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Short Communication

The Role of Piezo1 in the Immune System in Health and Disease

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Abstract

Mechanosensitive ion channels, particularly Piezo1, have emerged as pivotal mediators of cellular responses to mechanical cues in the immune system. This review summarizes the multifaceted roles of Piezo1 in regulating the function of diverse immune cell populations including monocytes, T cells, eosinophils, and dendritic cells (DCs) and its implications in physiological immune homeostasis and pathological conditions such as cardiovascular inflammation and cancer. Piezo1 transduces mechanical stimuli (e.g., shear stress, matrix stiffness) into intracellular calcium signaling, thereby modulating immune cell activation, migration, cytokine secretion, and lineage differentiation. In health, Piezo1 ensures proper immune surveillance and tissue repair by fine-tuning immune cell responses to mechanical microenvironments. In disease, dysregulated Piezo1 activity contributes to chronic inflammation, tumor progression, and immune evasion. Understanding Piezo1-mediated mechanotransduction in immunity offers novel therapeutic targets for inflammatory disorders and cancer immunotherapy.

Introduction

The immune system constantly adapts to both biochemical and mechanical cues from the microenvironment. Mechanical forces such as fluid shear stress in blood vessels, tissue stiffness in inflamed or tumorous regions, and cell-cell adhesion forces are integral to immune cell function, including migration, activation, and effector responses [7]. Mechanosensitive ion channels act as “mechanical sensors” that convert physical stimuli into electrochemical signals, with the Piezo family (Piezo1 and Piezo2) being the most well-characterized [5] Piezo1, widely expressed in immune and non-immune cells, is a non-selective cation channel with high permeability to calcium ions. Its activation by mechanical forces triggers downstream signaling cascades that shape immune cell behavior [16]. This review focuses on the role of Piezo1 in immune cell biology, highlighting its functions in health and disease, and discusses its potential as a therapeutic target.

Piezo1 in Innate Immune Cells

Monocytes

Monocytes, key mediators of innate immunity and inflammation, are highly responsive to shear stress especially in pathological conditions like aortic valve stenosis (AVS). In AVS, high shear stress (HSS) exerted on circulating monocytes as they pass through stenotic valves activates proinflammatory responses. Baratchi et al. [3]. demonstrated that HSS induces Piezo1-dependent calcium influx in monocytes, leading to activation of the β_2-integrin Mac-1 (CD11b/CD18), increased adhesion to endothelial cells, enhanced phagocytosis, and uptake of oxidized low-density lipoprotein (ox-LDL) [3]. These proinflammatory effects are reversed by transcatheter aortic valve implantation (TAVI), which reduces shear stress and downregulates Piezo1 expression in monocytes. Mechanistically, Piezo1 mediates shear stress-induced calcium signaling [2]. which drives monocyte activation and contributes to valvular inflammation in AVS. Targeting Piezo1 in monocytes may therefore alleviate inflammation in cardiovascular diseases associated with abnormal shear stress.

Eosinophils

Eosinophils play critical roles in allergic inflammation and parasitic immunity [10]. but their mechanosensitive properties remain understudied. Hwang et al. [8]. investigated the functional

role of Piezo1 in the human eosinophil cell line AML14.3D10, confirming Piezo1 (but not Piezo2) expression at the mRNA and protein levels [8]. Activation of Piezo1 with its specific agonist Yoda1 induced significant calcium influx, which was inhibited by Piezo1-selective (Dooku1) or non-selective (Ruthenium Red, Gd^{3+}, GsMTx4) inhibitors. Importantly, Piezo1 activation modulated the secretion of both pro-inflammatory (IL-1β, IL-6, IL-8) and anti-inflammatory (IL-10, TGF-β1) cytokines in AML14.3D10 cells. Supernatants from Piezo1-activated eosinophils enhanced capsaicin (TRPV1 agonist) and ATP (purinergic receptor agonist)-induced calcium responses in mouse dorsal root ganglion (DRG) neurons, linking eosinophil Piezo1 activity to sensory neuron function in pain and itch signaling. These findings suggest that Piezo1 regulates eosinophil-mediated inflammation and immune-sensory crosstalk in allergic or inflammatory disorders [6].

