence of pro-inflammatory and fibrosis-promoting macrophages, leading to renal fibrosis as demonstrated in some studies (Wen et al., 2019). Similarly, in cardiac fibrosis, elevated levels of IFN-γ+ Th1 cells have been linked to increased stimulation of TGF-β production by cardiac fibroblasts, and exacerbation of fibrosis (Nevers et al., 2017). In systemic sclerosis (SSc), IFN-γ is implicated in causing vascular damage, further complicating the fibrotic process (Ayano et al., 2015). Conversely, other models present a different narrative (Vu et al., 2019). For instance, in idiopathic pulmonary fibrosis (IPF) and the unilateral ureteral obstruction (UUO) models, IFN-γ may exert anti-fibrotic effects, highlighting the dual and often contradictory roles of Th1-derived cytokines in fibrosis (Luzina et al., 2008; Dong et al., 2016). This dichotomy underscores the complexity of Th1 function, which vary depending on the stage of the disease; they assist in tissue repair by enhancing inflammation through IFN-γ production during the inflammatory phase, but an uncontrolled increase in IFN-γ can lead to hyperinflammation and exacerbate the injury. While not studied specifically in Th1 cells within the context of fibrosis, SOCE regulates cytokine production in Th1 cells, which is integral for their function. Studies have reported that STIM1−/− or Orai1fl/fl Cd4Cre mice, which display partially reduced SOCE, have attenuated serum concentrations of IFN-γ and TNF-α. Additionally, murine T cells with specific knockout of STIM1/STIM2 or Orai1/Orai2 have their cytokine production capabilities abolished, impairing the ability of T cells to combat infections. (Oh-Hora et al., 2013; Shaw et al., 2014; Vaeth et al., 2016; Vaeth et al., 2017c).

Th2 Cells. A prevalent aspect of T cell behavior in the profibrotic phase is a bias towards Th2 cell responses. Th2 cells plays a vital role in various fibrotic disease, including those affecting the liver, skin, lungs, kidneys, and systemic sclerosis (Oriente et al., 2000; Lee et al., 2001). Th2 cytokine

profile has a profibrogenic signature. Emphasizing the potential role of SOCE in mediating Th2 profibrotic activity, studies have shown that IL-4 levels are significantly lower in T cells that lack either STIM1 or Orai1, compared to control T cells. Th2 and Tfh cells from mice with double STIM1/STIM2 knockout or Orai1/Orai2 knockout have nearly undetectable IL-4 levels (Gwack et al., 2008; Oh-Hora et al., 2008; Vaeth et al., 2017a; Vaeth et al., 2017c). Conversely, introducing STIM1 or STIM2 into murine CD4+ T cells *in vitro* caused an increase IL-4 production (Oh-Hora et al., 2008). Ex vivo stimulation of T-cell isolated from patients with loss of function in STIM1 and Orai1, showed reduction in the Th2 cytokines IL13, and IL-4 (Feske et al., 2000; Vaeth et al., 2016). SOCE is reported to regulate the defining transcription factor GATA3 that showed reduced levels when T-cells were treated with CRAC channel inhibitors (Yasuda et al., 2019). Several studies have demonstrated that IL-13 and IL-4 act as important inducers of fibrosis in several diseases. Together with TGF-β, IL-13 and IL-4 are thought to be the most prominent profibrotic cytokines in liver, lung and skin fibrosis models. They activate fibroblasts and its transition to myofibroblast. They also stimulate the polarization of Macrophage towards the profibrotic phenotype M2 and the subsequent of TGF-β secretion by macrophages. (Zurawski et al., 1993; Fichtner-Feigl et al., 2006; Borthwick et al., 2013; Zhu, 2015; Junttila, 2018). Given that SOCE can control the release of these cytokines form multiple T cell subsets (Feske et al., 2000; Vaeth et al., 2016), one can speculate that specific inhibition of CRAC channel activity in T cells might be protective against fibrosis.

