HHS Public Access

Author manuscript

Biochim Biophys Acta. Author manuscript; available in PMC 2018 June 01.

Published in final edited form as:

Biochim Biophys Acta. 2017 June ; 1864(6): 900–906. doi:10.1016/j.bbamcr.2016.11.028.

The Functions of Store-operated Calcium Channels

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Abstract

Store-operated calcium channels provide calcium signals to the cytoplasm of a wide variety of cell types. The basic components of this signaling mechanism include a mechanism for discharging Ca^{2+} stores (commonly but not exclusively phospholipase C and inositol 1,4,5-trisphosphate), a sensor in the endoplasmic reticulum that also serves as an activator of the plasma membrane channel (STIM1 and STIM2), and the store-operated channel (Orai1, 2 or 3). The advent of mice genetically altered to reduce store-operated calcium entry globally or in specific cell types has provided important tools to understand the functions of these widely encountered channels in specific and clinically important physiological systems. This review briefly discusses the history and cellular properties of store-operated calcium channels, and summarizes selected studies of their physiological functions in specific physiological or pathological contexts.

Keywords

Store-operated calcium channels; calcium signaling; mouse models; exocrine glands; neutrophils; keratinocytes

1. Introduction: What are Store-operated Channels?

Store-operated channels are plasma membrane ion (usually Ca^{2+}) channels that are regulated by the content of Ca^{2+} in intracellular stores, generally the endoplasmic reticulum. Thus, store-operated channels are most commonly encountered as a component of a biphasic Ca^{2+} signaling mechanism, involving both release of intracellular Ca^{2+} and Ca^{2+} entry through plasma membrane channels. The history of the idea of store-operated channels has been reviewed [1]. The concept originated from observations of the kinetics of refilling intracellular stores following their release [2–5]. In 1983, Berridge and collaborators, following on the general theory developed by Michell [6], demonstrated that the most

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The authors declare there are no conflicts of interest.

common mechanism for receptor-activated release of Ca^{2+} involved the second messenger, inositol 1,4,5-trisphospate (IP_3) [7,8]. A key early event in the story of store-operated channels was the discovery that a plant toxin, thapsigargin [9], passively released intracellular stores independently of receptor activation or IP_3 production [10], and also activated the same plasma membrane Ca^{2+} channels as a receptor agonist, and to the same extent [11]. In 1992, Hoth and Penner [12] published the first characterization of a store-operated Ca^{2+} current which they called I_{crac}, for *c*alcium-*r*elease *a*ctivated *c*alcium current. This current arose from channels with high Ca^{2+} selectivity resulting in strong inward rectification. Single channel conductance of these CRAC channels was very low, and could only be estimated from indirect noise analysis of the current [13,14]. Subsequently, research in a number of laboratories focused on two basic issues: the identity of the store-operated channels, and the nature of the signal linking intracellular Ca^{2+} store content to channel activation (reviewed in [15].

For some time, the leading candidate for the channel was one or more members of the TRPC ion channel family [16]. The seven mammalian TRPC channels are homologs of the *Drosophila* photoreceptor channel, TRP, and like the *Drosophila* channel, they appear to be activated by receptors coupled to phospholipase C and the production of IP_3 [17]. This is an expected property of store-operated channels, but store-operated channels are thought not to require phospholipase C or IP_3 formation, as illustrated by the action of thapsigargin. This distinction was controversial, with some laboratories demonstrating that store-depletion could activate TRPCs [18–26], while others found that store-depletion was neither necessary nor sufficient for their activation [27–31] (reviewed in [15]). A general finding however was that TRPC channels clearly did not have the channel properties expected of I_{crac}. Unlike CRAC channels, TRPC channels have only modest Ca^{2+} selectivity and thus the current-voltage relationships have significant outward components at positive voltages. Nonetheless, in certain experimental conditions, TRPC channels do appear to behave as if they respond to store depletion. In these instances, their activation depends on the molecular components of the classical CRAC channels, Orai and STIM, discussed below [32–34]. Thus it is possible, although not proven, that in these instances TRPC channels are not directly activated by store-depletion, but in a pathway downstream of store-operated CRAC channels.

