Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Curr Opin Immunol. Author manuscript; available in PMC 2019 June 01.

Published in final edited form as:

Curr Opin Immunol. 2018 June ; 52: 39–50. doi:10.1016/j.coi.2018.03.021.

Ion channelopathies of the Immune System

Martin Vaeth and **Stefan Feske***

Department of Pathology, New York University School of Medicine, New York, NY 10016, USA

Abstract

Ion channels and transporters move ions across membrane barriers and are essential for a host of cell functions in many organs. They conduct K^+, Na^+ and Cl^-, which are essential for regulating the membrane potential, H^+ to control intra- and extracellular pH and divalent cations such as Ca^{2+}, Mg^{2+} and Zn^{2+}, which function as second messengers and cofactors for many proteins. Inherited channelopathies due to mutations in ion channels or their accessory proteins cause a variety of diseases in the nervous, cardiovascular and other tissues, but channelopathies that affect immune function are not as well studied. Mutations in *ORAI1* and *STIM1* genes that encode the Ca^{2+} release-activated Ca^{2+} (CRAC) channel in immune cells, the Mg^{2+} transporter MAGT1 and the Cl^- channel LRRC8A all cause immunodeficiency with increased susceptibility to infection. Mutations in the Zn^{2+} transporters SLC39A4 (ZIP4) and SLC30A2 (ZnT2) result in nutritional Zn^{2+} deficiency and immune dysfunction. These channels, however, only represent a fraction of ion channels that regulate immunity as demonstrated by immune dysregulation in channel knockout mice. The immune system itself can cause acquired channelopathies that are associated with a variety of diseases of nervous, cardiovascular and endocrine systems resulting from autoantibodies binding to ion channels. These autoantibodies highlight the therapeutic potential of functional anti-ion channel antibodies that are being developed for the treatment of autoimmune, inflammatory and other diseases.

Introduction

Ion channels and transporters (ICT) move ions across hydrophobic lipid membrane barriers including the plasma membrane (PM) and membranes of intracellular organelles such as mitochondria, the endoplasmic reticulum (ER) and vacuoles. The passive transport of ions through ion channels is driven by concentration and electrical gradients between two compartments (e.g. the intra- and extracellular space). By contrast, ion transporters, pumps and exchangers move ions actively with or against their gradient by using energy provided by the hydrolysis of ATP or coupling transport to the potential of other ion gradients. The mammalian genome encodes for more than 600 ICT and accessory proteins that conduct Ca^{2+}, Mg^{2+}, Zn^{2+}, Fe^{3+}, Fe^{2+}, Cu^{2+}, Mn^{2+}, K^+, Na^+, H^+, Cl^-, HCO_3^- and trace elements, which play important roles in the regulation of cell function. Relatively few ICTs have

*Stefan Feske (feskes01@nyumc.org).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

known roles in the immune system based on genetic or solid pharmacological evidence (Tables 1 and 2)[1, 2], although it is likely that many more channels operate in immune cells and control their function.

Channelopathies are a heterogeneous group of diseases caused by the dysfunction of ICTs due to mutations in their pore-forming alpha subunits or accessory proteins that regulate their function. Channelopathies have been widely studied in many organ systems and linked to diseases such as epilepsy, ataxia or migraine in the nervous system, Brugada syndrome, long QT syndrome and atrial fibrillation in the heart, cystic fibrosis, neonatal forms of diabetes mellitus and polycystic kidney disease, to name a few[3]. In the immune system, only a few inherited ion channelopathies affecting ICTs conducting Ca^{2+}, Mg^{2+}, Zn^{2+} and Cl^{-} have been reported so far (Table 2). Their dysfunction is associated with immunodeficiency and in some cases autoimmunity and hematologic malignancies[1, 2, 4]. Disease-causing autoantibodies binding to ICTs in variety of organs can be considered as secondary (auto)immune channelopathies and will be discussed briefly at the end of this review[5].

ORAI1, STIM1 and CRAC channelopathy

The Ca^{2+} release-activated Ca^{2+} (CRAC) channel is the main Ca^{2+} influx channel in T cells and most other immune cells[1, 6, 7, 8]. Besides its important role in immunity, the CRAC channel mediates Ca^{2+} influx in many other cell types and tissues owing to its ubiquitous expression. The highly Ca^{2+} selective CRAC channel is composed of a hexameric complex of ORAI1 proteins or its homologues ORAI2 and ORAI3 (Figure 1)[8, 9]. ORAI proteins, named after the *horae* Eunomia, Dike, Eirene in Homer's *Iliad*, who were the custodians of the gates of Olympus[10], are highly conserved small tetraspanning plasma membrane proteins[11, 12, 13]. They contain intracellular N- and C-termini, which allow them to bind to stromal interaction molecule (STIM) 1 and STIM2 and other accessory proteins that modulate CRAC channel function[8, 14]. STIM1 and STIM2 are single-pass transmembrane proteins with an ER lumenal N terminus and cytoplasmic C terminus. They respond to a reduction in the Ca^{2+} concentration in the ER ($[Ca^{2+}]_{ER}$) and the dissociation of Ca^{2+} from their EF hand Ca^{2+} binding domains with extensive conformational changes, which allow them to interact with ORAI channels and phospholipids in the plasma membrane within ER-PM junctions. The molecular choreography of STIM activation and the subsequent activation of ORAI channels has been extensively reviewed elsewhere[8, 15, 16].

The Ca^{2+} influx mediated by CRAC channels, called store-operated Ca^{2+} entry (SOCE) because of its regulation by $[Ca^{2+}]_{ER}$, is initiated by engagement of immunoreceptors such as the TCR, BCR and FcR and subsequent activation of phospholipase Cγ (PLCγ) and IP_3 production, which results in Ca^{2+} release from the ER through inositol-1,4,5-trisphosphate (IP_3) receptor channels and activation of STIM1 and STIM2 (Figure 1). Ca^{2+} signaling following SOCE leads to the activation of many Ca^{2+} regulated enzymes and transcription factors among which the serine/threonine-phosphatase calcineurin and the nuclear factor of activated T cells (NFAT) have prominent roles in T cell function and immunity[17, 18, 19, 20, 21]. An important function of the SOCE-calcineurin-NFAT signaling pathway is the transcriptional regulation of gene expression. SOCE controls the expression of cytokines, transcription factors, glycolytic enzymes and mitochondrial genes that control

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

a variety of cellular processes including T cell differentiation, proliferation and metabolism[22, 23, 24, 25]. Besides gene regulation, SOCE also controls a multitude of other immune cell functions such as the degranulation of cytotoxic vesicles by $CD8^+$ T cells and NK cells or the production of reactive oxygen species (ROS) by neutrophils[26, 27, 28, 29, 30, 31]. It therefore comes as no surprise that defects in CRAC channel function have profound effects on immunity.

Loss-of-function (LOF) mutations in ORAI1 or STIM1 genes that abolish CRAC channel function and SOCE in T cells, NK cells and other immune and non-immune cells cause a unique disease syndrome called CRAC channelopathy (Table 2)[11, 32, 33, 34, 35, 36]. It is characterized by combined immunodeficiency (CID), autoimmunity and non-immune symptoms including congenital muscular hypotonia and ectodermal dysplasia with anhidrosis and amelogenesis imperfecta[4, 37]. CID in most patients manifests with severe viral, bacterial and fungal infections in the first months or years of life and generally requires treatment by hematopoeitic stem cell transplantation. Common pathogens include cytomegalovirus (CMV), Epstein-Barr virus (EBV), Candida albicans, Streptococcus pneumonia. Uncontrolled viral infections with EBV and human herpes virus 8 have resulted in EBV^+ B cell lymphoma and Kaposi sarcoma in a subset of patients with CRAC channelopathy[32, 34, 38]. Unlike severe combined immunodeficiency (SCID), ORAI1 and STIM1 deficient patients have mostly normal T, B and NK cells counts and lymphocyte development seems to proceed normally despite the absence of SOCE[4, 35]. However, some unconventional lymphocyte populations are altered in CRAC-deficient patients including iNKT cells, γδ T cells and in particular $Foxp3^+$ Treg cells[33, 34, 35]. Abnormal iNKT and γδ T cells may contribute to the CID phenotype. The main cause of CID in patients with LOF mutations in *ORAI1* and *STIM1*, however, is impaired T cell function. In the absence of SOCE, $CD4^+$ and $CD8^+$ T cells fail to proliferate and do not produce a large variety of cytokines required for T cell effector function and differentiation. The proliferation defect is not due to lack of the growth cytokine IL-2 but caused by an impaired switch of SOCE-deficient T cells to aerobic glycolysis, which is required to support the anabolic metabolism of stimulated T cells that allows them to grow and proliferate[39]. In the absence of SOCE and NFAT activation, T cells fail to express glucose transporters, glycolytic enzymes and transcription factors that control their expression and they do not activate the AKT-mTOR pathway[23]. The role of SOCE in metabolism is not limited to glycolysis, but extents further to the regulation of mitochondrial function and lipid metabolism[25]. CID in CRAC channelopathy is in part caused by impaired production of antigen-specific antibodies after vaccination or infection, despite overall normal or elevated serum immunoglobulin levels[4, 33, 35]. Studies in CRAC channel-deficient mice show that defective seroconversion results from the attenuated differentiation and function of follicular T helper (Tfh) cells that promote B cell maturation in the germinal centers (GC) of secondary lymphoid organs[24]. T cell-specific deletion of SOCE in mice strongly impaired antibody responses to immunization with T-dependent antigens and after viral infection[24].