Th17 Cells. Pathogenic Th17 cells play a role in fibrosis across various organs, notably in diseases of the liver, kidney and lungs. They secrete IL-17, which promotes fibrosis in both liver and kidneys (Meng et al., 2012; Peng et al., 2015). In IPF, PD1+ Th17 cells secrete both IL-17 and TGFβ enhancing collagen production through a STAT3-dependent mechanism (Celada et al., 2018). Inhibition of IL-17 secretion using a RORγt inhibitor inhibits liver fibrosis and decreases fibroblast collagen production, offering further protection against liver fibrosis. (Meng et al., 2012; Brodeur et al., 2015; Peng et al., 2015; Majd et al., 2016; Celada et al., 2018; Tsui et al., 2018). SOCE is integral to the regulation of Th17 cells, impacting their secretion of cytokines including IL-17A, IL-17F, and GM-CSF. This regulatory influence hints at SOCE's potential involvement in the pathogenesis of fibrosis through its modulation of Th17 cell activity. The deletion of Orai1 or STIM1 from T cells in mice significantly diminishes these cytokines, which in turn affects both inflammatory and fibrotic pathways (Ivanov et al., 2006; Ivanov et al., 2006; Ma et al., 2010; McCarl et al., 2010; McCarl et al., 2010; Vaeth et al., 2017c; Lian et al., 2018; Yasuda et al., 2019). SOCE is crucial for the differentiation of Th17 cells by regulating essential transcription factors such as RORγt. This regulation is evidenced by impaired RORγt expression in CD4+ T cells from Stim1 fl/fl Cd4 Cre mice, as well as reduced RORγt levels observed in Orai1−/− mice (Kim et al., 2014), highlighting the significance of SOCE for the differentiation of pathogenic Th17 cells (Gaffen et al., 2014). Additionally, STAT3C + Th17 cells rely on SOCE for their proinflammatory activity (Maus et al., 2017). These studies collectively demonstrate that disruptions in SOCE lead to decreased expression of signature genes and cytokines characteristic of pathogenic Th17 cells, consequently impacting their pathogenic potential and the manifestation of associated diseases (Vaeth et al., 2012; Calautti et al., 2018)

Tfh Cells. T follicular helper (Tfh) cells are increasingly recognized for their significant role in fibrosis. Beyond its previously described role in IL-4 secretion, there is growing evidence of Tfh cell involvement in fibrosis via secretion of IL-21. This cytokine directly activates fibroblasts and serves as a crucial mediator for Th17 and Th2 cell responses, enhancing their secretion of IL-13 and contributing to fibrosis (Brodeur et al., 2015). Neutralization of IL-21 has demonstrated a reduction in dermal inflammation and fibrosis in mouse models of graft-versus-host disease, underscoring its therapeutic potential (Taylor et al., 2018). Moreover, Tfh-like cells expressing inducible T-cell co-stimulator (ICOS), and programmed cell death 1 (PD1) receptors are markedly elevated in patients with systemic sclerosis (SSc), correlating with disease prognosis. These ICOS + Tfh-like cells are implicated in the perpetuation of fibrosis in SSc models, mediated by IL-21 (Brodeur et al., 2015; Taylor et al., 2018). It is noteworthy that SOCE is indispensable for Tfh cell regulation as even moderate levels of SOCE are sufficient to support Tfh cell function, while complete abrogation of SOCE severely impairs humoral immunity. SOCE influences a broad array of genes critical for initiating Tfh cell differentiation, including Icos, Cxcr5, Pdcd1, Btla, Cd40l, Ox40, IL-21, and IL-4, in both murine and human CD4+ T cells. Furthermore, the transcription factors IRF4 and BATF, essential for follicular T cell differentiation, are notably diminished in STIM1/STIM2 deficient Tfh cells, leading to increased production of autoantibodies (Vaeth et al., 2016; Vaeth et al., 2019). Thus, SOCE supports the essential functions of Tfh cells and modulates the expression of key receptors, ligands, and transcription factors crucial for their differentiation and function, highlighting its central role in regulating immune responses potentially within various fibrotic environments (Vaeth et al., 2016).

CD8 + Cytotoxic T Cells. The influence of SOCE on CD8+ T cells warrants significant attention. CD8+ T cells are crucial in mediating cytotoxic damage to epithelial and endothelial cells, processes that can significantly contribute to the pathology of fibrosis. CD8+ T cells are involved in the

secretion of IL-13 in conditions like systemic sclerosis, highlighting their role in inflammation (Ayano et al., 2015). The regulatory influence of SOCE on these cells encompasses their cytotoxic activity and their cytokine secretion (Weidinger et al., 2013). Interestingly, tempering SOCE activation in $CD8^+$ cytotoxic T cells has been shown to improve, rather than reduce, their cytotoxic activity towards cancer cells, highlighting the complexity and context-dependent nature of this regulation (Zhou et al., 2018). The reported dependence of CD8+ T cell cytotoxic functions on SOCE underscores the critical and complex nature of SOCE in controlling the balance between tissue repair and pathological fibrosis (Weidinger et al., 2013).

Treg Cells. In the intricate landscape of tissue repair, and the balance between activation signals that promote healing and the maintenance of inhibitory signals during fibrosis is clearly critical. The absence of these regulatory signals can lead to uncontrolled T cell activation, resulting in excessive inflammation/healing and subsequent fibrosis. This tolerogenic function is primarily governed by regulatory T cells (Tregs). Tregs control the activation of the other T cell subsets that are critical for maintaining immunological homeostasis. For instance, depletion of Foxp3 + CD4+ Treg cells has been linked to increased lung inflammation(Ichikawa et al., 2019). In the liver, Tregs mitigate the profibrotic activities of Th17 cells by reducing the production of IL-17 and IL-22, which in turn inhibits the activation of hepatic stellate cells, key players in liver fibrosis (Li et al., 2012). However, the role of Tregs in fibrosis is complex and context-dependent. While commonly T-regs dial down the excessive immune response, they have been reported in mice to paradoxically exacerbate cardiac remodeling post-myocardial infarction (Bansal et al., 2019) In this scenario, an expanded Treg population loses its regulatory capabilities, leading to increased production of TNF-α and IFN-γ, and their removal has been shown to reverse heart remodeling and fibrosis (Bansal et al., 2019). Along the same lines, in liver fibrosis, Tregs can delay the recovery of normal liver structure by inhibiting matrix metalloproteases production by Kupffer cells (Zhang et al., 2016b). This demonstrates the dualistic nature of Treg involvement in fibrosis, emphasizing their critical role in both promoting and inhibiting tissue repair depending on the physiological context.

