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Review article

Calcium release-activated calcium modulator 1 as a therapeutic target in allergic skin diseases

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ABSTRACT

Allergic skin disease is the most common skin condition, and considerably affects patients' life quality because of its recurrence and pruritus. Numbers of studies point out that immune cells, including mast cells and T cells, play pathogenic roles in allergic skin diseases, and share similarities in the activation and secretion of cytokines. Calcium Release-Activated Calcium Modulator 1(CRACM1/ORAI1) is a subtype of Ca^{2+} membrane channel, causing Ca^{2+} influx into the cells. As a second messenger, Ca^{2+} is an essential element that regulates immune responses, especially in the development and function of T and B cells. Thus, ORAI1 is considered to participate in allergic diseases. However, the specific mechanism of ORAI1 in skin disorders is still unclear. In order to investigate the roles of ORAI1 in allergic skin disorders, we reviewed the related articles and concluded that ORAI1 could be a potential therapeutic target for allergic skin diseases.

1. Introduction

Calcium influx is mainly driven by membrane channels and calcium release-activated calcium channel (CRAC) is included. Calcium release-activated calcium modulator 1 (CRACM1, also known as ORAI1), encoded by the ORAI1 gene, is a subunit of Ca^{2+} membrane channel [1,2]. ORAI1 gene locates in the human chromosome 12q24.31 with two exons and three transcripts. It is highly expressed in multiple cells and tissues, including immune cells and the skin [3,4] (http://www.genecards.org/cgi-bin/carddisp.pl?gene=orai1). Skin is a crucial defense organ in the body against external stimulus and has various immune cells, including T cells, B cells, and mast cells [1,2,4]. Allergic skin disease is one of the most common skin disorders with specific immune dysfunctions (see Table 1), and affects nearly 10–20% of people worldwide [5,6]. It is evident that ORAI1 is associated with atopic dermatitis and severe combined immunodeficiency (SCID) [1,2]. Furthermore, depletion of ORAI1 causes immune cell dysfunctions including impaired T cell activation, mast cell degranulation, and even dendrite cell maturation [7,8]. Although ORAI1 participates in several different immune disorders, its activation and the pathogenic roles in diseases showed similarities. In this review, we investigated the biological functions of ORAI1 in immune-related cells and skin diseases.

2. The regulatory function of ORAI1 in the Ca^{2+} signaling pathway

ORAI1 was first identified by Feske in 2006 and showed to take part in the processes of Ca^{2+} release *in vivo* [14]. Store-operated Ca^{2+} entry (SOCE) is one of the important channels that mediate the entry of extracellular Ca^{2+} into cells, and ORAI1 is its core component. ORAI1 mainly modulates nuclear factor of activated T cells (NFAT) nuclear translocation when Ca^{2+} store is depleted in the endoplasmic reticulum (ER) [14–16]. The complex of ORAI1 combined with stromal interaction molecule 1 (STMI1) could sense Ca^{2+} concentration, influence ORAI1 rearrangement [17], thus causing Ca^{2+} influx *via* the Ca^{2+} release-activated Ca^{2+} channel, and then the current of CRAC channel I_{CRAC} occurs (Fig. 1). As a second messenger, Ca^{2+} is an essential element that regulates immune responses, especially the development and

Abbreviations: CRACM1/ORAI1, Calcium Release-Activated Calcium Modulator 1; SOCE, store-operated Ca^{2+} entry; AD, atopic dermatitis; CSU, chronic spontaneous urticaria; STIM1, stromal interaction molecule 1; SCID, severe combined immunodeficiency; FcεR1α, Fc fragment of IgE receptor Iα; IP3, inositol triphosphate; IP3R, inositol triphosphate receptor; ER, endoplasmic reticulum

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Table 1
The roles of ORAI1 in the allergic diseases.

Disease	Main point	Reference
Atopic dermatitis	ORAI1 activation in atopic dermatitis would affect pruritus and induce Th2 cell immune responses.	[9,10]
Allergic rhinitis	ORAI1 deletion in the airways or ORAI1 antibody treatment would relieve allergic symptoms.	[11,12]
Chronic spontaneous urticaria	ORAI1 may participate in the pathogenesis and even antihistamine drug therapy among chronic spontaneous urticaria patients	[13]

Notes: In the allergic disease such as atopic dermatitis and CSU, ORAI1 may influence the disease development and prognosis *via* enhancing Th2 cell responses or calcium influx. CRACM1/ORAI1: Calcium Release-Activated Calcium Modulator 1.