Attempts to identify the signaling mechanism linking store depletion to store-operated channels were similarly frustrating and controversial. Some proposed candidates were cyclic GMP [35] (but see [36]), a product of cytochrome P450 [37,38], the IP_3 receptor [23,39] (but see [40]), a tyrosine kinase [41–43] (but see [44]), a small G-protein [45] and an as yet unidentified substance extracted from store-depleted cells termed “CIF” for calcium influx factor [46–48].

The first major breakthrough came in 2005 with the discovery of the signaling mechanism. By use of a limited siRNA screen, Roos et al. [49] demonstrated the essential role of a previously known Ca^{2+}-binding protein, STIM1. Their discovery was confirmed shortly thereafter and independently by Liou et al. [50] who also provided the first evidence that STIM1 functioned as a Ca^{2+} sensor in the endoplasmic reticulum. Just one year later, Feske et al. [51], by use of a whole genome siRNA screen, identified Orai1 as an obligate component of the store-operated Ca^{2+} entry (SOCE) pathway. Very shortly thereafter, two

other laboratories confirmed this finding [52,53]. Subsequently, multiple laboratories demonstrated that co-transfection of cells with STIM1 and Orai1 resulted in manifold amplification of store-operated Ca^{2+} entry and of I_{crac} [53–56], establishing these two proteins as the minimal constituents of store-operated Ca^{2+} signal generation. That Orai1 was indeed a pore-forming subunit of the CRAC channel was demonstrated by single amino acid mutations that altered the ion selectivity of the store-operated currents [57–59].

There are multiple forms of STIM proteins, two gene products, STIM1 and STIM2 [50], as well as a long splice variant of STIM1, STIM1L [60]. There are three Orai gene products, Orai1, 2 and 3, and two versions of Orai1, Orai1α and Orai1β, arising from alternative translation initiation [61,62]. Much less is known about the functions of Orai2 and 3. Orai1α and β both appear capable of supporting SOCE. However, in addition to its ability to form SOC channels, Orai1α, but not Orai1β, is an essential component of a distinct Ca^{2+} channel giving rise to a non-store-operated Ca^{2+} current termed I_{arc} [62,63]. The signal for the ARC channels is believed to be arachidonic acid, released from membrane lipids by the action of phospholipase A2 [64] or by a metabolite of arachidonic acid, leukotriene C4 [65]. ARC channels also require STIM1, but apparently not functioning as an endoplasmic reticulum Ca^{2+} sensor [66]. The pore of ARC channels is composed of a combination of Orai1 and 3 subunits in a pentameric structure [67]. As of this writing, little is known of the physiological function of ARC channels, as no publications on specific mouse models have appeared. Nonetheless, it should be remembered that mice lacking STIM1 or Orai1 will likely have lost I_{arc} as well as I_{crac}.

2. Cellular Function of Store-operated Ca^{2+} Entry

Early studies of store-operated Ca^{2+} entry involved observations of mechanisms and pathways by which intracellular stores are refilled after their discharge. The earliest models implicated a function for Ca^{2+} entry of recharging stores such that Ca^{2+} signals could persist from intracellular release mechanisms [2,4,5]. However, a number of more recent findings have cast doubt on a major role of store-operated channels in maintaining intracellular stores.

Calcium is required in the endoplasmic reticulum for correct protein synthesis and folding [68,69]. The loss of the ability of the endoplasmic reticulum to maintain its intracellular Ca^{2+} store content would thus be catastrophic to cell function and viability.

However, humans lacking functional Orai1, the major store-operated channel subunit, develop to birth but die young due to a severe combined immunodeficiency [70,71]. Mice lacking Orai1 also develop to birth [72,73]. Specific organs (lacrimal glands, mammary glands) from mice lacking Orai1, shown to completely lack store-operated entry develop normally but lack specific signaling functions [74,75]. However, other cell types show clear developmental deficiencies (skeletal muscle [72,76], sperm [77]).

