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OPINION ARTICLE

# Ion Channels and Transporters in Immunity—Where do We Stand?

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Ions are indispensable for cellular integrity. They constitute organellar identity and homeostasis within the physical barrier of biomembranes, support electrical potential across membranes, provide nutritional support, and serve as signaling entities that are able to adapt to varying challenges within milliseconds. Ion channels are the molecular mediators that shuttle ions between the different cellular compartments, often rather unspecific for certain cations or anions, often in a surprisingly selective manner. Their critical role in every cell type is undoubted.

Immune cells are specialized cell types with unique molecular properties. They need to be able to rapidly adapt to various kinds of sudden environmental changes, and, to defend the body from dangerous intruders, consequently respond by massive cellular rearrangements in terms of activation, differentiation, or function. These require pronounced molecular rearrangements, among which ions and ion channels take a central part. Within the last two decades, a number of excellent studies have shed light on the role of distinct ion channels and transporters in immunity. Foremost, the identification of the molecular components ORAI and STIM that mediate store-operated calcium signals in activating lymphocytic and innate immune cells has significantly pushed the field toward studying ion movements and their regulation as the basis for understanding immunity.[1–3] With the identification of detrimental mutations in ORAI- and STIM-encoding genes causing human immunodeficiencies due to lack of appropriate calcium entry machineries,[4] the stage was set for a comprehensive investigation of ion channels in health and disease. Since then, we have gained considerable insight into certain ion channel families and mechanisms. Much attention has been attributed to understanding ion homeostasis and ion signaling in T-cell immunity. Very recently, the attention has moved to VGCCs (voltage-gated $Ca^{2+}$ channel subunits) being relevant in calcium signaling and triggering downstream effector functions in T cells, without functioning as ion channels themselves.[5] To date, a growing number of ion-conducting channels and transporters have been identified to modulate T-, B-, NK, and dendritic cell function, monocytes, macrophages, and neutrophils, as well as mast cell homeostasis (Figure 1).[3] This is impressive, but we are still far away from understanding the complex relationships of ion conductance and cellular responses, notwithstanding their contribution to (human) diseases. So where do we go from here? In our opinion, there are a few critical questions that will guide our immediate and long-term attention, and require joint efforts to be deciphered.

First, it is still partly unclear which ion channels and family members are functionally expressed in diverse immune cell subsets, which proteins they colocalize or interact with, and under which preconditions they are active. We will surely untangle yet unrecognized ion channel members as players in immunity, with hitherto unforeseeable breakthroughs. Also, the contribution of subcellular localization and organellar distribution to distinct functions of ion channels should not be neglected. An interesting example is the report of subsecond-lasting calcium microdomains identified in T cells that shape activation responses via ORAI1, STIM1/2, and RYR1.[6]

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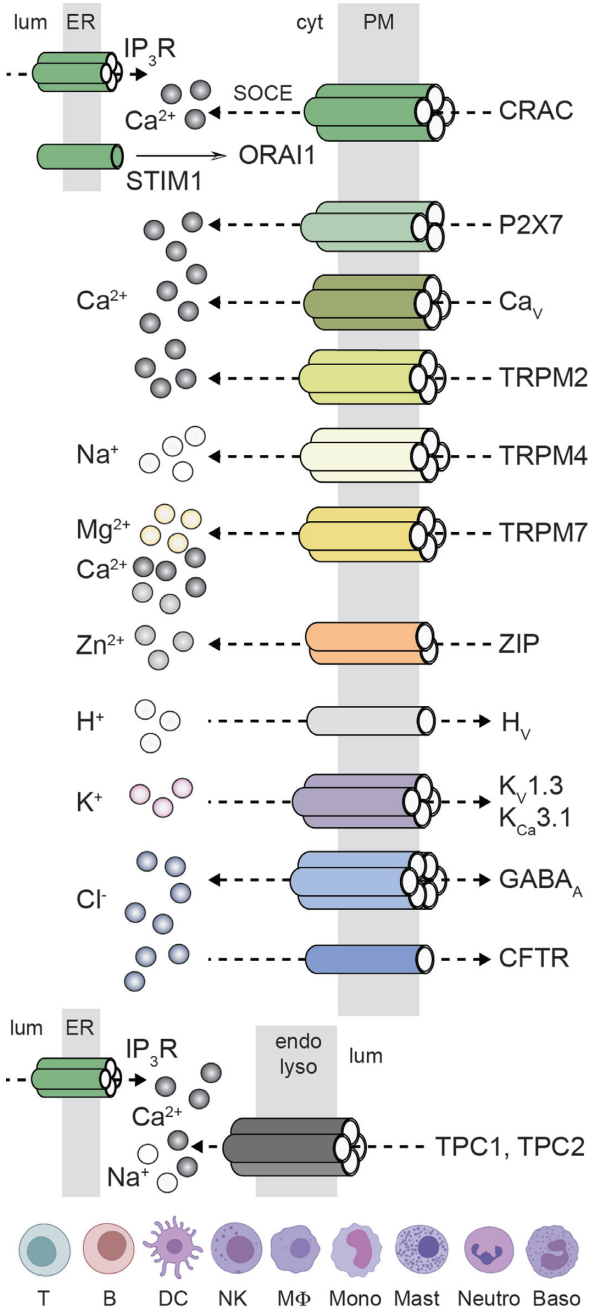


