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Perspective

TRP Channels in Cell-Mediated Immunosuppression: Implications towards Immunoregulatory Diseases

Tathagata Mukherjee, Subhasis Chattopadhyay*

Department of Biological Sciences, National Institute of Science Education and Research, Bhubaneswar, India

INTRODUCTION

Immunosuppression is the prime barrier towards mounting an optimal immune response against certain immunoregulatory diseases. In general, cell-mediated immunosuppression could be broadly defined as the abated effector immune responses associated with different immune cells like macrophages, dendritic cells and T cells, with a state having reduced ability to recognize or counter foreign antigens resulting from the modulation of cellular pathways/processes important to mount effector responses [1]. It could be either intrinsic/non-deliberate (e.g., persisting chronic diseases like HIV, cancer, aging, asplenia, etc.) or extrinsic/deliberate (e.g., therapeutic medications, immunomodulatory drugs, radiation therapy, etc.) depending on the persisting disease condition, ongoing treatment and/or longterm medication [2].

DESCRIPTION

Transient Receptor Potential (TRP) channels are evolutionary conserved non-selective cation-permeable ion channels with polymodal activation properties. TRP channels have been reported to be present in various cell types including immune cells, regulating gene expression and effector immune functions. Transient Receptor Potential Vanilloid 1 (TRPV1) and Transient Receptor Potential Ankyrin 1 (TRPA1) channels are thermosensitive (TRPV1: Heat-sensitive; TRPA1: Cold-sensitive) cation permeable ion channels that have been shown to regulate T cell activation, cytokine production, differentiation and effector functions as well as pro-inflammatory responses associated with macrophages [3]. Additionally, TRP channels are permeable to Ca^{2+} ions which serve as the second messenger of cells modulating various physiological processes such as gene transcription, differentiation and effector responses associated with T cells, B cells and macrophages [4]. The functional association of both TRPV1 and TRPA1 in cell-mediated immune responses in alliance with T cell and macrophage activation and increase of intracellular Ca^{2+} levels have already been reported earlier. Both TRPV1 and TRPA1 have been shown to have important roles towards various inflammatory disease models regulating disease severity and cellular functions [5]. These ion channels are also been speculated to have immunomodulatory roles associated with immunosuppression. However, reports showing the involvement of TRP channels towards immunosuppression remain scanty. Moreover, the role of TRPV1 and TRPA1 channels in the immunosuppression of T cells and macrophages has not been explored yet [6].

Recently, we have depicted how TRPV1 and TRPA1 channels could be intricated towards immunosuppression of T cells and macrophages. We have shown that expression of TRPV1 could be upregulated in FK506 (Tacrolimus) (a drug used during organ transplantation; calcineurin inhibitor) and tumor cell-conditioned media-directed immunosuppression of T cells and TRPV1 plays an important role towards regulating immunosuppression-driven intracellular Ca^{2+} levels [7]. Next, it has been shown how 17-AAG (Tanespimycin) (an Hsp90 inhibitor) driven suppression may affect TRPA1 expression on macrophages and regulate proinflammatory responses associated with macrophages. Furthermore, we have repurposed Telmisartan (TM) (an anti-hypertension drug; angiotensin receptor blocker) as an immunosuppressive model and shown the involvement of both TRPV1 and TRPA1 channels towards TM-driven suppression of T cell responses [8].

CONCLUSION

Despite the above observations, it is important to further explore out the underlying mechanisms associated with immunosuppression. Understanding the mechanisms of immunosuppression and immunosuppression-driven regulation of cell-mediated immune responses with the accompanying role and involvement of TRP channels would portray the in-depth cellular events responsible for the dwindled effector immune responses. The vertical explorations of cellular pathways might have the potential to design possible future immunotherapeutic strategies for TRP channel-directed altered physiological conditions in immune disorders associated with immunosuppression.

Correspondence to: Subhasis Chattopadhyay, Department of Biological Sciences, National Institute of Science Education and Research, Bhubaneswar, India; E-mail: subho@niser.ac.in

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