In several cell biological studies, a clear and specific requirement for Ca^{2+} entry through store-operated channels, independent of global Ca^{2+} changes, has been demonstrated [78–81]. Dissociation of the signaling function of store-operated channels from global Ca^{2+}

concentration was nicely demonstrated in studies of gene regulation in mast cells by Di Capite et al. [82]. These authors activated sustained Ca^{2+} oscillations in mast cells through the leukotriene receptor, which is known to activate phospholipase C and subsequently store-operated Ca^{2+} entry. This resulted in an increase in expression of the early gene, c-fos. In the absence of external Ca^{2+}, the oscillations ran down rapidly and there was no increase in c-fos. In the absence of external Ca^{2+}, oscillations could be maintained by blocking the plasma membrane with a relatively high concentration of lanthanum [83]. However, despite a pattern of global cytoplasmic oscillations indistinguishable from those in the presence of external Ca^{2+}, no increase in c-fos expression occurred. This result strongly suggests that for this particular pathway, it is specifically the Ca^{2+} entering through the store-operated channels that drives gene expression, not the global increase from the IP_3-induced Ca^{2+} oscillations.

3. Physiological Functions of Store-operated Calcium Entry

Prior to the discovery of the roles of STIM and Orai proteins in SOCE, patients were identified with loss of SOCE in lymphocytes, and were shown to have severe combined immunodeficiency [70,71,84]. The discoveries of STIM and Orai revealed additional patients with immunodeficiency associated with mutations in both STIM1 and Orai1 genes [85]. These patients do not survive very long unless they receive a bone marrow transplant. Following this, other deficiencies are observed, including diminished skeletal muscle development and ectodermal dysplasia (reviewed in [85,86]). Also following the discoveries of STIM and Orai, a number of laboratories began developing mouse models to investigate the roles of these proteins, and by inference SOCE, in a variety of physiological contexts. Not surprisingly, the first studies focused on the immune system [72,73,86]. Also, initial studies utilized whole-animal knockouts of Orai1 and STIM1, but these animals do not survive well and analysis of their various phenotypes may be complicated by interactions among different organ systems and cell types. Thus more recent studies have sometimes utilized animals with floxed genes crossed to transgenic animals expressing Cre recombinase driven by organ- or cell type-specific promoters (when appropriate transgenic mice are available). Below I summarize some studies, mostly from our laboratory, that illustrate the utility of these mouse models.

4. Mouse Models for Store-operated Calcium Entry

Mice lacking Orai1 tend to die perinatally, but can survive for prolonged periods if crossed into a mixed genetic background [72,73]. Similar to humans with null mutations in Orai1, these mice are deficient in both innate and acquired immunity [72,73,86]. The mice are generally small in stature, which may result in part from impaired skeletal muscle development [87], but also in impaired development of bone [88,89]. In Orai1 knockout mice, precursor cells for both osteoblasts (bone forming cells) and osteoclasts (bone resorbing cells) have impaired SOCE, the differentiation of the precursor cells to mature bone cells is impaired, the functions of the differentiated cells is reduced, and the mice are osteopenic, i.e., they have significantly decreased bone density [88,89].

SOCE has long been known to play a major signaling role in acquired immunity [90]. Until recently, less is known regarding the role of SOCE in innate immunity, although I_{crac} was first discovered as a store-operated current in mast cells [12]. Mast cells from Orai1 knockout mice showed significantly diminished SOCE, loss of I_{crac}, and grossly defective degranulation and cytokine secretion [72]. Similar findings were reported by Baba et al [91] with a STIM1 knockout mouse. Allergic reactions elicited in Orai1 knockout mice were significantly inhibited [72]. Interestingly, SOCE in T-cells from these mice was minimally affected, and expression of Orai1 (as determined by gene-trap) was low. This may indicate that mice show a milder phenotype with regard to acquired immunity as compared to humans.

Another major player in innate immunity is the neutrophil [92]. Neutrophils sense gradients of small molecules that indicate the location of sites of infection or inflammation and migrate to those sites by the process of chemotaxis [93]. Calcium has long been known to play a central role in neutrophil chemotaxis, largely from studies of the action of the chemoattractant fMLF. fMLF is a tripeptide that activates a G-protein-coupled pathway leading to phospholipase C activation and the generation of IP_3 [94,95]. A role for Ca^{2+} entry has also been documented [96], and the major entry mechanism appears to be SOCE [97,98]. Knockdown of either Orai1 or STIM1 in the neutrophil cell line, HL-60 significantly reduced fMLF induced Ca^{2+} signaling and significantly reduced fMLF induced chemotaxis [99]. If SOCE were to play a role in the directed movement of chemotaxis, one would expect that SOCE signaling would occur in an asymmetric fashion when the cells become polarized. Figure 1 shows that this is indeed the case; surprisingly STIM1 distributes to the rear of polarized HL-60 neutrophils. This is due in part because endoplasmic reticulum distributes to the real of the cell, but as shown in Figure 1, STIM1 concentrates toward the rear to a greater extent than endoplasmic reticulum.