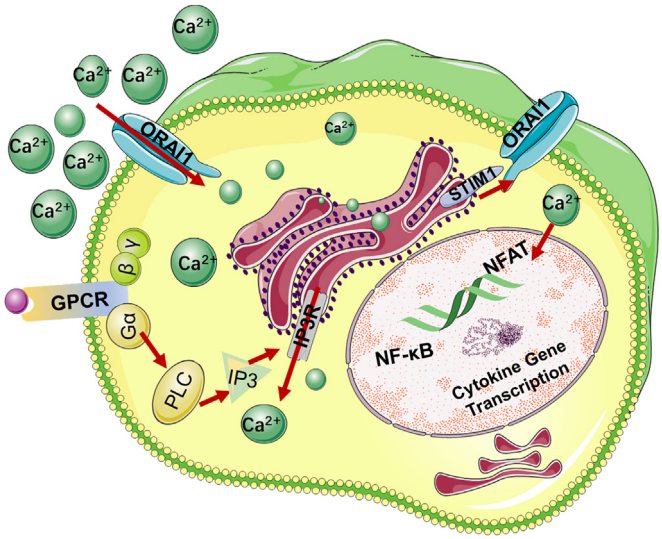

Fig. 1. The calcium in the ER stores is a major part in maintaining cell biological functions. IP3, produced by the phospholipase C, could interact with its receptor IP3R in ER and induce the release of calcium. After the depletion of calcium stores in ER, STIM1 would partially interact with ORAI1 and thus induce ORAI1 rearrangement and activation. Subsequently, extracellular calcium is imported into the cytosol and regulated the nuclear transcription, cytokine gene transcription.

function of T and B cells. During the processes of immune response regulation, Ca^{2+}-related channels, transcription factors (such as NFAT family, and nuclear factor kappa B subunit 1) and related signal pathways (including protein kinase C pathways) are also engaged in the following ORAI1 activation [18–21].

3. The factors and the regulatory mechanisms affecting ORAI1 function

As reported, multiple factors can regulate ORAI1 expression and functions. For instance, low extracellular H_2O_2 level can activate the interaction between STIM1 and ORAI1 in cells [22,23], while the activated and over-expressed ORAI1-STIM1 complex would reduce the direct oxidative stress [24]. Hypoxia induces ORAI1 upregulation and increases the calcium influx, thus inducing angiogenesis, cell invasion and migration [25]. In mast cells, immunoglobulin E (IgE) dependent signal pathway plays a major role in cell activation with Ca^{2+} changes. Lipids could inhibit calcium mobilization *via* ORAI1 through the interactions with STIM1 in mast cells, thus influencing the responses of Fc fragment in high-affinity IgE receptor 1a (FcεR1α) signaling[26]. In the presence of cholesterol, Ca^{2+} influx through ORAI1 is reduced, and linoleic acid abates ORAI1-STIM1 coupling, thereby inhibiting antigen-stimulated mast cell degranulation and Ca^{2+} responses in RBL mast cells [27,28]. In summary, the ORAI1 functions and expression are influenced by multiple factors, including oxidative stress, hypoxia, and even lipids. Besides the changes of calcium, the change of ORAI1 function may also contribute to the pathogenesis and development of some immune-related disorders.

4. The functions of ORAI1 in chronic disorders

Recent researches indicate that ORAI1 is involved in the pathogenesis and prognosis of multiple chronic disorders. In stroke patients, over-expressed STIM1/ORAI1 is an indicator of poor prognosis, and the patients with lower ORAI1 protein level show better recovery [29]. Studies have also confirmed the oncogenic roles of ORAI1 in the development and prognosis of tumors, such as prostatic cancer and colorectal cancer wherein high ORAI1 correlates with increased tumor proliferation [30–32]. Meanwhile, the colorectal cancer patients with low ORAI1 level also have better prognosis because of its inhibitory effect on the proliferation of tumor cells [33]. Furthermore, ORAI1 and its isoforms are abundantly expressed in melanoma [34], and ORAI1/STIM2 promote melanoma proliferation and migration accompanied by increasing intracellular Ca^{2+} level [35]. Therefore, we could infer that ORAI1 may serve as a potential therapeutic target for malignant tumors and can be used to predict tumor proliferation, progression, and even prognosis [33,36].

5. ORAI1 immunological responses

Immune cells, including mast cells, T cells and B cells, participate in the pathogenesis and prognosis of chronic disorders. Ca^{2+} is an essential element for the development and functions of T and B cells [30,37]. Therefore, ORAI1 may act as a biomarker in immune responses through up-regulating the influx of Ca^{2+}. However, the deeper mechanism needs to be investigated. In the following part, we would give a detailed description on further mechanisms of ORAI1 in the following immune cells.

5.1. ORAI1 immune responses in T cells

T cells are essential for human immunity, which carry out multiple functions, including killing infected cells and activating or recruiting other immune cells. ORAI1 significantly affects T cell activation and mediators' secretion. After the activation of T cells, ORAI1 and STIM1 are recruited by immunological synapse and then augments and increases Ca^{2+} influx [30,38]. Previous studies indicated that the modification and silencing of ORAI1 impaired Ca^{2+} influx and I_{CRAC} [39]. Deletion of ORAI1 through CRISPAR toolbox in human primary T cell subsets could imitate the mutation of immune-deficient patients along with reduced calcium influx and cytokines production [40]. ORAI1 N glycosylation limits the Ca^{2+} signal through SOCE in Jurkat T cells when exposed to tunicamycin [41]. ORAI1 R91W mutation causes a complete loss of I_{CRAC} and T-cell immunodeficiency, while wild-type R91 could complement this defect and the expression of ORAI1 could also restore the channel function in T cells [14]. Another mutation of ORAI1 exon 2 c.443T > G inducing lymphocytes activation is associated with a higher risk of hemophagocytic lymphohistiocytosis [42]. Moreover, recent studies show that ORAI1 deletion impair CRAC channel function and decrease the motility and function of T cells [3]. In diabetes, downregulated ORAI1 in T cells could undergo decrease calcium entry thus inducing T cell malfunction [43]. Meanwhile, the cell death of activated T effector cells severely is reduced along with significantly decreased NFAT translocation in the ORAI1 deficient T