Besides CID, many CRAC-deficient patients present with lymphoproliferation and autoimmunity characterized by autoimmune hemolytic anemia (AIHA) and thrombocytopenia associated with anti-erythrocyte, anti-platelet and other autoantibodies[4, 35]. The seemingly paradoxical combination of CID and autoimmunity is not

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

unique to patients with ORAI1 or STIM1 mutations but is common to many primary immunodeficiencies (PIDs)[40]. Autoantibody production in CRAC channelopathy patients likely results from impaired development or function of follicular Treg (Tfr) cells that suppress the GC reaction and prevent the formation of autoantibodies[41, 42]. Whereas Tfr cells are difficult to study in patients due to their paucity in the blood, mice with T cell- or Treg-specific deletion of *Stim1* and *Stim2* are almost completely devoid of $CXCR5^+$ Tfr cells in their lymph nodes and showed spontaneous development of large GCs and autoantibody production[24]. These findings indicate that SOCE is required for the differentiation of thymus-derived Treg cells into Tfr cells. A strong reduction of effector Treg (eTreg) cells was observed in ORAI1-deficient patients, likely accounting for their autoantibody production. Taken together, SOCE plays a dual role in controlling the function of Tfh cells that are required for the production of pathogen-specific antibodies and the function of Tfr cells that prevent spontaneous autoantibody production. Intriguingly, B cell-specific deletion of SOCE had no effect on antibody production after immunization[43], indicating that the humoral immunodeficiency in CRAC deficient patients is due to impaired T cell but not B cell function.

Non-immunological symptoms of CRAC channelopathy include ectodermal dysplasia and anhidrosis (EDA), constituting a new form of EDA with immunodeficiency (ID) that is distinct from EDA-ID due to mutations in *IKBKG* and *NFKBIA* genes in the nuclear factor kB (NF-kB) signaling pathway[35, 44]. Anhidrosis in CRAC channel-deficient patients is caused by impaired sweat gland function because SOCE is required for the opening of the Ca^{2+} activated Cl^- channel TMEM16A (or Ano1), which mediates Cl^- secretion[45]. Ectodermal dysplasia is mainly characterized by hypocalcified amelogenesis imperfecta due to impaired dental enamel formation and calcification[46]. It is noteworthy that gain-of-function (GOF) mutations in ORAI1 and STIM1 have been reported that cause constitutive Ca^{2+} influx. They cause disease with overlapping phenotypes, Stormorken syndrome and tubular aggregate myopathy, but are not associated with an overt immune phenotype[4].

MAGT1 and XMEN syndrome

Mg^{2+} is the most abundant divalent cation in immune cells and important for their proliferation and survival[47]. Several Mg^{2+} channels and transporters are expressed in immune cells including SLC41A1, SLC41A2, TRPM6, TRPM7 and MAGT1, but only the last two have so far been shown to regulate lymphocyte development and function[47]. TRPM7 is a non-selective, Mg^{2+}-permeable channel that also conducts other divalent cations including Ca^{2+}, Zn^{2+}, and Ni^{2+}. It is ubiquitously expressed and thought to regulate cellular Mg^{2+} homeostasis and thereby survival and proliferation[48]. Deletion of TRPM7 in murine T cells profoundly impairs T cell development, which suggests that Mg^{2+} influx through TRPM7 regulates thymocyte survival and/or proliferation, an interpretation that is complicated, however, by the fact that Mg^{2+} influx and cellular Mg^{2+} content in thymocytes were normal[49]. Since TRPM7 is also a functional serine threonine kinase, it remains possible that the function of TRPM7 in T cell development depends not on its channel but rather its kinase activity. A recent study using mice with macrophage specific deletion of TRPM7 showed that the channel mediates cytosolic Ca^{2+} elevations essential for LPS-induced macrophage activation and production of pro-inflammatory cytokines like IL-1β[50].

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Human diseases linked to TRPM7 have not been identified yet. In contrast to TRPM7, MAGT1 is a highly Mg^{2+} selective transporter with a tetraspanning PM topology (Figure 1). Together with MAGT2, which is much less selective for Mg^{2+} and can also conduct other bivalent cations such as Fe^{2+}, Mn^{2+} and Cu^{2+}, MAGT1 constitutes a new family of transporters without major similarities to other ICTs except the non-selective Mg^{2+} transporter TUSC3[51, 52].

Much of what we know about the physiological role of MAGT1 in immune function comes from patients with LoF mutations in *MAGT1* who suffer from X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN) disease (Table 2)[51] (reviewed in detail in [2, 53, 54, 55]). The disease is dominated by recurrent and persistent infections with EBV that often cause EBV-associated B cell lymphomas. Patients show $CD4^+$ lymphopenia and an inverted CD4:CD8 ratio that is due to diminished thymic production of $CD31^+$ naïve T cells[54, 55]. The immunodeficiency in XMEN patients is mainly caused by impaired function of NK cells and cytotoxic $CD8^+$ T cells[54, 55]. NK cells of XMEN patients lack expression of NKG2D, an activating NK cell receptor that is required for their antiviral and antitumor immunity. TCR stimulation was shown to result in Mg^{2+} influx, which is abolished in T cells of XMEN patients. While MAGT1 deficiency did not alter the total intracellular Mg^{2+} content (95% of intracellular Mg^{2+} is bound to phosphates and protein molecules), it impaired T cell activation by reducing the activation of PLCγ1, the production of IP_3 and the subsequent SOCE via CRAC channels (Figure 1). Defective SOCE in XMEN patients was only observed in T but not NK cells, which may be due to the effects of Mg^{2+} on the activation of the T cell-specific Tec kinase ITK[56]. Thus, it is likely that some defects in XMEN patients are a consequence of impaired SOCE, which is also required for T and NK cell function. The T cell activation defect in MAGT1-deficient patients can be overcome by strong and prolonged TCR stimulation[48], which may explain why XMEN patients do not develop other life-threatening infections besides EBV as seen in patients with CRAC channelopathy. Intriguingly, Mg^{2+} supplementation of T cells and NK cells from XMEN patients elevated their free intracellular Mg^{2+} levels, restored NKG2D expression on NK cells and significantly improved their cytotoxic function *in vitro*[51]. Furthermore, dietary supplementation of two XMEN patients with Mg^{2+} L-threonate was furthermore able to control of their EBV viremia[51]. Although XMEN patients provided clear evidence that MAGT1 and Mg^{2+} signaling are critical for NK and $CD8^+$ T cell function, the molecular mechanisms by which TCR stimulation activates MAGT1 or the mechanism of Mg^{2+}-dependent activation of PLCγ1 and other signaling pathways remains to be elucidated.

LRRC8A and Agammaglobulinemia

Leucine-rich repeat containing 8A (LRRC8A, also known as SWELL1) was identified by two siRNA screens as an essential component of the volume-regulated anion channel (VRAC). It mediates Cl^- secretion after cell swelling in response to changes in intracellular osmolytes or decreased extracellular osmolarity[57, 58]. LRRC8A is a tetraspanning plasma membrane protein that together with one or more of its four homologues (LRRC8B-E) forms a channel complex (likely a hexamer) (Figure 1)[59]. Mammalian LRRC8A contains 17 leucine-rich repeats at its C terminus that were shown to mediate signaling and activation of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

T cells[60, 61, 62]. LRRC8A is expressed in T and B cells and has important roles in adaptive immunity.

LRRC8A was first identified as a novel gene mutated in a 17 year-old girl who was heterozygous for a balanced chromosomal translocation, t(9;20)(q33.2;q12), that replaced two-and-a-half LRR domains by 35 novel amino acids encoded by intronic nucleotides and likely acts as a dominant negative on VRAC function[61]. The girl presented congenital agammaglobulinemia and B cell deficiency (Table 2)[61]. Expression of the truncated form of LRRC8A in murine bone-marrow cells and *Lrrc8a*-deficient mice confirmed its important role in B cell development and antibody production[61, 62]. *Lrrc8a*$^{-/-}$ animals not only showed increased prenatal and postnatal mortality, growth retardation, multiple tissue abnormalities and severely reduced peripheral B cell numbers, but also revealed a role of LRRC8A in thymocyte development and survival not found in human patients[62]. A spontaneous insertion mutation of *Lrrc8a* in mice (*ebo/ebo*) that causes a frameshift results in the expression of a truncated LRRC8A protein with its 15 C-terminal LRR domains missing (Table 1)[60]. T cells from *ebo/ebo* mice have abolished VRAC currents, suggesting that the LRR domains are required for channel function. However, T and B cell development, antibody responses after immunization as well as proliferation and cytokine production by T cells were normal[60]. These data suggest that the channel function of LRRC8A is dispensable for lymphocyte development and function[60]. The molecular mechanisms, including the relationship of the channel pore and LRR domains, by which LRRC8A regulates lymphocyte development and function require further study.

Zinc transporters, zinc deficiency and infections

Zn^{2+} is critical for normal immune function and nutritional Zn^{2+} deficiency in developing countries is a leading cause of immunodeficiency due to impaired innate and adaptive immune responses[63, 64]. Zn^{2+} levels in cells are regulated by two families of Zn^{2+} transporters, SLC30 (ZnT) and SLC39 (ZIP) proteins[65]. Two human diseases characterized by Zn^{2+} deficiency and impaired immune function have been linked to mutations in these gene families (Table 2). Acrodermatitis enteropathica (AE) is caused by LoF mutations in *SLC39A4* encoding the intestinal Zn^{2+} transporter ZIP4 and resulting in an inability to resorb intestinal Zn^{2+}. The disease resembles in many aspects systemic Zn^{2+} malnutrition and manifests with diarrhea, skin inflammation and blistering, alopecia, abnormal leukocyte populations and an increased susceptibility to infections[64]. Conditional deletion of *Slc39a4* in the intestinal epithelium of mice showed an important role of ZIP4 in Zn^{2+} uptake from the gut, maintenance of the intestinal stem cell niche and function of the gut mucosa, resulting in systemic Zn^{2+} deficiency but the effects on immune function were not tested[66].