Psoriasis is a debilitating disease of the skin, thought to result from an autoimmunity involving several components of the immune system, including neutrophils [100]. In a mouse model of psoriasis, targeted knockout of STIM1 in myeloid lineage cells (including neutrophils) hastened the reversal of psoriasis plaques following removal of a chemical activator of psoriasis [99]. This indicates that components of SOCE might serve as useful pharmacological targets for treatment of psoriasis or other autoimmunity-involved disorders of the skin.

Calcium signaling plays a major role in the development and maintenance of the epidermis, the major pathway being initiated by a calcium sensing receptor [101]. An outward gradient of calcium in the extracellular matrix orchestrates the differentiation of keratinocytes from an undifferentiated to a fully differentiated state. In the keratinocyte cell line, HaCaT, raising Ca^{2+} from 0.03 mM to 1.8 mM induces expression of the keratinocyte-associated gene, KRT1, and slows growth as cells become terminally differentiated [101]. This response involves the calcium sensing receptor, known to act through activation of phospholipase C [102]. Knockdown of either STIM1 or Orai1 reduced SOCE, I_{crac} and completely abrogated the $[Ca^{2+}]_i$ signal arising in response to a switch from 0.03 mM to 1.8 mM Ca^{2+}. Cell proliferation in low Ca^{2+}, growth suppression in high Ca^{2+} and expression of KRT1 were also substantially diminished [103].

Keratinocytes play an essential role in the process of healing of superficial wounds. On the basis of *in vitro* studies in the HaCaT cell line described above, impaired Ca^{2+} signaling in keratinocytes would be expected to impair the process of wound healing in skin. Figure 2 shows that in keratinocytes from mice with STIM1 knocked down specifically in epidermal cells, Ca^{2+} signals in response to either thapsigargin or raised Ca^{2+} were almost completely abrogated. Surprisingly however, loss of STIM1 in epidermal cells resulted in an improved outcome following skin injury, particularly at longer times. (Figure 2). The reason for this unexpected finding is not yet clear, but it may be due to diminished release of chemokines from keratinocytes which are known to be pro-inflammatory [104]. In addition to their obvious role as building blocks for restoring epidermal integrity, keratinocytes also release chemokines that signal recruitment of neutrophils [104]. Neutrophils provide an initial barrier against infection and mediate clearing of necrotic cells from the damaged area [104]. A general conclusion from this result is that one cannot always predict the consequences of genetic alterations *in vivo* based on findings in cell lines or primary cells *in vitro*. Additional studies will be needed to more fully understand the role of SOCE in keratinocytes during wound healing.

5. Store-operated Calcium Entry in Exocrine Glands

The Orai1 knockout mouse has been utilized to study the role of SOCE in two distinct types of exocrine glands, lacrimal glands and mammary glands. Much of the original evidence for the concept of SOCE was obtained from studies of Ca^{2+} signaling in exocrine glands, including lacrimal acinar cells [105,106]. Acinar cells isolated from the lacrimal glands of Orai1 knockout mice have no detectable SOCE in response to either thapsigargin or muscarinic receptor activation, and no detectable I_{crac} [74]. Pilocarpine-activated lacrimal secretion *in vivo* is substantially reduced in the knockout animals. Histological examination of the lacrimal glands shows that gland development and structure are normal with the exception, not unexpectedly, that secretory granule content following pilocarpine treatment in the knockout glands is increased. Methacholine stimulated secretion of peroxidase from wild-type lacrimal gland fragments in the presence of extracellular Ca^{2+} and to a lesser extent in the absence of Ca^{2+}. With fragments from knockout mice, the secretion in the presence was reduced to that seen in the absence of Ca^{2+}. However, the secretion in the absence of Ca^{2+}, presumably resulting from intracellular Ca^{2+} release, as well as the basal rate of secretion, were unchanged in the knockout preparation [74]. This study, perhaps as clearly as any, illustrates the highly specific role of Orai1 in signaling Ca^{2+} entry. Thus, lacrimal glands of Orai1 knockout mice lack SOCE, I_{crac}, and Ca^{2+}-dependent secretion. However, gland size, morphology and Ca^{2+}-independent secretion are unaffected. This indicates that the basic mechanism of synthesis and storage of the secretory product, the basic mechanism of Ca^{2+}-regulated exocytosis, and the signaling pathway through the formation of IP_3 and release of intracellular Ca^{2+} stores are quantitatively unaffected.

