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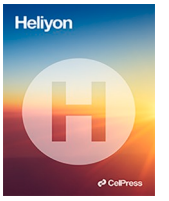

Review article

# Roles of mechanosensitive ion channels in immune cells

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ABSTRACT

Mechanosensitive ion channels are a class of membrane-integrated proteins that convert externalmechanical forces, including stretching, pressure, gravity, and osmotic pressure changes, some of which can be caused by pathogen invasion, into electrical and chemical signals transmitted to the cytoplasm. In recent years, with the identification of many of these channels, their roles in the initiation and progression of many diseases have been gradually revealed. Multiple studies have shown that mechanosensitive ion channels regulate the proliferation, activation, and inflammatory responses of immune cells by being expressed on the surface of immune cells and further responding to mechanical forces. Nonetheless, further clarification is required regarding the signaling pathways of immune-cell pattern-recognition receptors and on the impact of microenvironmental changes and mechanical forces on immune cells. This review summarizes the roles of mechanosensitive ion channels in immune cells.

## 1. Introduction

The capability of cells to sense external signals is a fundamental biological property, and the perception of mechanical forces is a crucial in this respect. Most cells contain such sensors, which are important for functions including motility, cell division, and differentiation. This perception requires the conversion of mechanical forces into biochemical signals; this signaling typically occurs via ion channels, membrane receptors, and intracellular signaling pathways. “Piezo” means “pressure” in Greek [1]. Piezo ion channels are expressed in various mechanically sensitive cell types [2]. Piezo1 exhibits remarkable sensitivity to lateral membrane tension and can be activated by pressure and blood flow-associated shear stress [3,4], whereas Piezo2 is primarily expressed in sensory tissues that respond to touch, proprioception, and baroreception [5–7]. In addition to the Piezo channels, other mechanosensitive ion channels occur in mammals.

Transient potential vanilloid receptor 4 (TRPV4), isolated from the rat kidney in 2000, is widely expressed, multimodally gated, and nonselective for cations [8]. TRPV4 primarily senses blood osmotic pressure [8], temperature [8], and endogenous or exogenous

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chemical stimulation [9], and can be indirectly activated via intracellular signaling pathways [10]. TRPV4 can be directly activated by applying a mechanical stimulus [11]. However, unlike PIEZO1, TRPV4 is not effectively activated through pressure-induced membrane stretching or cellular indentation [12]. Indeed, none of the transient receptor potential (TRP) ion channels appear to be sensitive to membrane stretching [13], hence the mechanism of TRPV4 activation in cellular mechanotransduction, and its role as a primary mechanosensor, remain controversial.

During inflammation, fluctuations in temperature, pH, osmotic pressure, oxygen content, and nutrient levels occur within the microenvironment. Immune cells, in addition to recognizing invading pathogens through pattern recognition receptors, can also use a series of microenvironmental recognition molecules to regulate their own immune responses, enabling precise responses to specific microenvironmental changes.

Although various studies have addressed immune-cell pattern-recognition receptor signaling pathways, and have examined the impact of these microenvironmental changes on immune cells, there has been limited research on the effects of mechanical forces on the immune system. This article reviews the regulatory effects of force-sensing on immune cells.

## 2. T lymphocytes

T-lymphocytes are the primary effector cells in adaptive immune responses. Their functions depend on signaling-pathway activation, which is mediated by T-cell receptors (TCRs). T lymphocyte activation and differentiation are affected by mechanical forces [14]. Basu et al. [15] demonstrated that T-cell cytotoxicity is enhanced by mechanical force. In mice, Jairaman et al. [16] found that Piezo1 had a selective inhibitory effect on Treg cells, while its absence did not influence T lymphocyte activation or effector T cell function. Liu et al. [17] demonstrated that Piezo1 deficiency impaired antigen-priming of T cells by antigen-presenting cells, while Piezo1 agonists enhanced TCR activation. Wang et al. [18] discovered that Piezo1 mediated substrate stiffness-induced production of inflammatory cytokines in dendritic cells, affecting the reciprocal differentiation of Th1 and Treg cells. In dendritic cells in a mouse cancer model, Piezo1 gene deletion inhibited Th1 cell production while promoting Treg cell development, thereby enhancing tumour growth. Hope et al. [19] found that fluid-shear stress enhanced T cell activation via Piezo1. Via mechanical stimulation, the Piezo1 channel maintains the niche around small arteries that participate in bone formation and lymph production in the bone marrow. *Piezo1*-knockout mice have fewer lymphoid progenitor cells [20]. Although these findings support the role of Piezo channels in regulating adaptive immune responses, further research is needed to clarify the specific mechanisms involved.