Transient neonatal Zn^{2+} deficiency is due to heterozygous mutations in *SLC30A2* that encodes ZnT2. It transports Zn^{2+} into lysosomes, and mutations result in decreased Zn^{2+} levels in breast milk and nutritional Zn^{2+} deficiency of babies. Thus, immunodeficiency caused by mutations in ZnT2, similar to ZIP4, is not due to its role in immune cell function but can be attributed to systemic Zn^{2+} deficiency. Nevertheless, genetic deletion of Zn^{2+} transporters such as ZIP3, ZIP6, ZIP8, ZIP10 and ZnT5 in mice indicates that ZIP and ZnT proteins have important roles in immune cell development and function. Mice lacking ZIP3

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

have reduced $CD4^+$ $CD8^+$ double-positive (DP) but increased $CD4^+$ and $CD8^+$ single positive thymocytes suggesting that ZIP3 regulates T cell development[67]. However, deletion of ZIP3 does not alter intracellular levels of Zn^{2+} and trace metals nor did it affect the expression of two known Zn^{2+}-responsive genes[67]. Stimulation of mature T cells was shown to cause Zn^{2+} influx via ZIP6. The increase in intracellular Zn^{2+} concentration inhibits the recruitment of the phosphatase SHP1 and results in sustained Ca^{2+} influx and T cell activation[68]. The lysosomal transporter ZIP8 is upregulated after T cell activation and its knockdown by RNAi attenuated IFNγ and perforin expression in human T cells[69]. In B cells, genetic deletion of ZIP10 reduces intracellular Zn^{2+} levels, increases caspase activation and apoptosis, resulting in impaired B cell development[70]. Residual ZIP10-deficient B cells proliferated poorly and had decreased GC formation and T cell-dependent and T cell-independent antibody production after immunization, suggesting that Zn^{2+} uptake via ZIP10 regulates humoral immunity[71].

Two members of a family of transmembrane channel-like (TMC) proteins, TMC6 (EVER1) and TMC8 (EVER2) were shown to form a complex and interact with ZnT1 in the ER membrane and facilitating Zn^{2+} uptake into the ER (Table 2)[72]. TMC8 prevented the influx of free Zn^{2+} into the nucleus and inhibited the activation of the Zinc-regulated transcription factor MTF1[72]. Autosomal recessive mutations in TMC6 and TMC8 are associated with epidermodysplasia verruciformis (EV), a dermatosis characterized by abnormal susceptibility to human papillomaviruses (HPVs) and a high rate of progression to squamous cell carcinoma on sun-exposed skin. Given the role of TMC6 and TMC8 in Zn^{2+} uptake into the ER, their mutation has been suggested to result in increased cytosolic Zn^{2+} concentrations and enhanced transcription of Zn^{2+}-dependent viral proteins in keratinocytes[72]. TMC8 is also expressed in T cells but is downregulated after TCR stimulation, resulting in increased concentrations of free cytosolic Zn^{2+} similar to primary T cells from EVER2-deficient patients[73]. Increased Zn^{2+} impairs T cell activation and proliferation, but the impact of this T cell defect on EV pathogenesis remains to be elucidated. Despite these tantalizing findings, many questions about the role of ZIP, ZnT and TMC proteins in Zn^{2+} conductance and innate and adaptive immune function remain including the molecular mechanisms by which they are activated and how they regulate immune cell function.

Autoantibody-mediated ion channelopathies

Human LoF mutations in ion channels that impair immune cell function are relatively rare. However, the immune system can itself affect ion channel and cell function through the formation of autoantibodies (AA)[3]. AA binding to ion channels on the cell membrane causes disease by a number of mechanisms including blocking ion conductance, causing internalization of channel proteins or through complement fixation with subsequent inflammatory cell damage. The diseases associated with autoantibodies targeting ion channels predominantly affect the nervous system and skeletal muscle. Examples are diseases of neuromuscular transmission associated with muscle weakness such as myasthenia gravis due to AA against the nicotinic acetylcholine receptor (nAChR) or the receptor tyrosine kinase MuSK that facilitates nAChR clustering[74], Lambert-Eaton syndrome due to AA against P/Q-type voltage-gated Ca^{2+} channels[75], and Isaac and Morvan

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

syndromes, which represent a form of neuromyotonia caused by AA against components of the voltage-gated K^+ channel (VGKC) complex[76]. AA against the neuronal N-methyl-D-aspartate (NMDA) receptor are responsible for the most common form of AA-mediated encephalitis that manifests with severe CNS and autonomic nervous system symptoms[77]. Anti-NMDA receptor AA can also be found in patients with SLE, where they cause neurological and psychological symptoms. Apart from the CNS and skeletal muscle, examples of other organs affected by AA against ion channels are the heart in patients with congenital heart block (targeting L- and T-type voltage-gated Ca^{2+} channels)[78] and cardiomyopathy (L-type Ca^{2+} channels, K^+ channels) and skin in pemphigus vulgaris patients (nAChR)[79]. For more detailed reviews of AA-mediated channelopathies see[3, 5]. It is noteworthy that the production of AA against ion channels is often the consequence of paraneoplastic syndrome caused by tumors including thymoma, small cell lung cancer or ovarian teratoma[3, 80].

Conclusions Outlook

Although the number of ion channels mutated in human patients with immune channelopathy syndromes are limited, genetic deletion of ion channels in mice has taught us that many more ion channels play important roles in regulating innate and adaptive immune responses than previously anticipated. Equally important, the fact that autoantibodies can bind to ion channels and interfere with their function indicates that the deliberate use of ion channel selective functional antibodies is a promising approach to the treatment of diseases in which ion channels contribute to pathophysiology. Indeed, functional monoclonal antibodies (mAb) are emerging as a promising new drug family for the therapeutic modulation of ion channels following on the heels of mAb against other protein classes that is continuing to revolutionize the treatment of cancer, autoimmunity and other diseases[81]. Generating inhibitory mAb against ion channels is generally more challenging compared to mAb against other protein classes due to the complex membrane topology and small extracellular loop domains of many channels[82]. mAb against about half a dozen ion channels have been generated that block channel function and are effective in preclinical studies[82]. Two of these channels, P2RX7 and ORAI1, have important roles in immune cell function and immunity (Tables 1 and 2). Two mAbs against human ORAI1 were shown to block CRAC currents, SOCE and cytokine production by PBMC and attenuate GvHD in a preclinical xenograft model[83, 84]. Similarly, mAb and nanobodies antagonizing P2X7 function on mast cells, macrophages and T cells ameliorated immune pathology in mouse models of colitis, glomerulonephritis and contact hypersensitivity[85, 86]. While no therapeutic mAb targeting ion channels have been approved for clinical use yet, preclinical studies with mAb are promising and a variety to technological platforms are available to efficiently produce functional mAb against ion channels that may be useful to treat autoimmune disease.

Acknowledgments

We thank Dr. A. R. Concepcion for critically reading the manuscript and acknowledge support by the COST Action BM-1406. This work was funded by NIH grants AI097302, AI125997 and AI107448. S.F. is a scientific cofounder of CalciMedica; M.V. declares no conflict of interest.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

