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MEETING ABSTRACT

A1.2

From hypersensitivity to leukemia: insights into function and pharmacology of cation channels

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While the immune system protects our body against numerous pathogens, it must not overshoot. Otherwise, pro-inflammatory diseases or anaphylactic reactions may develop. Thus, several mechanisms are in place to ensure an appropriate immune response at the right time. Immune cells themselves are tightly controlled by their intricate cellular cation homeostasis and signalling.

The ubiquitously expressed organellar two-pore channel, TPC1, for instance, has been suggested to be involved in spatial Ca^{2+} homeostasis in different cell types. We recently demonstrated a crucial role of TPC1 in controlling organellar Ca^{2+} homeostasis. *Tpc1*-deficient (*Tpc1*$^{-/-}$) mice develop enhanced systemic anaphylaxis upon crosslinking of IgE receptors. Genetic deletion or pharmacologic inhibition of TPC1 enhances mast cell degranulation and histamine release due to accelerated Ca^{2+} liberation mainly from the endoplasmic reticulum (ER). Accordingly, pharmacologic activation of TPC1 ameliorates mast cell degranulation, highlighting TPC1 as a potential drug target against allergic hypersensitivity [1].

Similarly, we have linked the dual-function transient-receptor-potential protein, TRPM7, combining a Ca^{2+}- and Mg^{2+}-permeable channel with a serine/threonine kinase, to immune system homeostasis. Exploring the role of the TRPM7 kinase moiety in mast cells, we found that its genetic disruption prompts altered susceptibility to allergic reactions in mice [2]. Using a homozygous kinase-dead mouse model with a single point mutation at the active site of the kinase, *Trpm7*^{K1646R}, we demonstrated that its activity controls TGF-β-induced CD103 expression, intestinal T cell colonization as well as proinflammatory T_H17 cell differentiation, but is dispensable for anti-inflammatory, regulatory T cell differentiation. Notably, we identified SMAD2 as novel substrate of the TRPM7 kinase. Ultimately, genetic disruption of the TRPM7 kinase activity prevents the development of acute graft-*versus*-host-disease in an established mouse model [3].

To date, specific pharmacologic modulators of TRPM7 channel or kinase are limited. Previously, we were able to discover the natural compound, waixenicin A, isolated from the Hawaiian soft coral, as first potent and selective TRPM7 channel inhibitor [4]. Currently, we are screening for potent TRPM7 kinase inhibitors utilizing *in silico* techniques. Our first translational results imply that TRPM7 is also important for the differentiation of human T cells as well as for the activation and proliferation of chronic leukemia cells. Therefore, TRPM7 channel and kinase may represent valid pharmacological targets for the treatment of pro-inflammatory diseases and chronic leukemia.

Keywords: immune system – cation channels – calcium – homeostasis – T cell differentiation – mast cell reactivity – TPC1 – TRPM7

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