## 3. B lymphocytes

Mechanical forces play an important role in regulating B-lymphocyte activation. Wang et al. [21] applied traction-force microscopy to show that the application of mechanical force triggers the spreading–contraction phenomenon in B-cell activation. They characterized the regulatory mechanisms related to the production and maintenance of traction force, providing new research directions. Antigens trigger B cell activation by exerting mechanical force on the B cell receptor (BCR). Studies indicate that less mechanical force is needed to activate the BCR on memory B cells in comparison with naïve B cells. This allows memory B cells to respond more rapidly to re-invading antigens [22]. The stiffness profile of antigen-presenting substrates also influences the initiation of B cell activation. B cells can discriminate between changes in mechanical force intensity induced by different substrate stiffnesses via protein kinase C beta (PKCβ)-mediated focal adhesion kinase (FAK) activation. In autoimmune diseases such as rheumatoid arthritis, defects in this ability could lead to deregulated activation of autoreactive B cells [23].This reveals the molecular mechanism whereby B cells distinguish antigen-presenting substrates, by differentiating between mediated FAK activation and the corresponding responses.

Crosstalk between Piezo1 and focal adhesion, two major cellular mechanotransduction factors, has been widely reported [24,25]. Before being identified a mechanosensitive ion channel, Piezo1 was shown to enhance integrin activation and regulate actin polymerization [26,27]. It has been proposed that high or low intensity Piezo1 activation result, respectively, in sustained or transient calcium signaling downstream, with corresponding FAK suppression or activation [25]. Understanding this crosstalk between Piezo1 and focal adhesion will enhance our comprehension of how Piezo1 modulates cell adhesion and the varied responses to piezo1 activation.

## 4. Macrophages

Macrophages are widely distributed in the blood and tissue [28]. As they exhibit tissue specificity, macrophages often exhibit different immune-related functions in different tissue types. Atcha et al. [29] found that murine bone marrow-derived macrophages activated LPS-mediated inflammation via Piezo1 when subjected to mechanical forces. Leng et al. [30] showed that Piezo1 deficiency in macrophages reduced glycolysis, inhibiting the production of proinflammatory factors by regulating CaMKII expression and HIF1α stability. Similarly, an increase in $Ca^{2+}$-dependent glycolysis via Piezo1 activation has been observed in mammalian red blood cells, which undergo mechanical distortion when passing through two narrow capillaries; this distortion requires enhanced glycolysis to fulfil the elevated energy demands [31,32].

In mice, Angel et al. [33] found that, after pulmonary infection with *Pseudomonas aeruginosa*, monocytes in the alveoli can induce EDN1 expression and secretion via Piezo1. Signaling between EDN1 and the HIF1α receptor promotes HIF1α stability, leading to the secretion of proinflammatory cytokines. The secreted CXCL2 can recruit neutrophils to migrate to the alveoli, counteracting infection. This provides a mechanistic basis for the regulation of macrophage inflammatory responses by Piezo1. Mechanical channels other than the Piezo1 channel have been found to participate in macrophage-induced inflammation. TRPV4 activation in mouse alveolar

macrophages increases the production of reactive oxygen and nitrogen species, ultimately increasing vascular permeability [34].