1. Feske S, Wulff H, Skolnik EY. Ion channels in innate and adaptive immunity. Annu Rev Immunol. 2015; 33:291–353. [PubMed: 25861976]
2. Chaigne-Delalande B, Lenardo MJ. Divalent cation signaling in immune cells. Trends Immunol. 2014; 35(7):332–344. [PubMed: 24932518]
3. Kim JB. Channelopathies. Korean J Pediatr. 2014; 57(1):1–18. [PubMed: 24578711]
4. Lacruz RS, Feske S. Diseases caused by mutations in ORAI1 and STIM1. Ann N Y Acad Sci. 2015; 1356:45–79. [PubMed: 26469693]
5. RamaKrishnan AM, Sankaranarayanan K. Understanding autoimmunity: The ion channel perspective. Autoimmun Rev. 2016; 15(7):585–620. [PubMed: 26854401]
6. Feske S. Calcium signalling in lymphocyte activation and disease. Nat Rev Immunol. 2007; 7(9): 690–702. [PubMed: 17703229]
7. Feske S, Skolnik EY, Prakriya M. Ion channels and transporters in lymphocyte function and immunity. Nat Rev Immunol. 2012; 12(7):532–547. [PubMed: 22699833]
8. Prakriya M, Lewis RS. Store-Operated Calcium Channels. Physiol Rev. 2015; 95(4):1383–1436. [PubMed: 26400989]
9•. Vaeth M, Yang J, Yamashita M, Zee I, Eckstein M, Knosp C, et al. ORAI2 modulates store-operated calcium entry and T cell-mediated immunity. Nature communications. 2017; 8:14714. This paper (Ref. 9) describes the generation of ORAI2-deficient mice and demonstrates that ORAI2 and ORAI1 together form a heteromeric CRAC channel complex in T cells. Only combined, but not individual, deletion of ORAI1 and ORAI2 abolishes CRAC channel function in mouse T cells and impairs immunity to infection, inflammatory bowel disease and graft-versus-host disease.
10. Britannica TEoE. Hora. 2007. [cited February 06, 2018]Available from: https://http://www.britannica.com/topic/Hora-Greek-mythology
11••. Feske S, Gwack Y, Prakriya M, Srikanth S, Puppel SH, Tanasa B, et al. A mutation in Orai1 causes immune deficiency by abrogating CRAC channel function. Nature. 2006; 441(7090):179–185. This paper (Ref.11) and the reports by Vig et al. (Ref.12) and Zhang et al. (Ref.13) describes the identification of ORAI1 (TMEM142A) as the gene encoding the pore forming subunit of the CRAC channel. This study used positional cloning in immunodeficient patients lacking CRAC channel function and RNAi in drosophila S2 cells to demonstrate the essential role of ORAI1 for T cell activation and adaptive immunity. [PubMed: 16582901]
12. Vig M, Peinelt C, Beck A, Koomoa DL, Rabah D, Koblan-Huberson M, et al. CRACM1 is a plasma membrane protein essential for store-operated Ca2+ entry. Science. 2006; 312(5777): 1220–1223. [PubMed: 16645049]
13. Zhang SL, Yeromin AV, Zhang XH, Yu Y, Safrina O, Penna A, et al. Genome-wide RNAi screen of Ca(2+) influx identifies genes that regulate Ca(2+) release-activated Ca(2+) channel activity. Proc Natl Acad Sci U S A. 2006; 103(24):9357–9362. [PubMed: 16751269]
14. Shaw PJ, Qu B, Hoth M, Feske S. Molecular regulation of CRAC channels and their role in lymphocyte function. Cell Mol Life Sci. 2013; 70(15):2637–2656. [PubMed: 23052215]
15. Derler I, Jardin I, Romanin C. Molecular mechanisms of STIM/Orai communication. Am J Physiol Cell Physiol. 2016; 310(8):C643–662. [PubMed: 26825122]
16. Soboloff J, Rothberg BS, Madesh M, Gill DL. STIM proteins: dynamic calcium signal transducers. Nat Rev Mol Cell Biol. 2012; 13(9):549–565. [PubMed: 22914293]
17. Vaeth M, Feske S. NFAT control of immune function: new frontiers for an abiding trooper. F1000Res. 2018 in press.
18. Macian F. NFAT proteins: key regulators of T-cell development and function. Nat Rev Immunol. 2005; 5(6):472–484. [PubMed: 15928679]
19. Muller MR, Rao A. NFAT, immunity and cancer: a transcription factor comes of age. Nat Rev Immunol. 2010; 10(9):645–656. [PubMed: 20725108]
20. Kar P, Mirams GR, Christian HC, Parekh AB. Control of NFAT Isoform Activation and NFAT-Dependent Gene Expression through Two Coincident and Spatially Segregated Intracellular Ca(2+) Signals. Mol Cell. 2016; 64(4):746–759. [PubMed: 27863227]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

21. Kar P, Parekh AB. Distinct spatial Ca2+ signatures selectively activate different NFAT transcription factor isoforms. Mol Cell. 2015; 58(2):232–243. [PubMed: 25818645]
22. Feske S, Giltnane J, Dolmetsch R, Staudt LM, Rao A. Gene regulation mediated by calcium signals in T lymphocytes. Nat Immunol. 2001; 2(4):316–324. [PubMed: 11276202]
23••. Vaeth M, Maus M, Klein-Hessling S, Freinkman E, Yang J, Eckstein M, et al. Store-Operated Ca(2+) Entry Controls Clonal Expansion of T Cells through Metabolic Reprogramming. Immunity. 2017; 47(4):664–679. e666. This paper (Ref. 23) identified Ca^{2+} influx through CRAC channels as a metabolic checkpoint for T cell activation and clonal expansion. Ca^{2+} and calcineurin signaling controls the expression of glucose transporters, glycolytic enzymes and transcription factors that control the metabolic reprograming of T cells after TCR stimulation. In addition, the study indicates that Ca^{2+} influx is critical for the activation of the AKT-mTOR pathway and mitochondrial function. [PubMed: 29030115]
24. Vaeth M, Eckstein M, Shaw PJ, Kozhaya L, Yang J, Berberich-Siebelt F, et al. Store-Operated Ca(2+) Entry in Follicular T Cells Controls Humoral Immune Responses and Autoimmunity. Immunity. 2016; 44(6):1350–1364. [PubMed: 27261277]
25. Maus M, Cuk M, Patel B, Lian J, Ouimet M, Kaufmann U, et al. Store-Operated Ca(2+) Entry Controls Induction of Lipolysis and the Transcriptional Reprogramming to Lipid Metabolism. Cell Metab. 2017; 25(3):698–712. [PubMed: 28132808]
26. Zhou X, Friedmann KS, Lyrmann H, Zhou Y, Schoppmeyer R, Knorck A, et al. A calcium optimum for cytotoxic T lymphocyte and natural killer cell cytotoxicity. J Physiol. 2018
27. Klein-Hessling S, Muhammad K, Klein M, Pusch T, Rudolf R, Floter J, et al. NFATc1 controls the cytotoxicity of CD8(+) T cells. Nat Commun. 2017; 8(1):511. [PubMed: 28894104]
28. Weidinger C, Shaw PJ, Feske S. STIM1 and STIM2-mediated Ca(2+) influx regulates antitumour immunity by CD8(+) T cells. EMBO Mol Med. 2013; 5(9):1311–1321. [PubMed: 23922331]
29. Pores-Fernando AT, Zweifach A. Calcium influx and signaling in cytotoxic T-lymphocyte lytic granule exocytosis. Immunol Rev. 2009; 231(1):160–173. [PubMed: 19754896]
30. Maul-Pavicic A, Chiang SC, Rensing-Ehl A, Jessen B, Fauriat C, Wood SM, et al. ORAI1-mediated calcium influx is required for human cytotoxic lymphocyte degranulation and target cell lysis. Proc Natl Acad Sci U S A. 2011; 108(8):3324–3329. [PubMed: 21300876]
31. Zhang H, Clemens RA, Liu F, Hu Y, Baba Y, Theodore P, et al. STIM1 calcium sensor is required for activation of the phagocyte oxidase during inflammation and host defense. Blood. 2014; 123(14):2238–2249. [PubMed: 24493668]
32. McCarl CA, Picard C, Khalil S, Kawasaki T, Rother J, Papolos A, et al. ORAI1 deficiency and lack of store-operated Ca2+ entry cause immunodeficiency, myopathy, and ectodermal dysplasia. J Allergy Clin Immunol. 2009; 124(6):1311–1318. e1317. [PubMed: 20004786]
33. Picard C, McCarl CA, Papolos A, Khalil S, Luthy K, Hivroz C, et al. STIM1 mutation associated with a syndrome of immunodeficiency and autoimmunity. N Engl J Med. 2009; 360(19):1971–1980. [PubMed: 19420366]
34. Fuchs S, Rensing-Ehl A, Speckmann C, Bengsch B, Schmitt-Graeff A, Bondzio I, et al. Antiviral and regulatory T cell immunity in a patient with stromal interaction molecule 1 deficiency. J Immunol. 2012; 188(3):1523–1533. [PubMed: 22190180]
35. Lian J, Cuk M, Kahlfuss S, Kozhaya L, Vaeth M, Rieux-Laucat F, et al. ORAI1 mutations abolishing store-operated Ca(2+) entry cause anhidrotic ectodermal dysplasia with immunodeficiency. J Allergy Clin Immunol. 2017
36. Maus M, Jairaman A, Stathopulos PB, Muik M, Fahrner M, Weidinger C, et al. Missense mutation in immunodeficient patients shows the multifunctional roles of coiled-coil domain 3 (CC3) in STIM1 activation. Proc Natl Acad Sci U S A. 2015; 112(19):6206–6211. [PubMed: 25918394]
37. Feske S. CRAC channelopathies. Pflugers Arch. 2010; 460(2):417–435. [PubMed: 20111871]
38. Byun M, Abhyankar A, Lelarge V, Plancoulaine S, Palanduz A, Telhan L, et al. Whole-exome sequencing-based discovery of STIM1 deficiency in a child with fatal classic Kaposi sarcoma. J Exp Med. 2010; 207(11):2307–2312. [PubMed: 20876309]
39. Pearce EL, Poffenberger MC, Chang CH, Jones RG. Fueling immunity: insights into metabolism and lymphocyte function. Science. 2013; 342(6155):1242454. [PubMed: 24115444]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