cells, while the decrease was restored when increasing the ORAI1 expression [44]. T-cell development is slightly reversed after ORAI1 homolog compensation such as ORAI2 in the CRACM1/ORAI1 defective mice [44]. Decreased ORAI1 also affects cytokine release. In SCID patients with declined ORAI1 expression, cytokines production by lymphocytes, such as IL-2 and IL-4, are impaired [8,14]. Decreased leukotriene C4 (LTC4) and IgE release are also observed in allergic rhinitis mice with ORAI1 deletion [11]. Besides, in ORAI1-R93W-mutated mice T_{reg} cells, CRAC function is partially impaired, which is also accompanied with decreased cytokines, such as IL-2, IL-4, and TNF-α [1]. From the above, we speculate that ORAI1 deletion may impair the calcium influx and T cell functions and decrease the transcription of cytokines, thus injuring various immune responses.

5.2. ORAI1 immune responses in B cells

ORAI1 is extremely important in mediating B-cell receptor (BCR) stimulation, proliferation, and even survival. After BCR stimulation, B-cell proliferation is substantially decreased in ORAI1 knockout mice [7], and the sensitivity of tumor cells apoptosis is improved [45]. The antibodies such as IgE and IgG1 produced by B cells are increased in the sensitized passive cutaneous anaphylaxis animal model [20,46]. B cell calcium signal is inhibited by IgG antibodies, and ORAI1 could enhance the SOCE in some aspect [37]. Once the BCR stimulation starts, the ORAI1-STIM1 complex enhances the intracellular Ca^{2+} concentration [37]. In chicken B cells, the depletion of ORAI1 exhibits protective roles on cell death in response to oxidative stress since the calcium uptake in mitochondria was decreased [47]. However, the function of ORAI1 on the antibody production by B cells is dispensable. In SCID patients with impaired CRAC current, auto-antibodies produced by B cells were observed although the number of serum immunoglobulin is normal or even elevated [21,48]. Thus, we may conclude that ORAI1 could enhance mitochondria Ca^{2+} uptake and B cell activation, therefore inducing the mediator release. However, we should also pay attention to the antibodies produced after B cell activation although the calcium influx is impaired.

5.3. ORAI1 immune responses in mast cells

Studies show that ORAI1 takes essential roles in degranulation and cytokine release of mast cells [1]. Firstly, Ca^{2+} influx is found in mast cells spontaneous motility, which partially leads to mast cell degranulation [49]. During the reactive oxygen stress process, mast cell degranulation can be activated by increasing Ca^{2+} influx *via* ORAI1 [50]. The interaction of cationic liposomes and STIM1-ORAI1 complex can inhibit mast cell activation and extracellular calcium influx [51]. The depletion of ORAI1 down-regulates SOCE and intracellular Ca^{2+} level, and decreases degranulation and migration in BMMCs or RBL-2H3 cells [52,53]. In human mast cells, ORAI1 inhibitor could reduce the degranulation level and alleviate the calcium influx *via* SOCE [54]. Down regulated ORAI1 of HMC-1 cell would inhibit the signal transduction including MAPK pathway and NF-κB pathway [55]. Cross-linking of IgE and FcεR1α initiates the activation of mast cells through Syk signaling and then allergic mediators are released, such as IL-6, TNF-α, and LTC4 [56]. In activated human lung mast cells, lipid mediator LTC4 production is reduced along with the reduction of β-hexosaminidase release and extracellular calcium influx following the deletion of ORAI1[57]. LTC4 and other mast cell derived cytokines, such as TNF-α and L-6, are also partially reduced in mice with ORAI1 deletion [1]. ORAI1 siRNA transfection in RBL-1 mast cell line inhibits Syk activity thus affecting mast cell degranulation [58]. Then, mast cell releases histamine and delayed inflammatory mediators *via* ORAI1, thereby exacerbating mast cell responses [59,60]. Through the suppressed expression of ORAI1 and STIM1, glycyrrhizic acid(GA) which functions as mast cell stabilizer would inhibit the mast cell activation and attenuate the vascular permeability, thus decreasing the calcium influx [61]. GA also decreases Th2 cytokines in RBL-2H3 cells by inhibiting the expression of ORAI1 and STIM1 [61].