SOCE is essential for the development, function, and maintenance of Tregs. Deletion of STIM1 and STIM2 significantly affects both the numbers and the function of Tregs (Oh-Hora et al., 2008; Fuchs et al., 2012; Oh-Hora et al., 2013; Schaballie et al., 2015; Lian et al., 2018; Vaeth et al., 2019). Specifically, hematopoietic or thymocyte-specific knockouts of STIM1 and STIM2 lead to a noticeable reduction in the development of Foxp3+ Treg cells. The complete elimination of SOCE in T cells by Orai1 and Orai2 double knockout in mice results in reduced numbers of thymic and peripheral Treg cells (Oh-Hora et al., 2008; Maul-Pavicic et al., 2011; Fuchs et al., 2012; Oh-Hora et al., 2013; Desvignes et al., 2015; Schaballie et al., 2015; Lian et al., 2018; Vaeth et al., 2019). Patients with loss-of-function mutations in Orai1 exhibit significant reductions in both thymic and peripheral Treg cells compared to healthy controls (Vaeth et al., 2016; Vaeth and Feske, 2018). Obviously, the critical and widespread functions of SOCE in both the pro-inflammatory and pro-tolerogenic responses of the immune system would need to be taken into consideration in any therapeutic attempts targeting SOCE in fibrosis. Potential differences in the CRAC channel molecular composition between different T cell subsets might offer opportunities for specific targeting of SOCE in a specific T cell subset (e.g., Tregs, or Tfh). This underscores the necessity of additional studies into CRAC channel composition and stoichiometry in various cell types within the fibrotic environment within critical organs such as the heart, skin, liver, and lungs.

Innate Immunity. Innate immunity serves as a cornerstone in the development and exacerbation of fibrotic diseases, operating through an array of effector cells that react to tissue damage and infection. This essential immune layer ensures rapid pathogen clearance and orchestrates the complex inflammatory responses that initiate tissue repair and subsequent fibrosis. Key players such as neutrophils, monocytes, macrophages, mast cells, and dendritic cells mediate these processes by secreting cytokines, executing phagocytosis, and interacting within the damaged tissue microenvironment. However, an imbalance in these innate responses often leads to pathological fibrosis, significantly impacting disease progression. SOCE mediates innate immune functions through multiple layers—either directly by influencing the functions of these immune components or indirectly by affecting their activation and polarization through its effects on cytokine secretion (discussed above) and the metabolic control of other adaptive and parenchymal components, as detailed elsewhere (Clemens and Lowell, 2019). The following sections delve into the specific functions of SOCE, underscoring its influence in balancing protective innate immune responses against the risks of chronic fibrotic pathology.

Neutrophils. Neutrophils play a multifaceted role in promoting inflammation and fibrogenesis in various diseases. They orchestrate this through several mechanisms including phagocytosis, degranulation, ROS production, the formation of neutrophil extracellular traps, secretion of exosomes, and the release of cytokines and chemokines, as well as through autophagic processes. Neutrophilia, or an increased presence of neutrophils, is a common characteristic across numerous fibrotic diseases (Downey et al., 2009; Gifford and Chalmers, 2014; Ding et al., 2021; Achaiah et al., 2022; Jegal, 2022; Yan et al., 2023). SOCE influences neutrophil activation and the production of ROS. Studies using mice with a hematopoietic deletion of Orai1 and/or Orai2 showed that these proteins collaboratively regulate SOCE