**Figure 1.** Schematic representation of selected ion channels and transporters acting on innate and adaptive immune cells. Their contribution to healthy and dysfunctional immunity, their molecular regulators, and their expression patterns in immune cell subsets remain to be addressed in the upcoming years. B—B cell, Baso—basophilic granulocyte, CFTR—cystic fibrosis transmembrane conductance regulator, CRAC—calcium release-activated channel, cyt—cytosol, DC—dendritic cell, endo—endosome, ER—endoplasmic reticulum, GABA—gamma-amino butyric acid, $IP_3R$—inositol-3-phosphate receptor calcium channel, lum—lumen, lyso—lysosome, Mast—mast cell, MΦ—macrophage, Mono—monocyte, Neutro—neutrophilic granulocyte, NK—natural killer cell, PM—plasma membrane, P2X—purinergic receptor, SOCE—store-operated calcium entry, STIM—stromal interaction molecule, T—T cell, TPC—two-pore channel, TRPM—melastatin-like transient receptor potential family, V—voltage-gated, and ZIP—Zrt/Irt-like protein.

Second, to understand modulating interactors of ion channels at a molecular level will help to understand the conditions of variability of cellular responses, which may also contribute to disease manifestation. For example, CNNM/ARL15 complexes have recently been identified as intermolecular interaction hubs of TRPM7 channels.[7] Or the above mentioned VGCCs may function as accessory proteins modulating calcium signals.[5] Adding another level of complexity, research on intermolecular modulators of ion channels and transporters is only in its infants and will likely take off in the next years.

Third, it is important to investigate signaling entities and effectors downstream of yet understudied ion channels and ion species in the context of the immune system, conducting for example, zinc ions. $Zn^{2+}$ has recently been attributed to finetuning T-cell activation via ZIP transporters, yet its contribution in relation to calcium, magnesium and other cations is unclear.[3] To date, TRPM7 remains the only identified ion channel conducting the sum of these ion species, and due to its dual function serving also as serine/threonine kinase, it has been clearly linked to the regulation of immune homeostasis promoting proinflammatory conditions.[3,8]

So far, it is not yet feasible to supersede animal models with alternate approaches such as induced pluripotent stem cells (iPSC) or organoids with respect to studying *in vivo* immune reactions. Thus, fourth, to gain an organismal view of ion channels in the living system, animal models will help to unravel system-level effects in immunity. Mouse models are especially relevant in the context of infectious diseases and in mimicking autoimmune manifestations or allergies. Also, lately, an overwhelming number of studies have proven their success in deciphering ion channel functions *in vivo*.[3,4,8]

Fifth, it is indispensable to study the human immune system with its specialized machinery, which is not always necessarily phenocopied by murine pathology.[9] Increasing numbers of human channelopathies have been described, ranging from CRAC mutations to XMEN disease with magnesium deficiency,[4] and to gain better insight into ion channel function and therapeutic potential, studying primary human immune cells is a prerequisite both for understanding healthy and diseased conditions. As most immune cell types can be retrieved from whole blood with relative ease, we will surely expect outstanding discoveries.

Lastly, ion channel pharmacology has not only been a hot topic since the emergence of CFTR chloride channel blockers.[10] For an ultimate application in clinical practice, our studies on ion homeostasis and channel function will lay the groundworks toward investigating druggabilities of ion channels. Nonetheless, very view preclinical candidates have made it into the clinics so far, the various reasons for which still need to be evaluated fully.

We believe that now is the right time to tackle these challenges, using state-of-the-art interdisciplinary and complementary approaches. It is worthwhile to combine pharmacology, electrophysiology and its elaborate patch-clamp techniques, molecular immunology and *in vivo* models of (murine) immunity, and the study of human immune cell function in health and disease. Together, these will further our understanding of the versatile and momentous functions of ion channels in immunity.

## Author Contribution

B.H. and S.Z. wrote the manuscript. B.H. designed the figure. S.Z. finalized the manuscript. Both authors agreed on publishing.

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## Data Availability

There are no original data shown.

## Conflict of Interest Statement

The authors declare that there are no conflicts of intertest.

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