5.4. ORAI1 immune responses in dendrite cells and NK cells

In the above-mentioned immune cells, ORAI1 and STIM1 proteins function as key molecules in the Ca^{2+} signaling pathway of CRAC channel [14,62]. In addition to T cells, B cells, and mast cells, the vital roles of ORAI1 in other immune cells cannot be neglected. Previous studies showed that ORAI1 and STIM1 transcripts could be detected in human and mouse dendrite cells (DCs) [63,64]. ORAI1 promotes DC functions including cell maturation and migration and even cytokine production. LPS-stimulated DCs would activate CRAC channels including ORAI1, while the inhibition of I_{CRAC} would abrogate the release of IL-6 and TNF-α [64]. Besides, with ORAI1 silence, mice DCs show a decrease in cell migration and IL-12 secretion when cells are sensitized by leptin [65]. The siRNA against ORAI1 in human DCs also leads to the inhibition of DC maturation with reduced expression of surface markers, such as CD25 and CD83. Meanwhile, the production of cytokines, such as IL-10, IL-12, and IFN-γ, are all diminished [66].

Natural killer (NK) cells participate in the innate immunity by killing infected target cells [67,68]. The activation of NK cells induces the release of cytokines and chemokines through ORAI1-dependent Ca^{2+} influx. In ORAI1-deficient NK cells, the lysis of target cells and IL-1β synthesis are weakened; the recognition ability of cytokines, such as TNF-α and IFN-γ, toward target cells has also been impaired [32,69]. Moreover, the inhibition of ORAI1-dependent Ca^{2+} release increases the cytotoxicity of NK cells and enhance the elimination of cancer cells [70], while the inhibition or deletion of ORAI1 would not affect the cell adhesion pathways [68]. The ORAI1 null mutation may also contribute to fewer cytokine secretion of NK T cells, causing immunodeficiency and susceptibility to infections [68]. Thus, ORAI1-deficient patients are highly susceptible to infections such as viral infection [21]. In atopic dermatitis like mice we observed lower NK cell activity and more susceptible to virus [71]. Taken together, we may infer that targeting on ORAI1 may improve NK cell malfunction and reduce the risk of virus infection.

5.5. ORAI1 immune responses in eosinophils

Like the immune cells mentioned above, ORAI1 also has a crucial role in eosinophils [15]. In mice with allergic rhinitis, ORAI1 expression is upregulated accompanied by high infiltration of eosinophils [72]. The infiltration of eosinophil cells decreases in anti-ORAI1 antibody intervention group when compared with that in control [73]. And when transfected with sh-ORAI1 in nasal epithelial cells, eosinophils and inflammation responses decreased [11]. Since peripheral blood eosinophils are elevated in atopic dermatitis patients, we suspected that targeting ORAI1 on eosinophils may alleviate the cell infiltration and then relieve the inflammatory responses.

In summary, ORAI1 induces the activation of immune-related cells, including T cells, B cells, and mast cells, by affecting calcium channel currents and intracellular calcium release. It is evident that ORAI1 is a key molecule in the calcium signaling pathway, and ORAI1 could regulate most of the cells involved in the calcium signaling pathway. Also, the deletion or inhibition of ORAI1 affects biological effects in above cells, while some effects are not influenced, including DCs cell adhesion signal and B cell autoantibodies production.

6. ORAI1 as a therapeutic target in allergic skin diseases

Skin is the largest immune organ in our body that plays essential roles in resistance to external microbes and pathogens [12,74]. Many allergic skin diseases, such as urticaria and atopic dermatitis, belong to immune or autoimmune disorders [75]. These diseases with hypersensitivity are common in all population, and the life prevalence of

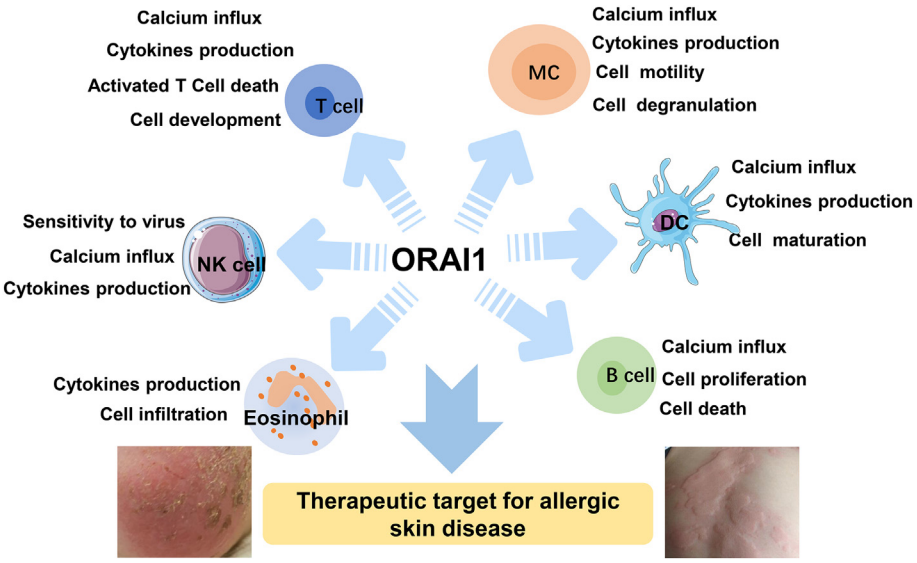

Fig. 2. ORAI1 immune responses in allergic skin disease as a therapeutic target. The immune related cells including mast cell, T cell, B cell, NK cell, Dendrite cell and even eosinophils mediate immune responses such as cell activation, cytokine production and cell maturation *via* ORAI1. Deletion or ablation of ORAI1 would induce impaired immune responses, since above immune cells participated in the pathogenesis of allergic skin disease, therefore, targeting on ORAI1 may alleviate the allergic symptoms.