40. Grimbacher B, Warnatz K, Yong PFK, Korganow AS, Peter HH. The crossroads of autoimmunity and immunodeficiency: Lessons from polygenic traits and monogenic defects. J Allergy Clin Immunol. 2016; 137(1):3–17. [PubMed: 26768758]
41. Chung Y, Tanaka S, Chu F, Nurieva RI, Martinez GJ, Rawal S, et al. Follicular regulatory T cells expressing Foxp3 and Bcl-6 suppress germinal center reactions. Nat Med. 2011; 17(8):983–988. [PubMed: 21785430]
42. Linterman MA, Pierson W, Lee SK, Kallies A, Kawamoto S, Rayner TF, et al. Foxp3+ follicular regulatory T cells control the germinal center response. Nat Med. 2011; 17(8):975–982. [PubMed: 21785433]
43. Matsumoto M, Fujii Y, Baba A, Hikida M, Kurosaki T, Baba Y. The Calcium Sensors STIM1 and STIM2 Control B Cell Regulatory Function through Interleukin-10 Production. Immunity. 2011; 34:1–12. [PubMed: 21272780]
44. Picard C, Casanova JL, Puel A. Infectious diseases in patients with IRAK-4, MyD88, NEMO, or IkappaBalpha deficiency. Clin Microbiol Rev. 2011; 24(3):490–497. [PubMed: 21734245]
45. Concepcion AR, Vaeth M, Wagner LE 2nd, Eckstein M, Hecht L, Yang J, et al. Store-operated Ca2+ entry regulates Ca2+-activated chloride channels and eccrine sweat gland function. J Clin Invest. 2016; 126(11):4303–4318. [PubMed: 27721237]
46. Eckstein M, Vaeth M, Fornai C, Vinu M, Bromage TG, Nurbaeva MK, et al. Store-operated Ca(2+) entry controls ameloblast cell function and enamel development. JCI Insight. 2017; 2(6):e91166. [PubMed: 28352661]
47. Brandao K, Deason-Towne F, Perraud AL, Schmitz C. The role of Mg2+ in immune cells. Immunol Res. 2013; 55(1–3):261–269. [PubMed: 22990458]
48. Bates-Withers C, Sah R, Clapham DE. TRPM7, the Mg(2+) inhibited channel and kinase. Advances in experimental medicine and biology. 2011; 704:173–183. [PubMed: 21290295]
49•. Jin J, Desai BN, Navarro B, Donovan A, Andrews NC, Clapham DE. Deletion of Trpm7 disrupts embryonic development and thymopoiesis without altering Mg2+ homeostasis. Science. 2008; 322(5902):756–760. Using knockout mice, the studies by Kumar et al. (Ref. 52) and Jin et al. (Ref. 49) show that the Cl^- channel LRRC8A and the Mg^{2+} and Ca^{2+} permeable channel TRPM7, respectively are essential for T cell development. These are the only channels known to date that have a profound effects on thymopoiesis. [PubMed: 18974357]
50. Schappe MS, Szteyn K, Stremska ME, Mendu SK, Downs TK, Seegren PV, et al. Chanzyme TRPM7 Mediates the Ca(2+) Influx Essential for Lipopolysaccharide-Induced Toll-Like Receptor 4 Endocytosis and Macrophage Activation. Immunity. 2018; 48(1):59–74. e55. [PubMed: 29343440]
51. Chaigne-Delalande B, Li FY, O'Connor GM, Lukacs MJ, Jiang P, Zheng L, et al. Mg2+ regulates cytotoxic functions of NK and CD8 T cells in chronic EBV infection through NKG2D. Science. 2013; 341(6142):186–191. [PubMed: 23846901]
52. Goytain A, Quamme GA. Identification and characterization of a novel mammalian Mg2+ transporter with channel-like properties. BMC Genomics. 2005; 6:48. [PubMed: 15804357]
53••. Li FY, Chaigne-Delalande B, Kanellopoulou C, Davis JC, Matthews HF, Douek DC, et al. Second messenger role for Mg2+ revealed by human T-cell immunodeficiency. Nature. 2011; 475(7357):471–476. This is the first paper (Ref. 53) to report patients with a novel form of primary immunodeficiency named X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia (XMEN) disease, which is due to loss-of-function mutations in the gene encoding the Mg^{2+} transporter MAGT1. The paper demonstrates the important role of MAGT1 and Mg^{2+} for $CD8^+$ T cell and NK cell function. [PubMed: 21796205]
54. Li FY, Chaigne-Delalande B, Su H, Uzel G, Matthews H, Lenardo MJ. XMEN disease: a new primary immunodeficiency affecting Mg2+ regulation of immunity against Epstein-Barr virus. Blood. 2014; 123(14):2148–2152. [PubMed: 24550228]
55. Ravell J, Chaigne-Delalande B, Lenardo M. X-linked immunodeficiency with magnesium defect, Epstein-Barr virus infection, and neoplasia disease: a combined immune deficiency with magnesium defect. Curr Opin Pediatr. 2014; 26(6):713–719. [PubMed: 25313976]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

56. Kanellopoulou C, George AB, Masutani E, Jiang P, Ravell JC, Chaigne-Delalande B, et al. Defective activation of IL2-inducible T cell kinase (ITK) in XMEN disease. J Immunol. 2017; 198(Supplement):52.15.

57•. Qiu Z, Dubin AE, Mathur J, Tu B, Reddy K, Miraglia LJ, et al. SWELL1, a plasma membrane protein, is an essential component of volume-regulated anion channel. Cell. 2014; 157(2):447–458. These studies (Ref. 57, 58) independently identify LRRC8A as an essential component of the volume-regulated anion channel (VRAC), which is critical for mediating the regulatory volume decrease in cells after swelling in hypotonic conditions. [PubMed: 24725410]

58•. Voss FK, Ullrich F, Munch J, Lazarow K, Lutter D, Mah N, et al. Identification of LRRC8 heteromers as an essential component of the volume-regulated anion channel VRAC. Science. 2014; 344(6184):634–638. These studies (Ref. 57, 58) independently identify LRRC8A as an essential component of the volume-regulated anion channel (VRAC), which is critical for mediating the regulatory volume decrease in cells after swelling in hypotonic conditions. [PubMed: 24790029]

59. Abascal F, Zardoya R. LRRC8 proteins share a common ancestor with pannexins, and may form hexameric channels involved in cell-cell communication. Bioessays. 2012; 34(7):551–560. [PubMed: 22532330]

60. Platt CD, Chou J, Houlihan P, Badran YR, Kumar L, Bainter W, et al. Leucine-rich repeat containing 8A (LRRC8A)-dependent volume-regulated anion channel activity is dispensable for T-cell development and function. J Allergy Clin Immunol. 2017; 140(6):1651–1659. e1651. [PubMed: 28192143]

61••. Sawada A, Takihara Y, Kim JY, Matsuda-Hashii Y, Tokimasa S, Fujisaki H, et al. A congenital mutation of the novel gene LRRC8 causes agammaglobulinemia in humans. J Clin Invest. 2003; 112(11):1707–1713. This paper (Ref. 61) identified a novel gene, LRRC8, and shows that a heterozygous truncation mutation in LRRC8 in human patients is associated with an autosomal form of agammaglobinemia and impaired B cell development. [PubMed: 14660746]

62•. Kumar L, Chou J, Yee CS, Borzutzky A, Vollmann EH, von Andrian UH, et al. Leucine-rich repeat containing 8A (LRRC8A) is essential for T lymphocyte development and function. J Exp Med. 2014; 211(5):929–942. Using knockout mice, the studies by Kumar et al. (Ref. 52) and Jin et al. (Ref. 49) show that the Cl^- channel LRRC8A and the Mg^{2+} and Ca^{2+} permeable channel TRPM7, respectively are essential for T cell development. These are the only channels known to date that have a profound effects on thymopoiesis. [PubMed: 24752297]

63. Hojyo S, Fukada T. Roles of Zinc Signaling in the Immune System. J Immunol Res. 2016; 2016:6762343. [PubMed: 27872866]

64. Kambe T, Fukue K, Ishida R, Miyazaki S. Overview of Inherited Zinc Deficiency in Infants and Children. J Nutr Sci Vitaminol (Tokyo). 2015; 61(Suppl):S44–46. [PubMed: 26598882]

65. Baltaci AK, Yuce K. Zinc Transporter Proteins. Neurochem Res. 2017

66. Geiser J, Venken KJ, De Lisle RC, Andrews GK. A mouse model of acrodermatitis enteropathica: loss of intestine zinc transporter ZIP4 (Slc39a4) disrupts the stem cell niche and intestine integrity. PLoS Genet. 2012; 8(6):e1002766. [PubMed: 22737083]

67. Dufner-Beattie J, Huang ZL, Geiser J, Xu W, Andrews GK. Generation and characterization of mice lacking the zinc uptake transporter ZIP3. Mol Cell Biol. 2005; 25(13):5607–5615. [PubMed: 15964816]

68•. Yu M, Lee WW, Tomar D, Pryshchep S, Czesnikiewicz-Guzik M, Lamar DL, et al. Regulation of T cell receptor signaling by activation-induced zinc influx. J Exp Med. 2011; 208(4):775–785. This paper (Ref. 68) shows Zn^{2+} influx from the extracellular space and Zn^{2+} signaling in T cells upon TCR stimulation resulting in T cell activation. The authors identified ZIP6 as a critical transporter that mediates TCR-induced Zn^{2+} influx. [PubMed: 21422171]

69. Aydemir TB, Liuzzi JP, McClellan S, Cousins RJ. Zinc transporter ZIP8 (SLC39A8) and zinc influence IFN-gamma expression in activated human T cells. J Leukoc Biol. 2009; 86(2):337–348. [PubMed: 19401385]

70. Miyai T, Hojyo S, Ikawa T, Kawamura M, Irie T, Ogura H, et al. Zinc transporter SLC39A10/ZIP10 facilitates antiapoptotic signaling during early B-cell development. Proc Natl Acad Sci U S A. 2014; 111(32):11780–11785. [PubMed: 25074913]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

71. Hojyo S, Miyai T, Fujishiro H, Kawamura M, Yasuda T, Hijikata A, et al. Zinc transporter SLC39A10/ZIP10 controls humoral immunity by modulating B-cell receptor signal strength. Proc Natl Acad Sci U S A. 2014; 111(32):11786–11791. [PubMed: 25074919]

72. Lazarczyk M, Pons C, Mendoza JA, Cassonnet P, Jacob Y, Favre M. Regulation of cellular zinc balance as a potential mechanism of EVER-mediated protection against pathogenesis by cutaneous oncogenic human papillomaviruses. J Exp Med. 2008; 205(1):35–42. [PubMed: 18158319]