Calcium signaling is known to be essential for mammalian oocyte fertilization [107–109]. Indirect evidence has implicated Orai1 and SOCE as playing a role in mammalian oocyte fertilization [110]. However, surprisingly, female Orai1 knockout mice are fertile, and bear litters of normal size when mated to a wild type male. However, pups do not gain weight and die after about four days, unless fostered to a wild type dam [75]. This indicates that Orai1

knockout female mice fail to lactate adequately. The exocrine function of mammary glands differs in some respects from other exocrine glands. Hormonal actions associated with birthing activate a constitutive secretion of milk containing calcium and other nutrients into alveolar structures. Secretion is initiated on demand by suckling through a reflex mechanism involving activation of oxytocin receptors on basket myoepithelial cells that surround the alveoli [111,112]. Analysis of milk from Orai1 knockout female mice showed a decrease in Ca^{2+} concentration of about 50% [75]. This likely reflects an alternative function of Orai1 in transporting Ca^{2+} in epithelial cells [113]. However, protein concentration in milk was normal and it is unlikely that this alteration is sufficient to account for the lactation phenotype. Mammary glands of Orai1 knockout female mice were engorged suggesting that the constitutive formation of milk proceeded normally but the discharge of stored milk was impaired. Consistent with this interpretation, oxytocin induced Ca^{2+} oscillations in isolated myoepithelial cells were substantially reduced in cells from Orai1 knockout mice. Visualization of alveolar contractions demonstrated that alveolar contractions in response to oxytocin were substantially diminished as well [75]. Thus, the failure of lactation in Orai1 deficient female mice likely results primarily from a failure of Ca^{2+} signaling in myoepithelial cells.

6. Conclusions

Our understanding of the physiological functions of store-operated calcium channels has been greatly augmented through studies of mouse models with altered genetic expression of the basic components, STIM and Orai. Hopefully this information will eventually allow exploitation of this pathway to alleviate any of a large number of diseases known to involve aberrant calcium signaling [114–116].

Acknowledgments

Work from the authors' laboratory was supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences.

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Highlights

Store-operated calcium entry is a widely distributed signaling mechanism involving plasma membrane calcium channels activated when endoplasmic reticulum calcium stores are reduced.

The major molecular players in store-operated calcium entry are the endoplasmic reticulum calcium sensors, STIM1 and STIM2, and the plasma membrane channel pore forming subunits, Orai1, 2 and 3.

Use of genetically modified mice has revealed multiple physiological roles for store-operated channels, including roles in both acquired and innate immunity, in keratinocyte differentiation, and in exocrine gland function.