urticaria ranges from 1%–24% with all types [76]. Mast cell dysfunction, imbalanced Th subtype cells, and NK cells are involved in the pathogenesis of allergic skin diseases [77–80]. Among these factors, intracellular Ca^{2+} level and CRAC channel may be the key points. Our previous studies showed that ORAI1 gene polymorphism induces the risk of chronic spontaneous urticaria [13]. In this study we reviewed the importance of ORAI1 in allergic/immune-related skin diseases. As we summarized the roles of ORAI1 in immune-related cells above, here we would like to discuss whether ORAI1 is a potent target for allergic skin diseases.

T cells and mast cells are indispensable in the pathogenesis of immune-related skin diseases. Abnormal T cells and imbalanced Th1/Th2 type cytokines may also be pathogenic factors of chronic urticaria and atopic dermatitis [81,82]. ORAI1 activation engages ORAI1/NFAT signaling in keratinocytes, promotes the production of thymic stromal lymphopoietin, contributes to Th2/Th22 imbalance and subsequently aggravates pruritus [2,75], leading to the occurrence of immune-related skin diseases such as atopic dermatitis. As mast cell activation and Th cell imbalance take roles in the development of atopic dermatitis. In clinics, ORAI1 genetic polymorphism rs3741596 (Ser218Gly) promotes AD development, because rs3741596GG/GA genotype carriers present a higher ORAI1 mRNA expression [10]. Thus, we may conclude that ORAI1 may be a risk factor of atopic dermatitis and targeting ORAI1 may give a prospective to treat refractory atopic dermatitis. Research on tribuli fructus extract in AD mice model also indicated that the inhibition of ORAI1 attenuated the skin inflammation [83]. Inhibiting ORAI1 expression in AD keratinocytes may relieve itch to some degree [2]. ORAI1 inhibitors, oligonucleotide agents' aptamers, are useful in AD treatment because of its role in reducing Ca^{2+} release and β-hexosaminidase *via* SOCE in human mast cells [54]. While focusing on the efficacy of targeting ORAI1, we should also pay attention to the adverse drug effects. Researchers observed deletion of ORAI1 in epidermis would impair the skin barrier with the aberrant function of keratinocytes proliferation and migration [84].

It is evident that ORAI1 gene polymorphism influences the susceptibility to CSU (rs12320939 and rs3741596) and the drug responses to non-sedating antihistamines (rs3741595) [13]. However, the detailed mechanism of ORAI1 in the pathogenesis of CSU remains elusive, and whether ORAI1 could play as a therapeutic target in urticaria needs more exploration. Since ORAI1 regulates calcium signal and affects immune cell activation, and immune cells especially mast cells and basophils drive the development of CSU, we conclude that ORAI1 could play a role in the treatment of allergic skin diseases, including CSU, by regulating the abnormal function of immune cells. Targeting on ORAI1 level in T cells and NK cells may alleviate the progression of allergic skin diseases [78–80]. ORAI1-deleted cells show immune dysfunctions including decreased mast cell degranulation and T cell activation, thus ORAI1 ablation or deletion could provide a precise therapeutic target for allergic skin diseases (Fig. 2).

7. Conclusions

As a critical membrane protein, ORAI1 serves as a Ca^{2+} channel that mediates extracellular Ca^{2+} influx by forming complexes with STIM1. In addition to SOCE, ORAI1 regulates immune cells activation and cytokines release, which are involved in allergic diseases. Targeting ORAI1 in immune cells by siRNA silencing or deletion would induce the dysfunction of immune responses, including decrease of cytokine release and cell mobility, thus causing relieved or attenuated inflammation and allergic reactions. Based on these considerations, ORAI1 may serve as a potential target to treat allergic skin diseases.

Author contributions statement

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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References

[1] M. Vig, et al., Defective mast cell effector functions in mice lacking the CRACM1