Dendritic Cells

Dendritic cells (DCs) are professional antigen-presenting cells that bridge innate and adaptive immunity. Wang et al. [20]. showed that DC-specific Piezo1 deficiency in mice alters the reciprocal differentiation of T helper 1 (Th1) and regulatory T (Treg) cells [3]. Piezo1 in DCs is activated by inflammatory stimuli (e.g., LPS) or mechanical stiffness (50 kPa, mimicking inflamed tissue), leading to increased secretion of the pro-inflammatory cytokine IL-12 and decreased production of the anti-inflammatory cytokine TGF-β1 [4]. Mechanistically, Piezo1 integrates two signaling pathways in DCs: (1) the SIRT1-HIF1α-glycolysis)metabolic axis, which regulates cytokine production by altering energy metabolism, and (2) the calcium-calcineurin-NFAT pathway, which modulates transcriptional activity of cytokine genes. In cancer, DC-specific Piezo1 deletion promotes tumor growth by reducing Th1 cell differentiation and increasing Treg cell accumulation [4]. Pharmacological activation of Piezo1 with Yoda1 in human DCs recapitulates these findings, enhancing IL-12 secretion and T_h1 differentiation while inhibiting Treg polarization. Thus, Piezo1 in DCs is a key regulator of anti-tumor immunity by shaping T cell lineage commitment.

Piezo1 in Adaptive Immune Cells: T Cells

T cells rely on migration and activation to exert their effector functions, processes heavily influenced by mechanical cues. Two studies highlight the critical role of Piezo1 in T cell biology.

T Cell Migration

Liu et al. [12]. investigated the role of Piezo1 in integrin-dependent chemotactic migration of human $CD4^+$ T cells. Piezo1 deficiency (via siRNA knockdown) impaired T cell motility on ICAM-1-coated surfaces and reduced transwell migration in response to chemokines (CCL19, SDF1α) [12]. Live-cell imaging and interference reflection microscopy (IRM) revealed that Piezo1 redistributes to the leading edge of migrating T cells in response to chemokine stimulation, a process dependent on focal adhesion kinase (FAK) activation and local increases in membrane tension. Piezo1 activation at the leading edge triggers calcium influx and subsequent calpain activation, which is required for recruitment of the integrin LFA1 (CD11a/CD18) to the leading edge. This "outside-in" signaling cascade FAK activation → membrane tension → Piezo1 recruitment → calcium/calpain activation → LFA1 recruitment ensures efficient T cell migration. Disruption of Piezo1 abrogates LFA1 polarization and Akt phosphorylation, impairing T cell movement to inflamed or tumorous tissues.

T Cell Differentiation and Exhaustion

Piezo1 also modulates T cell lineage differentiation and functional exhaustion. Qu and Zhang [17,21]. reviewed that Piezo1 deficiency in $CD4^+$ T cells disrupts the balance between pro-inflammatory Th1/ Th17 cells and immunosuppressive Treg cells [2,17,21,20] Loss of Piezo1 leads to mitochondrial metabolic reprogramming (downregulation of SIRT3, reduced oxidative phosphorylation) and accumulation of reactive oxygen species (ROS), driving T helper 9 (Th9) cell differentiation via HIF-1α signaling. In the tumor microenvironment (TME), chronic mechanical stress (e.g., high stiffness, shear stress) induces sustained Piezo1 activation in $CD8^+$ T cells, leading to immune synapse destabilization, reduced TCR clustering, and upregulation of checkpoint molecules (PD-1, TIM-3) [1]. This promotes T cell exhaustion and impairs anti-tumor immunity. In hormone receptor-negative breast cancer, high Piezo1 expression correlates with reduced $CD8^+$ T cell infiltration and poor prognosis. Inhibiting Piezo1 (e.g., with GsMTx4) restores T cell infiltration and effector function, highlighting its potential as a target to reverse T cell exhaustion in cancer.