73. Lazarczyk M, Dalard C, Hayder M, Dupre L, Pignolet B, Majewski S, et al. EVER proteins, key elements of the natural anti-human papillomavirus barrier, are regulated upon T-cell activation. PLoS One. 2012; 7(6):e39995. [PubMed: 22761942]

74. Meriggioli MN, Sanders DB. Muscle autoantibodies in myasthenia gravis: beyond diagnosis? Expert review of clinical immunology. 2012; 8(5):427–438. [PubMed: 22882218]

75. Spillane J, Ermolyuk Y, Cano-Jaimez M, Lang B, Vincent A, Volynski KE, et al. Lambert-Eaton syndrome IgG inhibits transmitter release via P/Q Ca2+ channels. Neurology. 2015; 84(6):575–579. [PubMed: 25589670]

76. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan's syndrome and acquired neuromyotonia. Brain: a journal of neurology. 2010; 133(9):2734–2748. [PubMed: 20663977]

77. Kayser MS, Dalmau J. Anti-NMDA Receptor Encephalitis in Psychiatry. Curr Psychiatry Rev. 2011; 7(3):189–193. [PubMed: 24729779]

78. Karnabi E, Boutjdir M. Role of calcium channels in congenital heart block. Scand J Immunol. 2010; 72(3):226–234. [PubMed: 20696020]

79. Lakshmi MJD, Jaisankar TJ, Rajappa M, Thappa DM, Chandrashekar L, Divyapriya D, et al. Correlation of antimuscarinic acetylcholine receptor antibody titers and antidesmoglein antibody titers with the severity of disease in patients with pemphigus. J Am Acad Dermatol. 2017; 76(5): 895–902. [PubMed: 28089115]

80. Vernino S. Autoimmune and paraneoplastic channelopathies. Neurotherapeutics. 2007; 4(2):305–314. [PubMed: 17395141]

81. Kaplon H, Reichert JM. Antibodies to watch in 2018. MAbs. 2018:1–21.

82. Wilkinson TC, Gardener MJ, Williams WA. Discovery of functional antibodies targeting ion channels. J Biomol Screen. 2015; 20(4):454–467. [PubMed: 25473082]

83. Cox JH, Hussell S, Sondergaard H, Roepstorff K, Bui JV, Deer JR, et al. Antibody-mediated targeting of the orai1 calcium channel inhibits T cell function. PLoS One. 2013; 8(12):e82944. [PubMed: 24376610]

84••. Lin FF, Elliott R, Colombero A, Gaida K, Kelley L, Moksa A, et al. Generation and characterization of fully human monoclonal antibodies against human Orai1 for autoimmune disease. J Pharmacol Exp Ther. 2013; 345(2):225–238. This paper (Ref. 81) and the one by Cox et al. (Ref. 80) report the generation of monoclonal antibodies (mABs) binding to an extracellular domain of ORAI1. Both papers demonstrate that the mABs inhibit CRAC channel function, T cell proliferation, cytokine production and, as in the case of Cox et al. graft-versus-host disease in mice. These are the first reports of successful immune modulation using mABs targeting an ion channel, thus raising the possibility that mABs against ion channels can be developed for the treatment of autoimmune and other immunological disorders. [PubMed: 23475901]

85. Kurashima Y, Amiya T, Nochi T, Fujisawa K, Haraguchi T, Iba H, et al. Extracellular ATP mediates mast cell-dependent intestinal inflammation through P2X7 purinoceptors. Nature communications. 2012; 3:1034.

86. Danquah W, Meyer-Schwesinger C, Rissiek B, Pinto C, Serracant-Prat A, Amadi M, et al. Nanobodies that block gating of the P2X7 ion channel ameliorate inflammation. Science translational medicine. 2016; 8(366):366ra162.

87. Gwack Y, Srikanth S, Oh-Hora M, Hogan PG, Lamperti ED, Yamashita M, et al. Hair loss and defective T- and B-cell function in mice lacking ORAI1. Mol Cell Biol. 2008; 28(17):5209–5222. [PubMed: 18591248]

88. Kaufmann U, Shaw PJ, Kozhaya L, Subramanian R, Gaida K, Unutmaz D, et al. Selective ORAI1 Inhibition Ameliorates Autoimmune Central Nervous System Inflammation by Suppressing

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Effector but Not Regulatory T Cell Function. J Immunol. 2016; 196(2):573–585. [PubMed: 26673135]

89. Kim KD, Srikanth S, Tan YV, Yee MK, Jew M, Damoiseaux R, et al. Calcium signaling via Orai1 is essential for induction of the nuclear orphan receptor pathway to drive Th17 differentiation. J Immunol. 2014; 192(1):110–122. [PubMed: 24307733]
90. Kim KD, Srikanth S, Yee MK, Mock DC, Lawson GW, Gwack Y. ORAI1 deficiency impairs activated T cell death and enhances T cell survival. J Immunol. 2011; 187(7):3620–3630. [PubMed: 21873530]
91. Vig M, DeHaven WI, Bird GS, Billingsley JM, Wang H, Rao PE, et al. Defective mast cell effector functions in mice lacking the CRACM1 pore subunit of store-operated calcium release-activated calcium channels. Nat Immunol. 2008; 9(1):89–96. [PubMed: 18059270]
92. Ma J, McCarl CA, Khalil S, Luthy K, Feske S. T-cell-specific deletion of STIM1 and STIM2 protects mice from EAE by impairing the effector functions of Th1 and Th17 cells. Eur J Immunol. 2010; 40(11):3028–3042. [PubMed: 21061435]
93. Oh-Hora M, Komatsu N, Pishyareh M, Feske S, Hori S, Taniguchi M, et al. Agonist-selected T cell development requires strong T cell receptor signaling and store-operated calcium entry. Immunity. 2013; 38(5):881–895. [PubMed: 23499491]
94••. Oh-Hora M, Yamashita M, Hogan PG, Sharma S, Lamperti E, Chung W, et al. Dual functions for the endoplasmic reticulum calcium sensors STIM1 and STIM2 in T cell activation and tolerance. Nat Immunol. 2008; 9(4):432–443. Using mice with T cell specific deletion of Stim1 and Stim2 genes, this study (Ref. 89) showed that STIM1 is the main activator of CRAC channels in T cells, whereas STIM2 plays a lesser albeit significant role. Combined deletion of Stim1 and Stim2 genes abolished Ca^{2+} influx in T cells and impaired T cell activation, proliferation and cytokine production. In addition, STIM1/STIM2-deficiency impaired the development and suppressive function of $Foxp3^{+}$ regulatory T cells resulting in autoimmune inflammation of mice. [PubMed: 18327260]
95. Schuhmann MK, Stegner D, Berna-Erro A, Bittner S, Braun A, Kleinschnitz C, et al. Stromal interaction molecules 1 and 2 are key regulators of autoreactive T cell activation in murine autoimmune central nervous system inflammation. J Immunol. 2010; 184(3):1536–1542. [PubMed: 20028655]
96. Clemens RA, Chong J, Grimes D, Hu Y, Lowell CA. STIM1 and STIM2 cooperatively regulate mouse neutrophil store-operated calcium entry and cytokine production. Blood. 2017; 130(13): 1565–1577. [PubMed: 28724541]
97. Di A, Gao XP, Qian F, Kawamura T, Han J, Hecquet C, et al. The redox-sensitive cation channel TRPM2 modulates phagocyte ROS production and inflammation. Nat Immunol. 2011
98. Melzer N, Hicking G, Gobel K, Wiendl H. TRPM2 cation channels modulate T cell effector functions and contribute to autoimmune CNS inflammation. PLoS One. 2012; 7(10):e47617. [PubMed: 23077651]
99. Faouzi M, Penner R. Trpm2. Handb Exp Pharmacol. 2014; 222:403–426. [PubMed: 24756715]
100. Bertin S, Aoki-Nonaka Y, de Jong PR, Nohara LL, Xu H, Stanwood SR, et al. The ion channel TRPV1 regulates the activation and proinflammatory properties of CD4(+) T cells. Nat Immunol. 2014; 15(11):1055–1063. [PubMed: 25282159]
101. Link TM, Park U, Vonakis BM, Raben DM, Soloski MJ, Caterina MJ. TRPV2 has a pivotal role in macrophage particle binding and phagocytosis. Nat Immunol. 2010; 11(3):232–239. [PubMed: 20118928]
102. Knowles H, Heizer JW, Li Y, Chapman K, Ogden CA, Andreasen K, et al. Transient Receptor Potential Melastatin 2 (TRPM2) ion channel is required for innate immunity against Listeria monocytogenes. Proc Natl Acad Sci U S A. 2011; 108(28):11578–11583. [PubMed: 21709234]
103. Badou A, Jha MK, Matza D, Flavell RA. Emerging roles of L-type voltage-gated and other calcium channels in T lymphocytes. Front Immunol. 2013; 4:243. [PubMed: 24009608]
104. Omilusik K, Priatel JJ, Chen X, Wang YT, Xu H, Choi KB, et al. The Ca(V)1.4 Calcium Channel Is a Critical Regulator of T Cell Receptor Signaling and Naive T Cell Homeostasis. Immunity. 2011

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

105. Wang H, Zhang X, Xue L, Xing J, Jouvin MH, Putney JW, et al. Low-Voltage-Activated CaV3. 1 Calcium Channels Shape T Helper Cell Cytokine Profiles. Immunity. 2016; 44(4):782–794. [PubMed: 27037192]