pore subunit of store-operated calcium release-activated calcium channels, Nat Immunol 9 (1) (2008) 89–96.
[2] S.R. Wilson, et al., The epithelial cell-derived atopic dermatitis cytokine TSLP activates neurons to induce itch, Cell 155 (2) (2013) 285–295.
[3] T.X. Dong, et al., Intermittent Ca(2+) signals mediated by Orai1 regulate basal T cell motility, Elife 6 (2017).
[4] C.A. McCarl, et al., ORAI1 deficiency and lack of store-operated Ca2+ entry cause immunodeficiency, myopathy, and ectodermal dysplasia, Journal of Allergy and Clinical Immunology 124 (6) (2009) 1311–1318.
[5] S. Weidinger, N. Novak, Atopic dermatitis, Lancet 387 (10023) (2016) 1109–1122.
[6] P.M. Brunner, et al., Early-onset pediatric atopic dermatitis is characterized by TH2/TH17/TH22-centered inflammation and lipid alterations, J Allergy Clin Immunol 141 (6) (2018) 2094–2106.
[7] Y. Gwack, et al., Hair loss and defective T- and B-Cell function in mice lacking ORAI1, Molecular and Cellular Biology 28 (17) (2008) 5209–5222.
[8] S. Feske, Immunodeficiency due to defects in store-operated calcium entry, Ann N Y Acad Sci 1238 (2011) 74–90.
[9] M. Furue, et al., Atopic dermatitis: immune deviation, barrier dysfunction, IgE autoreactivity and new therapies, Allergol Int 66 (3) (2017) 398–403.
[10] W.C. Chang, et al., ORAI1 genetic polymorphisms associated with the susceptibility of atopic dermatitis in Japanese and Taiwanese populations, Plos One 7 (1) (2012).
[11] Y. Wang, L. Lin, C. Zheng, Downregulation of Orai1 expression in the airway alleviates murine allergic rhinitis, Exp Mol Med 44 (3) (2012) 177–190.
[12] L. Lin, F. Dai, T. Sun, The Orai1 antibody treatment for a mouse model of allergic rhinitis, Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 51 (1) (2016) 43–49.
[13] A. Patrizi, et al., Advances in pharmacotherapeutic management of common skin diseases in neonates and infants, Expert Opin Pharmacother 18 (7) (2017) 717–725.
[14] S. Feske, et al., A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function, Nature 441 (7090) (2006) 179–185.
[15] J. Lian, et al., ORAI1 mutations abolishing store-operated Ca2+ entry cause anhidrotic ectodermal dysplasia with immunodeficiency, J Allergy Clin Immunol 142 (4) (2018) 1297–1310.
[16] M. Vaeth, et al., Store-operated Ca2+ entry controls clonal expansion of T cells through metabolic reprogramming, Immunity 47 (4) (2017) 664–679 (e6).
[17] R. Palty, Z. Fu, E.Y. Isacoff, Sequential steps of CRAC channel activation, Cell Rep 19 (9) (2017) 1929–1939.
[18] J.H. Izquierdo, et al., Calcium, channels, intracellular signaling and autoimmunity, Reumatol Clin 10 (1) (2014) 43–47.
[19] C.T. Berry, M.J. May, B.D. Freedman, STIM- and Orai-mediated calcium entry controls NF-kappaB activity and function in lymphocytes, Cell Calcium 74 (2018) 131–143.
[20] C.A. McCarl, et al., Store-operated Ca2+ entry through ORAI1 is critical for T cell-mediated autoimmunity and allograft rejection, Journal of Immunology 185 (10) (2010) 5845–5858.
[21] M. Vaeth, et al., Store-operated Ca(2+) entry in follicular T cells controls humoral immune responses and autoimmunity, Immunity 44 (6) (2016) 1350–1364.
[22] M. Grupe, et al., Activation of store-operated I(CRAC) by hydrogen peroxide, Cell Calcium 48 (1) (2010) 1–9.
[23] T.X. Chen, et al., Hydrogen peroxide is a critical regulator of the hypoxia-induced alterations of store-operated Ca2+ entry into rat pulmonary arterial smooth muscle cells, American Journal of Physiology-Lung Cellular and Molecular Physiology 312 (4) (2017) L477–L487.
[24] N. Henke, et al., Stromal interaction molecule 1 (STIM1) is involved in the regulation of mitochondrial shape and bioenergetics and plays a role in oxidative stress, Journal of Biological Chemistry 287 (50) (2012) 42042–42052.
[25] X. Liu, et al., Orai1 is critical for Notch-driven aggressiveness under hypoxic conditions in triple-negative breast cancers, Biochim Biophys Acta 1864 (4 Pt A) (2018) 975–986.
[26] D. Holowka, B. Baird, Roles for lipid heterogeneity in immunoreceptor signaling, Biochimica Et Biophysica Acta-Molecular and Cell Biology of Lipids 1861 (8) (2016) 830–836.
[27] I. Derler, et al., Cholesterol modulates Orai1 channel function, Science Signaling 9 (412) (2016).
[28] D. Holowka, et al., Polyunsaturated fatty acids inhibit stimulated coupling between the ER Ca2+ sensor STIM1 and the Ca2+ channel protein Orai1 in a process that correlates with inhibition of stimulated STIM1 oligomerization, Biochimica Et Biophysica Acta-Molecular and Cell Biology of Lipids 1841 (8) (2014) 1210–1216.
[29] M. Dong, et al., Increased expression of STIM1/Orai1 in platelets of stroke patients predictive of poor outcomes, Eur J Neurol 24 (7) (2017) 912–919.
[30] L. Wang, et al., Orai1 mediates tumor-promoting store-operated Ca2+ entry in human gastrointestinal stromal tumors via c-KIT and the extracellular signal-regulated kinase pathway, Tumour Biol 39 (2) (2017) (p. 1010428317691426).
[31] C. Dubois, et al., Remodeling of channel-forming ORAI proteins determines an oncogenic switch in prostate cancer, Cancer Cell 26 (1) (2014) 19–32.
[32] M. Raphael, et al., TRPV6 calcium channel translocates to the plasma membrane via Orai1-mediated mechanism and controls cancer cell survival, Proc Natl Acad Sci U S A 111 (37) (2014) E3870–E3879.
[33] L. Gui, et al., High expression of Orai1 enhances cell proliferation and is associated with poor prognosis in human colorectal cancer, Clin Lab 62 (9) (2016) 1689–1698.
[34] M. Umemura, et al., Store-operated Ca2+ entry (SOCE) regulates melanoma proliferation and cell migration, PLoS One 9 (2) (2014) e89292.
[35] H. Stanisz, et al., Inverse regulation of melanoma growth and migration by Orai1/STIM2-dependent calcium entry, Pigment Cell Melanoma Res 27 (3) (2014) 442–453.
[36] I. Jardin, J.A. Rosado, STIM and calcium channel complexes in cancer, Biochim Biophys Acta 1863 (6 Pt B) (2016) 1418–1426.