in neutrophils, with a noted decrease in SOCE in Orai2−/− neutrophils, suggesting different functions of Orai2 in innate versus adaptive immune cells (Demaurex and Saul, 2018; Grimes et al., 2020). Knockout of Orai1 or Orai2 impaired SOCE in neutrophils, while double Orai1/Orai2 knockout abolishes SOCE and disrupts various neutrophil functions such as phagocytosis, degranulation, leukotriene synthesis, and the production of ROS (Grimes et al., 2020). Orai1/Orai2 double knockout in the undifferentiated neutrophilic promyelocyte HL-60 cells, significantly impaired SOCE and cell proliferation (Diez-Bello et al., 2017). In differentiated HL-60 cells, Orai1 knockdown impairs Ca^{2+} influx (Steinckwich et al., 2007; Steinckwich et al., 2011), and the polarized migratory phenotype of neutrophils (Schaff et al., 2010). Polymorphonuclear neutrophils from a patient with Orai1 loss of function mutation showed mildly reduced SOCE (Elling et al., 2016). A STIM1-independent mechanism for Orai1 was proposed for complement C5a receptor activation and neutrophil recruitment (Sogkas et al., 2015b). It is worth noting that in this study they reported a surprisingly normal SOCE magnitude in neutrophil isolated from Orai1-deficient hematopoietic chimeric mice. This discrepancy might be due to the differences in isolation methods that could change the activation status, cellular response and the dominant channel composition of neutrophils (Clemens and Lowell, 2019). Activation of Orai1 is consistently high in blood neutrophils of cystic fibrosis patients, regardless of their CFTR modulator treatment. There is also an enhanced colocalization of Orai1/STIM1 in lung epithelial, interstitial, and luminal immune cells in both asthma and cystic fibrosis patients (Goriounova et al., 2023).

Monocytes and Macrophages. Monocytes from the CX3CR1+ CD117 + subset in bone marrow migrate to injury sites and differentiate into macrophages or dendritic cells, key for clearing debris and managing inflammation and tissue repair (Wynn and Barron, 2010; Jakubzick et al., 2017; Lee et al., 2018). Macrophages respond to cytokines and environmental stimuli with dynamic phenotypic changes that significantly impact fibrosis and tissue repair. While IFN-γ and TNF-α promote an inflammatory M1 state needed to induce inflammation typical at the early stages of tissue repair, IL-4 and IL-13 induce an M2 polarization for the subsequent profibrotic phenotype. Although the simplified M1-M2 classification hides the complexity of macrophage functions across various stages of disease and healing, it provides nonetheless an idea on the dynamic phenotypes that macrophages can acquire during tissue repair process (Wynn and Barron, 2010; Murray et al., 2014; Wynn and Vannella, 2016). Macrophages activated by IL-4 and IL-13 exhibit a profibrotic signature that correlates with increased disease severity in systemic sclerosis (Taroni et al., 2017) and contribute to pulmonary fibrosis (Aegerter et al., 2022). In liver fibrosis, macrophages can replace Kupffer cells and influence disease outcomes based on their polarization (Wen et al., 2021). The function of monocytes in liver fibrosis is also twofold, as they can promote repair or contribute to fibrosis, depending on their subtype and environmental cues. Therapeutic targeting of macrophages using the CCR2/CCR5 antagonist, cenicriviroc, has reduced fibrosis markers in non-alcoholic steatohepatitis (NASH) (Friedman et al., 2018; Ratziu et al., 2020; Kurth et al., 2023).

STIM and Orai proteins are expressed in monocytes and macrophages and their expression levels dynamically changes based on the polarization and activation status as well as the tissue microenvironment. For instance, in resting monocytes the expression levels of Oai1, Orai2, and Orai3 are different, resting blood monocytes show similar levels of all three Orais, while bone marrow and peritoneal macrophages have a higher expression of Orai3, with Orai1 being predominantly expressed in inflammatory macrophages (Saul et al., 2016; Clemens and Lowell, 2019). In the context of fibrosis, SOCE in monocytes and macrophages seems to be pivotal. SOCE can influence macrophage polarization indirectly by modulating the production of IL-13 and IL-4 by different T-cell subsets as discussed earlier, thereby playing a crucial role in immune response regulation. On the other hand, the regulation of CRAC channels in macrophages is less clear, with studies showing opposing results. CRAC channels in human monocytes were proposed to be essential for ROS production and bacterial elimination, with the oxidant-resistant Orai3 playing a critical role in maintaining CRAC channel activity during oxidative stress (Saul et al., 2016). Other studies suggested that STIM1 is necessary for effective phagocytosis in peritoneal macrophages, while a lack of STIM2 reduces their migration and cytokine output (Braun et al., 2009; Sogkas et al., 2015a). Another report showed that SOCE is important for macrophage chemotaxis (Fresquez et al., 2024). There is also some evidence pointing to a role for Orai1 in LDL-triggered SOCE in macrophage-like THP-1 cells (Liang et al., 2016). Protective effects in models of autoimmune diseases and sepsis have been observed with the use of Stim1−/− chimeras or with CRAC channel blockers such as BTP2, although it remains uncertain whether these effects are directly attributable to macrophages (Sogkas et al., 2015a; Sogkas et al., 2018). On the other hand, studies by Vaeth et al. showed that macrophages deficient in both STIM1 and STIM2 display no noticeable functional impairments despite the absence of SOCE (Vaeth et al., 2015).