Piezo1 in Disease: Cancer and Inflammation

Cancer

Piezo1 plays dual roles in cancer, acting as both a pro-tumor and anti-tumor regulator depending on the cell type and microenvironment [17,22,21]. In tumor cells, Piezo1 promotes proliferation, invasion, and metastasis by activating oncogenic signaling pathways (e.g., Hippo/YAP, MAPK, Akt/mTOR). For example, in ovarian cancer, Piezo1 activation by TME stiffness activates the Hippo/YAP axis, driving epithelial-mesenchymal transition (EMT) and metastatic potential [1]. In breast cancer, Piezo1 acts as a "mechanical switch": in 2D environments, it reduces cell adhesion and accelerates random migration, while in 3D confined spaces, it enhances traction forces and invasion by upregulating matrix metalloproteinases (MMPs). In immune cells within the TME, Piezo1 dysregulation fosters immunosuppression: DC-specific Piezo1 deficiency reduces Th1 differentiation, Th 9 polarization promotes Treg expansion, and eosinophil-derived cytokines enhance sensory neuron activation. Targeting Piezo1 either alone

or in combination with immune checkpoint inhibitors (e.g., PD-1 blockade) offers a novel strategy to reverse immunosuppression and enhance anti-tumor immunity.

Inflammatory Disorders

Beyond cancer, Piezo1 contributes to chronic inflammatory diseases [13,21,22]. In cardiovascular inflammation (e.g., AVS), Piezo1-mediated monocyte activation drives valvular inflammation, which is reversed by TAVI [3,11]. In allergic inflammation, Piezo1 in eosinophils modulates cytokine secretion and immune-sensory crosstalk, potentially exacerbating symptoms like itch and pain [8] In inflammatory bowel disease (IBD), Piezo1 inhibition reduces intestinal inflammation by limiting group 3 innate lymphoid cell (ILC3) activation [12]. These findings suggest that Piezo1 is a central mediator of inflammation across multiple organ systems, making it a promising therapeutic target for chronic inflammatory disorders.

Therapeutic Potential of Targeting Piezo1

The diverse roles of Piezo1 in immune-mediated diseases highlight its therapeutic potential. Several strategies are under investigation: (1) Pharmacological modulators: Yoda1 (Piezo1 agonist) and Dooku1/GsMTx4 (Piezo1 inhibitors) have shown efficacy in preclinical models. For example, Yoda1 enhances DC-mediated Th1 differentiation to boost anti-tumor immunity, while GsMTx4 reduces monocyte inflammation in AVS [3,18,21, 22]. (2) Gene therapy: siRNA-mediated Piezo1 knockdown in T cells or DCs reverses T cell exhaustion and restores anti-tumor immunity [12,17,22,]. CRISPR/Cas9-mediated Piezo1 knockout in hematopoietic cells may offer long-term therapeutic benefits in chronic inflammation. (3) Combination therapy: Combining Piezo1 inhibition with immune checkpoint blockers (e.g., anti-PD-1) enhances T cell infiltration and effector function in the TME, improving cancer immunotherapy outcomes [17,22].

Conclusion

Piezo1 has emerged as a critical regulator of immune cell function, integrating mechanical cues into biological responses that govern immune homeostasis and disease. Its role in monocytes, eosinophils, DCs, and T cells highlights its versatility in shaping innate and adaptive immunity. These research findings not only deepen our understanding of the complex regulatory network of the immune system but also lay a solid theoretical foundation for the development of innovative therapeutic strategies. Dysregulated Piezo1 activity contributes to chronic inflammation and cancer progression, making it a promising therapeutic target.

Looking ahead, Piezo1, as a highly promising therapeutic target, is expected to bring revolutionary treatment strategies for immune-related diseases. Further in-depth exploration of the molecular mechanisms of Piezo1 in different immune cells and disease contexts will provide more accurate theoretical support for precision medicine. Addressing the challenges of specificity and delivery of Piezo1 modulators, as well as expanding the scope of its research in more disease types, will open up new avenues for the clinical translation of Piezo1-related therapies. It is anticipated that more research efforts will be invested in the future to advance Piezo1 from basic research to clinical application, bringing new hope and benefits to numerous patients worldwide.

Research ethics and patient consent: Not applicable

Availbility of data and material: Not applicable

Declaration of conflicting interests

All authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors' contributions

All authors contributed to the study conception and design. The first draft of the manuscript was written by Dr. Hu and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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