[37] Y. Baba, T. Kurosaki, Role of calcium signaling in B cell activation and biology, B Cell Receptor Signaling 393 (2016) 143–174.
[38] M.I. Lioudyno, et al., Orai1 and STIM1 move to the immunological synapse and are up-regulated during T cell activation, Proc Natl Acad Sci U S A 105 (6) (2008) 2011–2016.
[39] M. Vig, et al., CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry, Science 312 (5777) (2006) 1220–1223.
[40] X. Chen, et al., Functional interrogation of primary human T cells via CRISPR genetic editing, J Immunol 201 (5) (2018) 1586–1598.
[41] K. Dorr, et al., Cell type-specific glycosylation of Orai1 modulates store-operated Ca2+ entry, Science Signaling 9 (418) (2016).
[42] C. Klemann, et al., Hemophagocytic lymphohistiocytosis as presenting manifestation of profound combined immunodeficiency due to an ORAI1 mutation, J Allergy Clin Immunol 140 (6) (2017) 1721–1724.
[43] K.Y. Wang, et al., Efficacy and safety of omalizumab in pediatric patients with high immunoglobulin E levels: a case series, Allergy Asthma Proc 39 (4) (2018) 289–291.
[44] K.D. Kim, et al., ORAI1 deficiency impairs activated T cell death and enhances T cell survival, Journal of Immunology 187 (7) (2011) 3620–3630.
[45] P. Vacher, et al., Localized store-operated calcium influx represses CD95-dependent apoptotic effects of rituximab in non-Hodgkin B lymphomas, J Immunol 195 (5) (2015) 2207–2215.
[46] O. Dellis, et al., Epstein-Barr virus latent membrane protein 1 increases calcium influx through store-operated channels in B lymphoid cells, Journal of Biological Chemistry 286 (21) (2011) 18583–18592.
[47] S. Shanmughapriya, et al., Ca2+ signals regulate mitochondrial metabolism by stimulating CREB-mediated expression of the mitochondrial Ca2+ uniporter gene MCU, Sci Signal 8 (366) (2015) ra23.
[48] P.J. Shaw, S. Feske, Regulation of lymphocyte function by ORAI and STIM proteins in infection and autoimmunity, J Physiol 590 (17) (2012) 4157–4167.
[49] W. Yang, et al., Role of acid sphingomyelinase in the regulation of mast cell function, Clin Exp Allergy 44 (1) (2014) 79–90.
[50] B. Yang, et al., Food allergen-induced mast cell degranulation is dependent on PI3K-mediated reactive oxygen species production and upregulation of store-operated calcium channel subunits, Scandinavian Journal of Immunology 78 (1) (2013) 35–43.
[51] Y. Inoh, et al., Cationic liposomes suppress intracellular calcium ion concentration increase via inhibition of PI3 kinase pathway in mast cells, Biochim Biophys Acta 1859 (12) (2017) 2461–2466.
[52] Y.C. Chen, et al., Differential Ca(2+) mobilization and mast cell degranulation by FcepsilonRI- and GPCR-mediated signaling, Cell Calcium 67 (2017) 31–39.
[53] J. Lee, et al., Molecular mechanisms of spontaneous and directed mast cell motility, J Leukoc Biol 92 (5) (2012) 1029–1041.
[54] R.S. Sun, et al., Calcium influx of mast cells is inhibited by aptamers targeting the first extracellular domain of Orai1, Plos One 11 (7) (2016).
[55] P. Lianto, et al., Inhibitory effects of quail egg on mast cells degranulation by suppressing PAR2-mediated MAPK and NF-kB activation, Food Nutr Res 62 (2018).
[56] H. Bonnekoh, et al., The role of mast cells in autoinflammation, Immunol Rev 282 (1) (2018) 265–275.
[57] I. Ashmole, et al., The contribution of Orai(CRACM)1 and Orai(CRACM)2 channels in store-operated Ca2+ entry and mediator release in human lung mast cells, PLoS One 8 (9) (2013) e74895.
[58] S.W. Ng, et al., Sustained activation of the tyrosine kinase Syk by antigen in mast cells requires local Ca2+ influx through Ca2+ release-activated Ca2+ channels, Journal of Biological Chemistry 283 (46) (2008) 31348–31355.
[59] N.P. Azouz, I. Hammel, R. Sagi-Eisenberg, Characterization of mast cell secretory granules and their cell biology, DNA Cell Biol 33 (10) (2014) 647–651.
[60] I. Ashmole, P. Bradding, Ion channels regulating mast cell biology, Clin Exp Allergy 43 (5) (2013) 491–502.
[61] S. Han, et al., Anti-allergic activity of glycyrrhizic acid on IgE-mediated allergic reaction by regulation of allergy-related immune cells, Sci Rep 7 (1) (2017) 7222.
[62] S.Y.L. Zhang, et al., STIM1 is a Ca2+ sensor that activates CRAC channels and migrates from the Ca2+ store to the plasma membrane, Nature 437 (7060) (2005) 902–905.
[63] K. Itagaki, et al., Eicosanoid-induced store-operated calcium entry in dendritic cells, J Surg Res 169 (2) (2011) 301–310.
[64] N. Matzner, et al., Ion channels modulating mouse dendritic cell functions, J Immunol 181 (10) (2008) 6803–6809.
[65] J. Yan, et al., Orai1 is involved in leptin-sensitive cell maturation in mouse dendritic cells, Biochem Biophys Res Commun 503 (3) (2018) 1747–1753.
[66] R. Felix, et al., The Orai-1 and STIM-1 complex controls human dendritic cell maturation, Plos One 8 (6) (2013).
[67] A.G. Freud, et al., The broad spectrum of human natural killer cell diversity, Immunity 47 (5) (2017) 820–833.
[68] A. Maul-Pavicic, et al., ORAI1-mediated calcium influx is required for human cytotoxic lymphocyte degranulation and target cell lysis, Proceedings of the National Academy of Sciences of the United States of America 108 (8) (2011) 3324–3329.
[69] X. Zhou, et al., A calcium optimum for cytotoxic T lymphocyte and natural killer cell cytotoxicity, J Physiol 596 (14) (2018) 2681–2698.
[70] E. Gianchecchi, D.V. Delfino, A. Fierabracci, NK cells in autoimmune diseases: linking innate and adaptive immune responses, Autoimmun Rev 17 (2) (2017) 142–154.
[71] Y. Kawakami, et al., Defective natural killer cell activity in a mouse model of eczema herpeticum, J Allergy Clin Immunol 139 (3) (2017) 997–1006 (e10).
[72] N.L. Diny, N.R. Rose, D. Cihakova, Eosinophils in autoimmune diseases, Front Immunol 8 (2017) 484.
[73] L. Lin, et al., Up-regulation of Orai1 in murine allergic rhinitis, Histochem Cell Biol