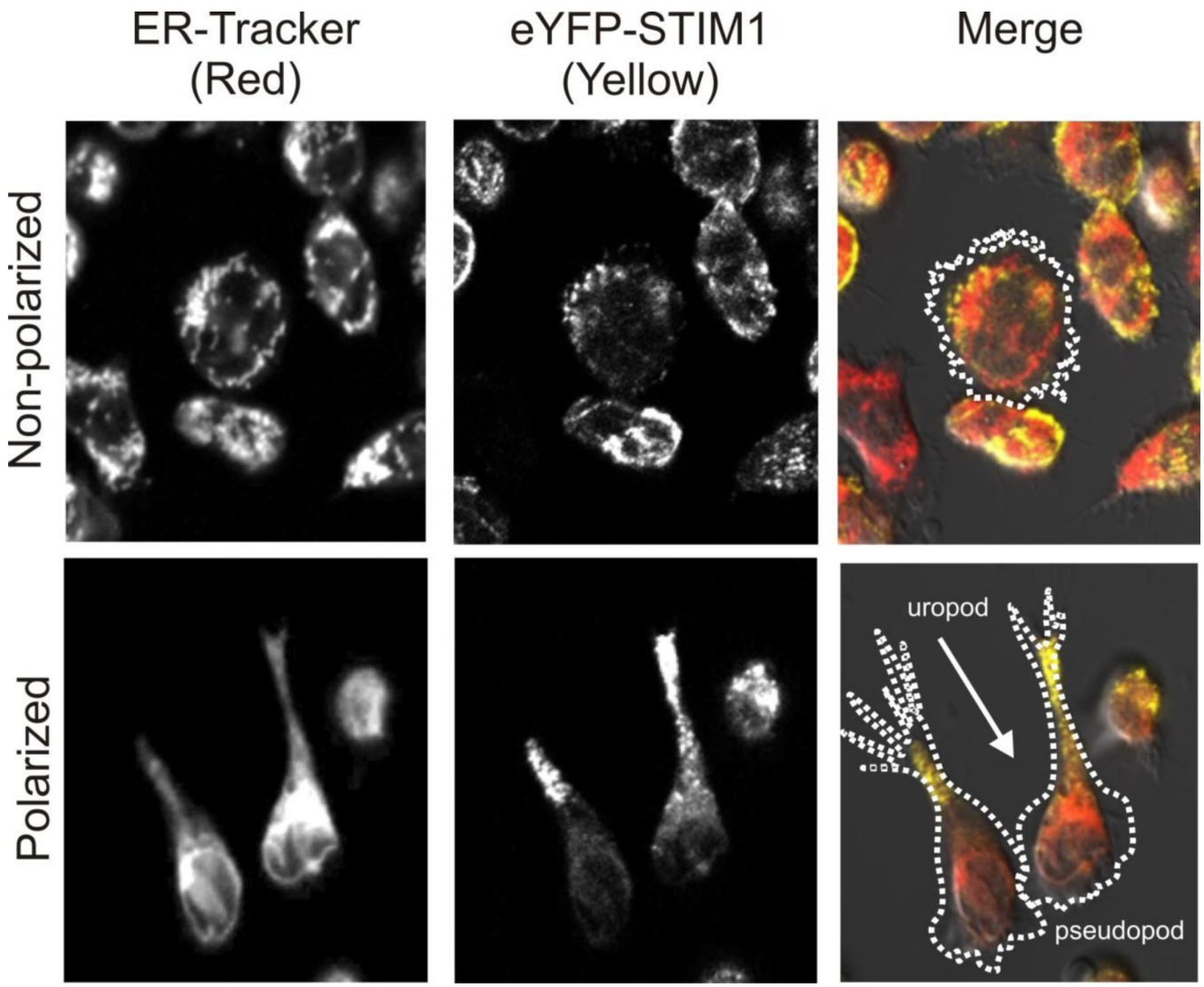

Figure 1. STIM1 distributes to the rear of polarized HL-60 neutrophils

Neutrophil-like HL-60 cells stably expressing eYFP-STIM1 [99] were stained with the endoplasmic reticulum labeling reagent, ER-Tracker Red (Molecular Probes). Cells were plated on coverslips covered with fibronectin (polarized cells) or fibronectin plus BSA (nonpolarized cells). In polarized cells, STIM1 clearly distributes to the rear (uropod), and to a significantly greater extent than the endoplasmic reticulum.

