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INTRINSIC ACTIVITY

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MEETING ABSTRACT

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TRPM7 ion channel and kinase drives AKT signaling and immune-cell activation

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Background: Ion channels of the TRP family are crucial for cellular homeostasis. TRPM7 is a unique member as ion-channel-coupled protein kinase. Besides its fundamental ability to transduce divalent cations such as Mg^{2+} and Ca^{2+}, it drives cellular signaling by a constitutively active intracellular kinase domain. In previous work we have demonstrated a role of TRPM7 kinase in T-cell signaling, promoting Th17 differentiation and gut immunity. In a murine model, TRPM7 kinase facilitated induction of acute graft-versus-host disease. SMAD2 thereby serves as TGF-β-dependent cellular substrate of TRPM7 kinase, driving proinflammatory signals and Th17 differentiation.

Methods: We here investigated TRPM7-dependent activation pathways of human immune cells and related cell lines, by a combinatorial approach of flow cytometry, western blot, imaging and *in vitro* assays.

Results: We have identified the AKT signaling hub downstream of TRPM7 kinase, facilitating activation of neutrophils and T cells. In human and murine neutrophils, we pinpointed this to AKT/mTOR-mediated induction of oxidative burst and directed cell migration [1]. In T cells, TRPM7-dependent Mg^{2+} conductance is crucial for cellular survival and proliferation, and the protein facilitates T-cell-receptor-mediated Ca^{2+} flux. We could show that TRPM7 is required for T-cell activation, involving induction of AKT-dependent signaling pathways. *In vitro*, we identified a direct interaction of TRPM7 kinase phosphorylating AKT protein, confirming previous hypotheses.

Discussion: Our data suggest TRPM7 kinase as potential target in inflammatory and/or malignant diseases, due to its interconnection with AKT signaling and pro-inflammatory cellular responses.

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Keywords: ion channels – immunity – AKT signalling – TRPM7 kinase

Reference:

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