Mast Cells. Mast cells, integral to the innate immune system, are traditionally linked to IgE-mediated allergic reactions. However, their significant involvement in chronic inflammatory and autoimmune diseases, often tied to fibrosis, has gained increasing attention. Mast cells are significant participants in various diseases characterized by tissue remodeling, such as asthma and atopic dermatitis. They release a variety of mediators that can induce inflammation and promote fibrosis, including cytokines and growth factors.

In systemic sclerosis, mast cells contribute significantly to the fibrotic process, particularly through the release of TGFβ. Their interaction with fibroblasts suggests a key role in tissue fibrosis, and their hyperactivity is noted in fibrotic disorders of the lungs, heart, and kidneys. Mast cells are considered critical players in the initiation of pulmonary fibrosis (Pesci et al., 1993; Tuder, 1996; Roberts and Brenchley, 2000; Hara et al., 2002; Levick et al., 2009; Veerappan et al., 2013; Hugle, 2014; Kong et al., 2014; Bagher et al., 2021).

Recent studies employing CRAC channel inhibitors underscore the crucial roles of STIM and Orai proteins in the FcεRI-mediated signaling of mast cells. The SOCE inhibitor, Synta66 has been shown to inhibit SOCE and lower cytokine and histamine outputs in human lung mast cells and cell lines (Ashmole et al., 2012; Wajdner et al., 2017). Knockdown studies in the RBL-2H3 mast cell line indicate that STIM1 and Orai1 are essential for SOCE, with Orai2 as a negative regulator of SOCE in these cells (Gross et al., 2007; Ma et al., 2008). This pattern was also observed in OUMS-27 cells, where reducing Orai2 levels resulted in heightened SOCE (Inayama et al., 2015). Recent experiments with Orai2-deficient mice also demonstrated that loss of Orai2 in mast cells led to enhanced SOCE and greater mast cell degranulation, indicating that Orai2 is a negative regulator of SOCE, akin to its role in T cells (Lian et al., 2018; Tsvilovskyy et al., 2018). Insights into the essential role of SOCE in mast cell regulation have been provided by gene knockout experiments in mice, where mast cells deficient in either Orai1 or STIM1 showed reduced Ca^{2+} influx and diminished anaphylactic responses due to lower histamine, leukotriene, and TNF-α production (Baba et al., 2008; Gwack et al., 2008; Vig et al., 2008).

Dendritic Cells

Dendritic cells (DCs), serve as mediators between the innate and adaptive branches of the immune system and play a vital role in the pathology of fibrosis. These cells are adept at capturing and processing antigens, a process essential for priming and facilitating T-cell responses. The maturation of DCs, a key step for effective antigen presentation, is intricately influenced by the inflammatory milieu and the specific microenvironment of the tissue they inhabit. This results in a diverse array of functions across different DC subsets (Sogkas et al., 2015a; Saul et al., 2016). SOCE plays a critical and nuanced role in regulating DC function, particularly in the context of fibrosis. In both murine and human DCs, the expression of key SOCE components, STIM and Orai proteins, varies according to DC subtype and species. For instance, murine DCs tend to express more STIM2 than STIM1, whereas human DCs predominantly express Orai1 (Matzner et al., 2008; Bandyopadhyay et al., 2011a; Félix et al., 2013). Early studies using SOCE inhibitors like SKF-96365 and 2APB have highlighted the essential role of CRAC channel function in DC maturation and migration, particularly following toll-like receptor (TLR) stimulation (Itagaki et al., 2011; Nunes-Hasler et al., 2017). Despite some contrasting evidence from Vaeth et al., which suggests that bone marrow-derived DCs (BMDCs) from Stim1fl/fl Stim2fl/fl Vav-Cre mice do not exhibit significant maturation or functional defects, possibly due to compensatory pathways, the importance of STIM1 in BMDCs remains significant (Vaeth et al., 2015; Bretou et al., 2017; Maschalidi et al., 2017). Indeed, studies showed that STIM1 is particularly crucial in influencing antigen cross-presentation, a process linked to its role in phago-lysosomal fusion (Sáez et al., 2018). STIM1 is implicated in enhancing DC migration, potentially through its interactions with TRP channels which affect lysosomal Ca^{2+} release and cellular motility (Sogkas et al., 2015a; Saul et al., 2016).

Fibrocytes

Fibrocytes combine monocyte functions like migration and antigen presentation with fibroblast-like ECM remodeling and collagen production (Reilkoff et al., 2011). Their fibroblastic differentiation is promoted by IL-4 and IL-13 (Lasek et al., 2014). Increased fibrocyte levels were observed in systemic sclerosis, and lung and spleen fibrosis (Mathai et al., 2010; Ozono et al., 2021) An example of this is in IPF, where high circulatory fibrocyte counts are associated with increased mortality from this advanced disease (Moeller et al., 2009). STIM1 and Orai1 were reported to be upregulated in monocyte derived fibrocyte. IL-4 dependent differentiation of Fibrocyte from peripheral blood monocytes, relies on SOCE and correlates with elevated expression of both STIM1 and Orai1 (Zhong et al., 2018). This suggests that targeting CRAC channels would decrease the migratory path for fibrocytes toward organ fibrosis.