106. Di Virgilio F, Dal Ben D, Sarti AC, Giuliani AL, Falzoni S. The P2X7 Receptor in Infection and Inflammation. Immunity. 2017; 47(1):15–31. [PubMed: 28723547]

107. Cekic C, Linden J. Purinergic regulation of the immune system. Nat Rev Immunol. 2016; 16(3): 177–192. [PubMed: 26922909]

108. Liu CSC, Raychaudhuri D, Paul B, Chakrabarty Y, Ghosh AR, Rahaman O, et al. Cutting Edge: Piezo1 Mechanosensors Optimize Human T Cell Activation. J Immunol. 2018

109. Fotiou E, Martin-Almedina S, Simpson MA, Lin S, Gordon K, Brice G, et al. Novel mutations in PIEZO1 cause an autosomal recessive generalized lymphatic dysplasia with non-immune hydrops fetalis. Nat Commun. 2015; 6:8085. [PubMed: 26333996]

110. Ouyang K, Leandro Gomez-Amaro R, Stachura DL, Tang H, Peng X, Fang X, et al. Loss of IP3R-dependent Ca2+ signalling in thymocytes leads to aberrant development and acute lymphoblastic leukemia. Nat Commun. 2014; 5:4814. [PubMed: 25215520]

111. Tang H, Wang H, Lin Q, Fan F, Zhang F, Peng X, et al. Loss of IP3 Receptor-Mediated Ca(2+) Release in Mouse B Cells Results in Abnormal B Cell Development and Function. J Immunol. 2017; 199(2):570–580. [PubMed: 28615414]

112. Romagnani A, Vettore V, Rezzonico-Jost T, Hampe S, Rottoli E, Nadolni W, et al. TRPM7 kinase activity is essential for T cell colonization and alloreactivity in the gut. Nat Commun. 2017; 8(1): 1917. [PubMed: 29203869]

113. Nishida K, Hasegawa A, Nakae S, Oboki K, Saito H, Yamasaki S, et al. Zinc transporter Znt5/ Slc30a5 is required for the mast cell-mediated delayed-type allergic reaction but not the immediate-type reaction. J Exp Med. 2009; 206(6):1351–1364. [PubMed: 19451265]

114. Beeton C, Wulff H, Standifer NE, Azam P, Mullen KM, Pennington MW, et al. Kv1. 3 channels are a therapeutic target for T cell-mediated autoimmune diseases. Proc Natl Acad Sci U S A. 2006; 103(46):17414–17419. [PubMed: 17088564]

115. Wulff H, Castle NA, Pardo LA. Voltage-gated potassium channels as therapeutic targets. Nat Rev Drug Discov. 2009; 8(12):982–1001. [PubMed: 19949402]

116. Di L, Srivastava S, Zhdanova O, Ding Y, Li Z, Wulff H, et al. Inhibition of the K+ channel KCa3. 1 ameliorates T cell-mediated colitis. Proc Natl Acad Sci U S A. 2010; 107(4):1541–1546. [PubMed: 20080610]

117. Barbet G, Demion M, Moura IC, Serafini N, Leger T, Vrtovsnik F, et al. The calcium-activated nonselective cation channel TRPM4 is essential for the migration but not the maturation of dendritic cells. Nat Immunol. 2008; 9(10):1148–1156. [PubMed: 18758465]

118. Serafini N, Dahdah A, Barbet G, Demion M, Attout T, Gautier G, et al. The TRPM4 channel controls monocyte and macrophage, but not neutrophil, function for survival in sepsis. J Immunol. 2012; 189(7):3689–3699. [PubMed: 22933633]

119. Vennekens R, Olausson J, Meissner M, Bloch W, Mathar I, Philipp SE, et al. Increased IgE-dependent mast cell activation and anaphylactic responses in mice lacking the calcium-activated nonselective cation channel TRPM4. Nat Immunol. 2007; 8(3):312–320. [PubMed: 17293867]

120. Lo WL, Donermeyer DL, Allen PM. A voltage-gated sodium channel is essential for the positive selection of CD4(+) T cells. Nat Immunol. 2012; 13(9):880–887. [PubMed: 22842345]

121. Capasso M, Bhamrah MK, Henley T, Boyd RS, Langlais C, Cain K, et al. HVCN1 modulates BCR signal strength via regulation of BCR-dependent generation of reactive oxygen species. Nat Immunol. 2010; 11(3):265–272. [PubMed: 20139987]

122. Concepcion AR, Salas JT, Saez E, Sarvide S, Ferrer A, Portu A, et al. CD8+ T cells undergo activation and programmed death-1 repression in the liver of aged Ae2a, b−/ − mice favoring autoimmune cholangitis. Oncotarget. 2015; 6(30):28588–28606. [PubMed: 26396175]

123•. Concepcion AR, Salas JT, Sarvide S, Saez E, Ferrer A, Lopez M, et al. Anion exchanger 2 is critical for CD8(+) T cells to maintain pHi homeostasis and modulate immune responses. Eur J Immunol. 2014; 44(5):1341–1351. This study (Ref. 118) identifies the anion exchanger Ae2 (SLC4A2) as a critical regulator of intracellular pH in $CD8^+$ T cells and shows that its function inhibits $CD8^+$ T cell activation, proliferation and cytokine production. [PubMed: 24515893]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

124. Jin Z, Mendu SK, Birnir B. GABA is an effective immunomodulatory molecule. Amino Acids. 2013; 45(1):87–94. [PubMed: 22160261]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Highlights

- Channels and transporters for Ca^{2+}, Mg^{2+}, Zn^{2+} and other ions regulate immunity
- Mutations in ORAI1 and STIM1 abolish Ca^{2+} influx and cause CRAC channelopathy
- XMEN disease results from mutations in the Mg^{2+} transporter MAGT1
- Loss of LRRC8A function blocks lymphocyte development and causes agammaglobulinemia
- Dual role of antibodies as the cause of channelopathy and a new class of therapeutics

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

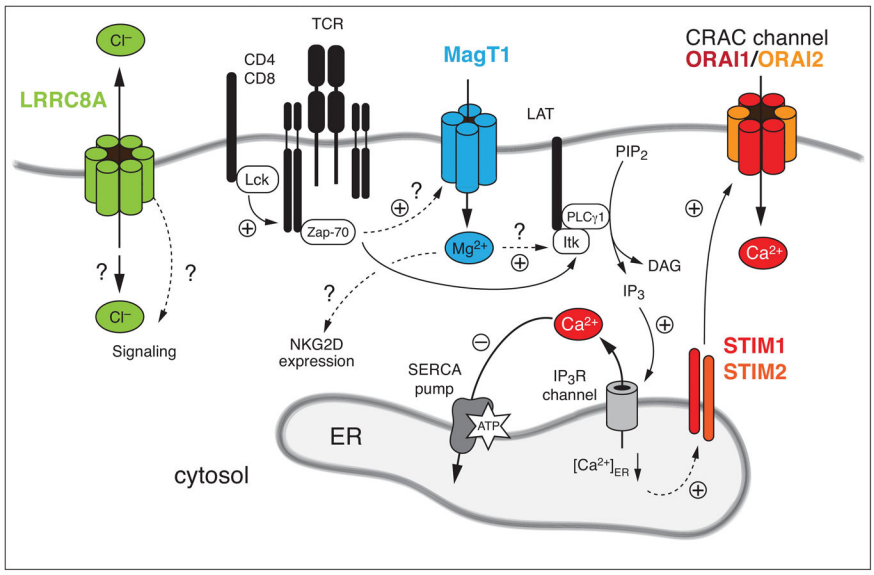

Figure 1. Mutations interfering with the function or expression of ion channels (ORAI1, STIM1, LRRC8A) or transporters (MAGT1) in T cells cause channelopathies and immunodeficiency

T cell receptor (TCR) stimulation activates the kinases Lck and ZAP-70 and phospholipase Cγ1, resulting in the hydrolysis of PIP_2 into the second messengers inositol-1,4,5-trisphosphate (IP_3) and diacylglycerol (DAG). IP_3 binding to IP_3 receptor channels leads to Ca^{2+} release from the endoplasmic reticulum (ER). The decrease in the ER Ca^{2+} concentration ($[Ca^{2+}]_{ER}$) activates stromal interaction molecules 1 (STIM1) and STIM2, which subsequently bind to and open Ca^{2+} release-activated Ca^{2+} (CRAC) channels formed by ORAI1 and ORAI2 proteins in the PM. The resulting influx of extracellular Ca^{2+} is called store-operated Ca^{2+} entry (SOCE). Free cytosolic Ca^{2+} is pumped back into ER Ca^{2+} stores by the sarcoplasmic/endoplasmic reticulum calcium ATPase (SERCA). LoF mutations in *ORAI1* or *STIM1* genes cause CRAC channelopathy with impaired T and NK cell function. TCR stimulation also activates the Mg^{2+} transporter (MAGT1) that mediates Mg^{2+} influx into T cells and promotes activation of PLCγ1, SOCE and expression of NKG2D. The mechanisms by which TCR stimulation activates MGAT1 and how Mg^{2+} causes PLCγ1 activation are not well understood (indicated by question marks). LoF mutations in the MAGT1 gene cause X-linked immunodeficiency with Mg^{2+} defect, EBV infection and neoplasia (XMEN) disease. LRRC8A is a volume-regulated anion channel (VRAC) that conducts Cl^- and is required for the regulatory volume decrease after cell swelling as well as T and B cell development. LoF mutations in *LRRC8A* cause agammaglobulinemia. For details see text.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Curr Opin Immunol. Author manuscript; available in PMC 2019 June 01.