134 (1) (2010) 93–102.
[74] R.A. Clark, K. Ghosh, M.G. Tonnesen, Tissue engineering for cutaneous wounds, J Invest Dermatol 127 (5) (2007) 1018–1029.
[75] K. Noske, Secreted immunoregulatory proteins in the skin, J Dermatol Sci 89 (1) (2018) 3–10.
[76] C. Antia, et al., Urticaria: a comprehensive review: epidemiology, diagnosis, and work-up, J Am Acad Dermatol 79 (4) (2018) 599–614.
[77] H. Kang, et al., 5 nm silver nanoparticles amplify clinical features of atopic dermatitis in mice by activating mast cells, Small 13 (9) (2017).
[78] M.R. Gaudinski, J.D. Milner, Atopic dermatitis and allergic urticaria: cutaneous manifestations of immunodeficiency, Immunol Allergy Clin North Am 37 (1) (2017) 1–10.
[79] R. Asero, et al., Chronic urticaria: a focus on pathogenesis, F1000Res 6 (2017) 1095.
[80] M.M. Rauber, et al., Functional and phenotypic analysis of basophils allows determining distinct subtypes in patients with chronic urticaria, Allergy 72 (12) (2017) 1904–1911.
[81] S. Ying, et al., T(H)1/T(H)2 cytokines and inflammatory cells in skin biopsy specimens from patients with chronic idiopathic urticaria: comparison with the allergen-induced late-phase cutaneous reaction, Journal of Allergy and Clinical Immunology 109 (4) (2002) 694–700.
[82] K. Malik, K.D. Heitmiller, T. Czarnowicki, An update on the pathophysiology of atopic dermatitis, Dermatologic Clinics 35 (3) (2017) 317.
[83] S.Y. Kang, et al., Effects of the fruit extract of *Tribulus terrestris* on skin inflammation in mice with oxazolone-induced atopic dermatitis through regulation of calcium channels, Orai-1 and TRPV3, and mast cell activation, Evid Based Complement Alternat Med 2017 (2017) 8312946.
[84] M. Vandenberghe, et al., ORAI1 calcium channel orchestrates skin homeostasis, Proceedings of the National Academy of Sciences of the United States of America 110 (50) (2013) E4839–E4848.