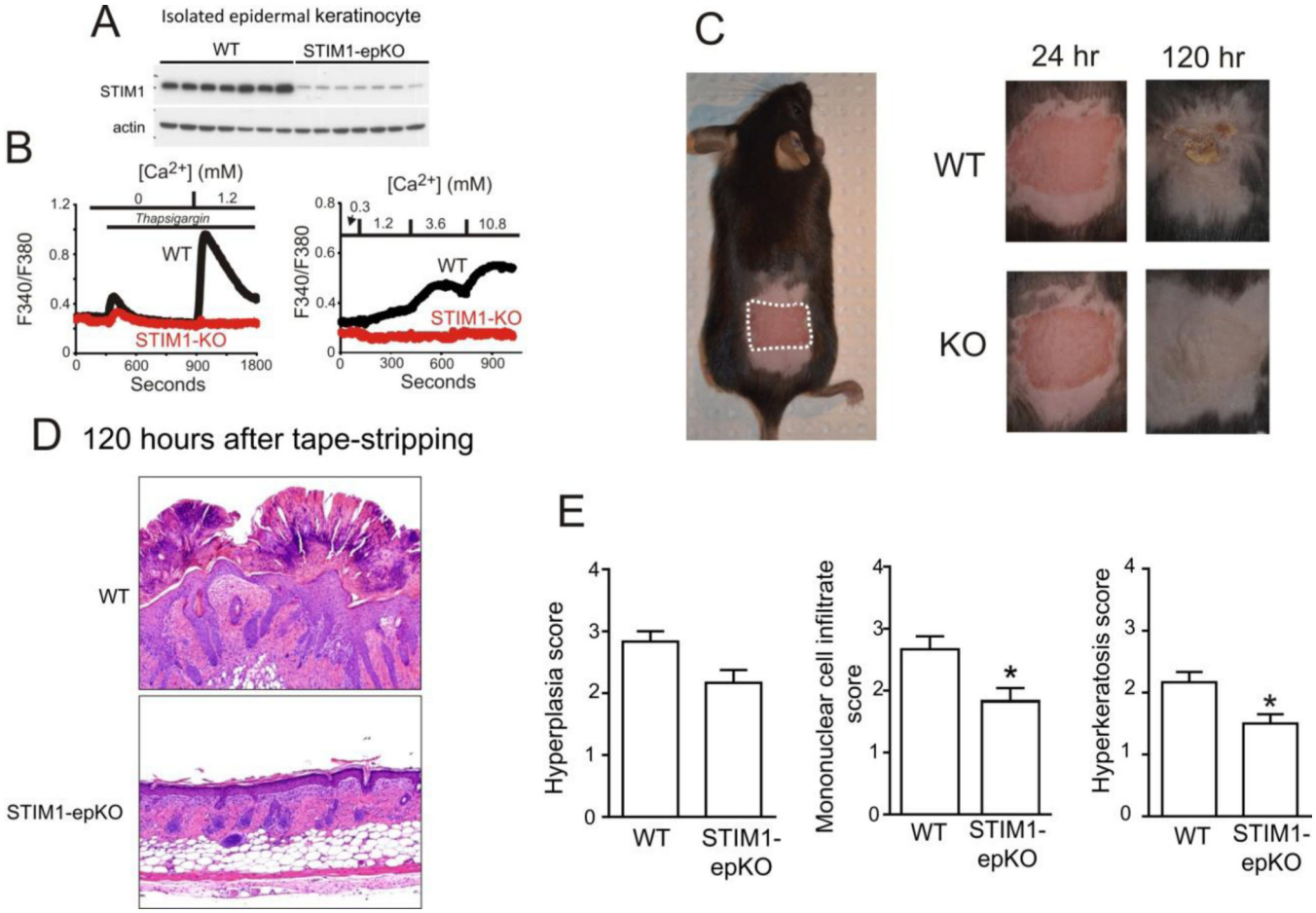

Figure 2. Wound healing in wild-type and in mice with epidermal-specific knockout of STIM1

Methods: Mice were crossed with *KRT14-cre* mice (Jackson laboratories). Isolation of keratinocytes was carried out as previously demonstrated [117]. Keratinocytes were cultured in CnT-07 (Zen-bio) according to manufacturer's instruction. Calcium imaging of keratinocytes were carried out as previously reported [103]. For superficial wounding of the epidermis, mice were subjected to a tape-stripping assay. 7–9 week old female mice were anesthetized with isoflurane. Mice backs were shaved and depilated by Nair cream. Depilated back skins were tape-stripped 20 times with Scotch tape (18 mm width). Lesions were rubbed with Vaseline to be moisturized. At the end of time-courses, lesioned skin was harvested for histological analysis. A: Epidermal specific knockout of STIM1 (STIM1-epKO) results in almost complete disappearance of STIM1 protein. B: Keratinocytes from STIM1-KO mice lack Ca^{2+} entry in response to thapsigargin or to elevated Ca^{2+}. C: Left panel shows an example of the wound area produced by tape stripping. Right panel shows examples of injured area in a wild type (WT) and knock-out (KO) mouse at 24 hours and 120 hours. D: Histological examination of skin at 120 hours shows extensive hyperkeratinization of skin of wild type mouse not the knockout (STIM1-epKO) mouse. E. Summary data show that skin from knockout (STIM1-epKO) mice has a slightly decreased

hyperplasia score and a significantly diminished mononuclear cell infiltrate and hyperkeratosis score ($P<0.05$).