Table 1

Ion channels and transporters (ICT) controlling immune responses in mice

ICTs and their regulatory proteins included in this table were selected because their role in immune cell function and immunity *in vivo* is supported by gene targeted mice and human channelopathies (see Table 2). Abbreviations: Ae2, anion exchange protein 2; Ca_V, voltage-gated calcium channel; CRAC, calcium release-activated calcium; EBV, Epstein-Barr virus; EAE, experimental autoimmune encephalomyelitis; IBD, inflammatory bowel disease; IEL, intraepithelial lymphocyte; Fcγ R, Tc gamma receptor; $GABA_A$, γ amino butyric acid receptor A; GvHD, graft versus host disease; H_V, voltage-gated proton channel; IP_3, inositol 1,4,5 trisphosphate; IP_3R, IP3 receptor; K_{Ca}, calcium-activated potassium channel; K_V, voltage-gated potassium channel; LRRC8A, leucine-rich repeat containing 8 family member A; MAGT, magnesium transporter; Na_V, voltage-gated sodium channel; P2RX, purinergic receptor; PCA, passive cutaneous anaphylaxis; RA, rheumatoid arthritis; ROS, reactive oxygen species; STIM, stromal interaction molecule; TASK, WIK-related acid-sensitive potassium channel; Tfh, follicular T helper cell; Treg, regulatory T cell; TRPM, transient receptor potential melastatin; TRPV, transient receptor potential vanilloid; ZIP, zinc/iron-regulated transporter-like protein; ZnT, zinc transporter; FcεRI, Fc epsilon receptor 1.

ICT	Permeability	Activation	Expression in	Immune Function *in vitro* and *in vivo*	References
ORAI1	Ca^{2+}	Antigen and G protein-coupled receptors, STIM1, STIM2	T, B, NK, mast cells, DC, ubiquitous	T cell function (proliferation, cytokine production, cytotoxicity, apoptosis, metabolism), T cell development (Treg, iNKT, IELs) and differentiation (Th17, iTreg, Th2, Tfh), immunity to viral, fungal and bacterial infection; T-dependent antibody responses; T cell-mediated auto- and alloimmunity (EAE, IBD, GvHD). NK cell function (degranulation, cytotoxicity). Mast cell function (degranulation, histamine release, cytokine production, PCA).	9, 11, 87, 88, 89, 90, 91
ORAI2	Ca^{2+}	Antigen and G protein-coupled receptors, STIM1, STIM2	T cells, ubiquitous	Together with ORAI1 regulates murine T cell function (proliferation, cytokine production) and T cell immune responses in vivo (IBD, GvHD, antiviral immunity)	9
STIM1, STIM2	–	Antigen and G protein-coupled receptors, Ca^{2+} depletion from ER stores	T, B, NK, mast cells, DC, macrophages, neutrophils, ubiquitous	Immune phenotype is similar to ORAI1. Neutrophil function (ROS and cytokine production)	31, 33, 92, 93, 94, 95, 96
TRPM2	Ca^{2+}, Na^{+}	ADPR, cADRP, NAADP, oxidative stress	T cells, macrophages	Macrophages function (cytokine production, inflammasome activation), T cell activation and cytokine production; immunity to Listeria infection; DSS colitis, obesity-induced diabetes, EAE	97, 98, 99
TRPV1	$Ca^{2+} > Na^{+}, K^{+}$	Chemical ligands, toxins, temperature, low pH	T cells, DCs, ubiquitous	T cell function (cytokine production); IBD	100
TRPV2	Ca^{2+}, Na^{+}	FcγR	Macrophages	Chemotaxis and phagocytosis by macrophages. *Trpv2*$^{-/-}$ mice show increased susceptibility to *L. monocytogenes.*	101, 102
Ca_V 1.2, 1.3, 1.4, (β3, β4 subunits)	Ca^{2+}	unknown	T cells, B cells, myeloid cells	T cell function; Positive selection of $CD4^+$ T cells (Ca_V1.4), $CD8^+$ T cell survival, cytokine production (Ca_V.1.3, Ca_V1.4), immunity to Listeria, Th2 cell function in asthma (Ca_V1.2).	103, 104

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

ICT	Permeability	Activation	Expression in	Immune Function *in vitro* and *in vivo*	References
Ca_v 3.1	Ca^{2+}	unknown	T cells	T cell function; autoimmunity (EAE)	105
P2RX7	Ca^{2+}, Na^+, K^+, other	Extracellular ATP	Ubiquitous	T cell function (proliferation, cytokine production, Th17 and Tfh differentiation, inhibition of Treg differentiation); autoimmunity (IBD), allograft rejection, GvHD, antitumor immunity. Innate immune cell function (inflammasome activation; DC priming).	106
P2RX1,2,3,4,5	Ca^{2+}, Na^+	Extracellular ATP	T, B, mast cells	T cell function (proliferation, cytokine production, thymocyte apoptosis (P2RX1,4,5). Mast cell activation and cytokine production (P2RX1,3). IgE receptor shedding (P2RX2). Hypocellularity of bone marrow and thymus in *P2rx2*$^{-/-}$/*P2rx3*$^{-/-}$ mice.	107
Piezo1	Ca^{2+}, Na^+	Mechanosensation	Ubiquitous	T cell function (activation, proliferation). Normal immune profiling in patients with *PIEZO1* mutations and lymphedema.	108, 109
$IP_3R1,2,3$	Ca^{2+}	IP_3	Ubiquitous	T cell activation, IP_3Rs regulate CRAC channel function. *Itpr1/2/3*$^{-/-}$ mice show defective thymocyte and B cell development, defective antibody and IL-10 production	110, 111
TRPM7	$Ni^{2+} > Zn^{2+} > Mg^{2+}, Ca^{2+}$	Regulation by intracellular Mg^{2+}, PIP_2, extracellular pH	T, B, NK cells, macrophages	Thymocyte development and cytokine secreation. Defective cytokine production, gut homing and GvHD induction of TRPM7-kinase dead T cells. Macrophage function (IL-1β production), LPS-induced peritonits.	49, 50, 112
MAGT1	Mg^{2+}	TCR	T, NK cells	$CD4^+$ T cell homeostasis, NKG2D expression by NK cells, cytotoxicity, immunity to viral infection (EBV)	2, 51, 53
ZIP3, 4, 6, 8, 10, 14	Zn^{2+}	TCR; unknown	T, B cells, Macrophages	T cell activation (ZIP6), IFNγ and perforin expression (ZIP8); T cell development (ZIP3). B cell development and B cell apoptosis, cytokine signaling (ZIP10). Macrophages: Inhibition of cytokine production (ZIP8, ZIP14). DC: Inhibition of expression of MHC class II and costimulatory molecules (ZIP6).	66, 67, 68, 69, 70, 71
ZnT5	Zn^{2+}	Unknown; FcεRI ?	Mast cells	NF-κB activation, FcεRI-dependent delayed type hypersensitivity	113
$K_v1.3$	K^+	Plasma membrane depolarization	T, B, plasma cells, DC, Macrophages	T cells function (Proliferation, cytokine production by Th17 cells). Autoimmunity (EAE, diabetes, RA), and T_{EM} antitumor immunity. Macrophage function (proliferation, iNOS expression). DC function (expression of costimulatory receptors and cytokines; chemotaxis)	1, 114, 115

Curr Opin Immunol. Author manuscript; available in PMC 2019 June 01.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Human immune channelopathies

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CRAC, calcium release-activated calcium; EBV, Epstein-Barr virus; EVER, Epidermodysplasia verruciformis; ICT, ion channel and transporters; MAGT, magnesium transporter; OMIM, online mendelian inheritance in man; STIM, stromal interaction molecule; TMC, transmembrane channel-like; VRAC, volume regulated anion channel; LRRC8A, leucine rich repeat containing 8 family member A; XL, X linked; ZIP, zinc/iron-regulated transporter-like protein; ZnT, zinc transporter.

ICT	Gene	Chromo- some	Inheri- tance	Disease	OMIM	Symptoms
ORAI1	*ORAI1*	12q24.31	AR	CRAC channelopathy	612782	Combined Immunodeficiency (CID; autoimmunity (AIHA, ITP); muscular hypotonia; ectodermal dysplasia with anhidrosis (EDA)
STIM1	*STIM1*	11p15.4	AR	CRAC channelopathy	12783	(same as ORAI1)
MAGT1	*MAGT1*	Xq21.1	XL	XMEN (X-linked immunodeficiency with magnesium defect, EBV infection and neoplasia)	300853	Chronic EBV infections, B cell lymphoma, splenomegaly, dysgammagloblobulinemia, decreased CD4/CD8 ration, increased susceptibility to viral infections
ZIP4	*SLC39A4*	8q24.3	AR	Acrodermatitis enteropathica (AE)	201100	Periorificial dermatitis, alopecia, and diarrhea; recurrent infections
ZnT2	*SLC30A2*	1p34.11	AD	Transient neonatal zinc deficiency	608118	Dermatitis (Perioral, genital, neck, fingers), diarrhea, hair loss.
TMC6, TMC8	*EVER1, EVER2*	17q25.3	AR	Epidermodysplasia verruciformis (EV)	605828, 605829	Dermatosis with abnormal susceptibility to human papillomavirus (HPV) infection and high rate of progression to squamous cell carcinoma.
VRAC (SWELL1)	*LRRC8A*	9q34.11	AD	Agammaglobulinemia	613506	Congenital agammaglobulinemia with B cell deficiency (infections not reported)

Curr Opin Immunol. Author manuscript; available in PMC 2019 June 01.