Smooth Muscle Cells

Vascular smooth muscle cells pivotal for blood vessel tone, express key proteins such as α-SMA, transgelin (SM22α), vimentin, and desmin. Following injury, these cells transition from a contractile to a synthetic phenotype, initiating proliferation, migration, and heightened production of extracellular matrix (ECM) components like collagen types I and IV (House et al., 2008). This expansion and augmented ECM deposition play crucial roles in atherogenesis and the progression of fibrosis. The process is propelled by bradykinin-induced synthesis of collagen type I, facilitated by autocrine activation of TGFβ1 and the mitogen-activated protein kinase pathways, showcasing the complex biochemical interactions that drive fibrotic changes in vascular tissues. (Campbell et al., 1990; Douillet et al., 2000; Weiskirchen et al., 2019). Extending this concept to respiratory diseases, particularly asthma, recent research underscores the significant role of SOCE in modulating airway

responsiveness and remodeling (Spinelli et al., 2012; Johnson et al., 2022). Using BALB/c and C57BL/6 mouse strains in asthma models demonstrate that increased SOCE, driven by elevated expression of STIM1 and Orai1, results in more pronounced airway contractions and accelerated Ca^{2+} oscillations in airway smooth muscle cells. This heightened SOCE activity is key to the greater airway responsiveness observed in BALB/c mice relative to C57BL/6 mice (Zeng et al., 2023b). STIM1 is a crucial catalyst for airway smooth muscle methacholine-triggered Ca^{2+} oscillations, remodeling and hyperresponsiveness, driving processes such as cell proliferation, migration, and secretion of cytokines and ECM proteins (Johnson et al., 2022), which are essential for fibrosis development. STIM1 and Orai1 are pivotal in the transition of vascular smooth muscle cells from a quiescent state to a proliferative one, a process triggered by platelet-derived growth factor (PDGF) and crucial for vascular repair and remodeling (Potier et al., 2009; Zhang et al., 2011, Gonzalez-Cobos et al., 2013). Mesangial cells of the kidney, although primarily recognized for their role in the renal glomerular structure, share remarkable similarities with vascular smooth muscle cells in their functional behavior and cellular properties. Mesangial cells are contractile cells that can also switch to a synthetic phenotype under stress or injury, playing a similar role in kidney disease as vascular smooth muscle cells do in vascular disease. Zeng et al. reported that the expression of STIM1 was increased in renal tissues of diabetic rat and HBZY-1 (mesangial) cells stimulated by high glucose. STIM1 appeared to regulate autophagy, cell proliferation and fibrosis via the PI3K/AKT/mTOR signal pathway(Zeng et al., 2023a).

SOCE as a Target for Fibrosis Treatment?

The development of antifibrotic therapies faces significant challenges due to the diversity of fibrotic conditions. A promising strategic approach could involve targeting universal pathways that are central to multiple fibrotic diseases, despite their distinct etiologies and risk factors. This strategy has the potential to lead to the creation of broad-spectrum antifibrotic drugs that are effective across various diseases and organ systems (Distler et al., 2019). Among these universal pathways, Ca^{2+} signaling emerges as a critical target in antifibrotic therapy. As discussed above, Ca^{2+} signaling plays a role in numerous biological processes and across stages and cell types that are involved in the development of fibrosis. This includes modulating the inflammatory phase, limiting the fibrotic response, and impacting tissue remodeling through gene regulation and biological processes. SOCE is particularly significant in this context, as it regulates a variety of biological processes that induce fibroblast activation and myofibroblast differentiation, including cell proliferation, secretion, migration, and metabolic modulation. SOCE and the pore-forming protein of CRAC channels, Orai1 play pivotal roles in pathological conditions and are considered promising therapeutic targets (Chen et al., 2010; Prakriya and Lewis, 2015; Feng et al., 2019).

Recent studies have identified several FDA-approved drugs that unexpectedly inhibit SOCE, suggesting broader implications for these medications in treating fibrotic diseases beyond their original indications. This discovery underscores the potential for drug repurposing in fibrotic conditions and highlights the importance of re-evaluating existing pharmaceuticals for their off-target effects on Ca^{2+} signaling pathways (Rahman and Rahman, 2017). For example, flecainide, an FDA-approved antiarrhythmic drug, has shown promise as a SOCE inhibitor in the treatment of fibrosis associated with Arrhythmogenic Cardiomyopathy, highlighting the potential for repurposing this drug to target SOCE-mediated fibrosis in other contexts as well (Maione et al., 2022). In addition to repurposing existing drugs, the ongoing development of SOCE inhibitors continues to advance, with several promising candidates identified for therapeutic use. These inhibitors exhibit potent inhibitory effects on SOCE, offering new avenues for treating fibrotic diseases (Norman et al., 2024). For instance, Tang et al. introduced a triazolyl thalidomide derivative named 10e, which seems to act as a potent SOCE inhibitor. This compound demonstrated significant anti-fibrotic effects by reversing the migratory ability and activation of TGFβ1//SMAD2/3-induced myofibroblasts, effectively dedifferentiating these cells back to fibroblasts through cytoskeleton remodeling (Tang et al., 2021). As mentioned earlier, inflammation is a crucial component and precursor for fibrosis and the inhibition of SOCE is an emerging concept in treatment of inflammatory disease such as inflammatory bowel disease, where SOCE inhibition seems to protect against bacterial invasion by maintaining the mucus barrier while suppressing inflammatory responses (Glauben et al., 2022) Promising results and safety profile of the SOCE inhibitor Auxora (formerly CM4620-IE) have been noted, suggesting that SOCE inhibition could potentially represent a groundbreaking therapeutic avenue for controlling inflammatory disease (Glauben et al., 2022). Studies highlighted the critical role of STIM1 and Orai1 in vascular remodeling(Johnson and Trebak, 2019) and the use of Orai1 inhibitors, which are currently advancing through clinical trials could potentially modulate vascular disease progression and the contribution of vascular cells to the fibrotic process. Through targeting of Orai1, therapeutic strategies can potentially mitigate the pathological remodeling that characterizes various vascular conditions, offering a novel approach to managing and possibly reversing these diseases (House et al., 2008; Berridge, 2012; Trebak, 2012; Prakriya and Lewis, 2015; Johnson and Trebak, 2019; Johnson et al., 2020; Shawer et al., 2021). Liu and colleagues showed that Mannan-binding lectin (MBL), a Ca^{2+}-dependent complement molecule, inhibited EMT in an idiopathic pulmonary fibrosis mouse model through attenuation of SOCE signaling, particularly by influencing Orai1 ubiquitination *via* the PDK1-SGK1 pathway (Liu et al., 2023). Another study reported blocking SOCE as a potential new approach

for treating systemic sclerosis (SSc). This study found a strong link between SSc pathogenesis and SOCE, with increased SOCE activity observed in SSc fibroblasts. The use of SOCE -albeit non-specific- inhibitors like 2-APB, SKF96365, and indomethacin on SSc fibroblasts reduced fibrosis markers, promoted fibroblast dedifferentiation and decreased collagen secretion, enhancing cell mobility. Therefore, targeting the increased SOCE activity in SSc could reverse fibroblast differentiation and ECM remodeling, potentially mitigating SSc progression (Wu et al., 2019). Hung et al. explored how Klotho, a protein known for its cardiovascular benefits, affects human atrial fibroblast activity and potentially offers anti-fibrotic effects. Experiments showed that a higher dose of Klotho decreased SOCE, significantly reduced fibroblast migration without affecting proliferation (Hung et al., 2022). Yang and collogues showed that paraquat (PQ)-induced pulmonary fibrosis through SOCE activation. Their study showed that PQ exposure increases the aggregation of STIM1 and enhances the distribution of Orai1 on cell membranes, triggering NFATc1 activation. The application of the SOCE inhibitor SKF96365 prior to PQ exposure effectively mitigated these effects. *In vitro*, SKF96365 pre-treatment reduced NFATc1 translocation. The use of SKF96365 *in vivo* preserved alveolar structure and significantly reduced collagen deposition in the lungs of PQ-exposed mice, thereby attenuating the fibrotic response (Yang et al. 2022). In liver fibrosis, CRAC channel blockers have been shown to mitigate activation of hepatic stellate cells, essential in liver fibrosis development. Inhibition of CRAC channels using BTP-2 reduced key fibrotic markers and cell proliferation (Kondo, Suzuki and Yamamura 2021). Similarly, inhibition of Orai1 mitigated the aberrantly high SOCE activity in chronic pancreatitis, by boosting SARAF expression, a CRAC channel inhibitory protein typically reduced in pancreatitis, thereby preventing the transition from early to end-stage disease in mice. This approach lessened fibrosis and significantly reduced chronic pancreatitis severity, building on previous studies inhibiting Orai1 with CM5480 for treatment of acute pancreatitis. CM5480 demonstrated substantial efficacy by reducing calcium overload in pancreatic acinar cells, thus preventing the activation of pro-inflammatory and pro-fibrotic pathways. This Orai1 inhibitor also showed promise in chronic pancreatitis models by decreasing fibrosis and improving pancreatic tissue architecture. These findings suggest that Orai1 inhibition could be a promising strategy for treating both early and advanced of acute pancreatitis stages as well as other diseases characterized by aberrant SOCE activity. (Gerasimenko and Gerasimenko, 2022; Pallagi et al., 2022; Szabo et al., 2023).

Collectively, while SOCE inhibition presents a compelling therapeutic strategy, it is crucial to consider the potential complications that may arise from chronic inhibition. A study investigating the long-term effects of SOCE inhibition in a

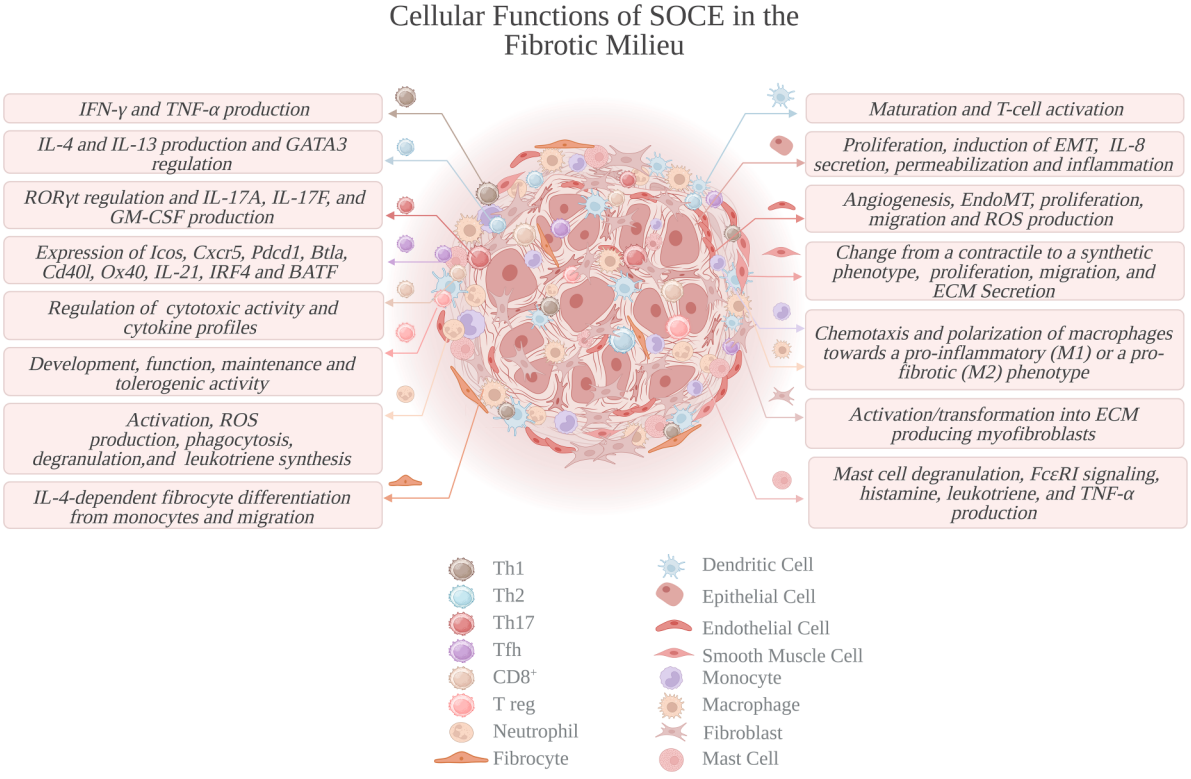

Figure 1. Cell types involved in the fibrotic process and the putative functions of SOCE, in each cell type, in regulating transcription, cytokine secretion, cell function and tissue remodeling (generated with BioRender).

mouse model revealed significant cardiovascular risks, emphasizing the need for careful evaluation of these risks in the development of SOCE-targeted therapies (Yu et al., 2022b).

Concluding Remarks

Fibrosis represents a significant clinical challenge due to its multifactorial etiology and the complex interplay of cellular and molecular mechanisms that drive its progression. Here, we discussed the critical roles of myofibroblasts, fibroblasts, immune cells, and epithelial and endothelial cells, each contributing uniquely to the fibrotic process through mechanisms that often involve SOCE (Figure 1). While it would seem that SOCE inhibition across cell types might be beneficial in the treatment of fibrosis, further understanding of the CRAC channel composition in different cell types, the remodeling of its expression and regulation during the fibrotic process would both hone and hasten any future therapeutic strategies. Further research into the cellular functions of SOCE in fibrosis coupled to the expansion of our therapeutic toolkit targeting other Orai isoforms as well as targeting potential heteromeric Orai l/2/3 channel compositions might slow, or even reverse the progression of fibrosis. As research continues in this area, we will likely gain greater appreciation of the interplay between different cell types within the fibrotic environment, channel composition and regulation and how the delicate balance of Ca^{2+} homeostasis within each cell type is altered. We will likely uncover novel mechanisms downstream of SOCE that could, by themselves, offer additional opportunity for therapeutic targeting of fibrosis. We look forward to future research into this disease with largely unmet therapeutic needs.

Declaration of Conflicting Interests

MT is a scientific advisor for companies pursuing SOCE as targets for human disease. These are Seeker Biologics (Cambridge, MA), Eldec Pharmaceuticals (Durham, NC) and Vivreon Biosciences (San Diego, CA).

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