Mechanosensitive ion channels participate in the progression of other diseases. Xie et al. [35] found that macrophages from ischemic tissues inhibited fibroblast growth factor-2 secretion by activating Piezo1 channels, inhibiting angiogenesis and reperfusion. Ma et al. [36] showed that the macrophages of patients with hereditary xerocytosis exhibited increased phagocytosis via an increase in Piezo1 activity; this induced production of the iron regulator hepcidin, eventually leading to iron overload. While this finding may explain the age-related onset of iron overload in patients with genetic hereditary xerocytosis, the effects of aging, and of other cells expressing Piezo1, remain to be excluded.

Macrophages are classified primarily as M1 (pro-inflammatory, induced by IFN-γ and lipopolysaccharides) and M2 (anti-inflammatory, induced by IL-4 and IL-13) macrophages, and there are smaller numbers of specialized macrophage classes, such as $CD169^{+}$ and $TCR^{+}$ macrophages [37–39]. Atcha et al. [40] found that greater matrix-stiffness led to Piezo1 activation, inhibiting $Ca^{2+}$ influx-mediated macrophage polarization to the M2 type, while enhancing macrophage inflammatory responses.

## 5. Neutrophils

Neutrophils are an important part of the innate immune system, accounting for 50–70 % of the circulating leukocytes in humans. Recent studies on mechanical channels in neutrophils have focused on TRPV4, which is highly expressed in human leukocytes and mouse neutrophils [41,42]. Yin et al. [43] reported that TRPV4 activation affects neutrophil respiratory burst, adhesion, and migration. Inhibition of TRPV4 resulted in a reduced neutrophil response to platelet-activating factor (PAF), potentially mitigating pathological changes in acute lung injury. However, these experimental results require verification using animal models. For *Mycobacterium tuberculosis*-infected mice, Naik et al. [44] found that *Trpv4*-knockdown controlled chronic infection by reducing IFN-γ expression and reduced neutrophil-driven inflammation. Nonetheless, the specific molecular mechanisms involved remain unclear.

Zhu et al. [45] reported that Piezo1 channels in neutrophils were activated by hyperglycaemia, promoting thrombus formation. However, few studies have addressed the expression and roles of mechanical channels in neutrophils, and many of the molecular mechanisms require further investigation.

## 6. Other immune cells

Mechanosensitive ion channels are also active in other immune cell types. Baratchi et al. [46] found that, in monocytes, Piezo1 was activated by high shear-stress (such as in aortic stenosis), causing calcium influx and monocyte adhesion. Son et al. [47] showed that eosinophils sense mechanical forces through surface integrins, which trigger intracellular calcium release and signature migration-associated cytoskeletal reorganization; nonetheless, the specific molecular mechanisms and the type of mechanical channels involved in this require further research.

Recently discovered immune-related cells may be regulated by mechanical forces. Chang et al. [48] found that fibroblast reticular cells within intestinal PI nodes (Peyer's patches) responded to fluid flow through the conduit network via Piezo1. Disruption of fluid flow or Piezo1 deficiency in the CCL-19-expressing matrix caused structural changes in perivascular fibroblast reticular cells and endothelial microvenules, ultimately affecting Peyer's patch lymphocytes and initiating mucosal immunity [48]. This finding provides a new potential therapeutic mechanism for diseases involving intestinal-fluid malabsorption.

## 7. Conclusions

Piezo mechanosensitive channels are believed to participate in multiple diseases, and are triggered by mechanical changes in tissue. Mechanical forces can affect the functions of multiple immune-cell types, regulating immune responses. Research on the effects of Piezo channels on immune cells is still in its early stages, and the specific molecular mechanisms are not yet fully understood.

Considering that macrophages and neutrophils can respond to multiple signals and polarize into different phenotypes, affecting both physiological and pathological responses, it is particularly important to focus on their polarization following piezo-channel activation. In tumours, M2 macrophages and N2 neutrophils exacerbate tumour pathology; moreover, tumour tissue is significantly harder than normal tissue, which is also likely to affect piezo channel activation. In addition, because macrophages can be tissue-specific, the Piezo1 channel may play different roles in different diseases. While this has been demonstrated for some diseases, the specific molecular mechanisms and targeting of these molecules as potential therapeutic agents require further research. Recent research on mechanical channels in neutrophils has focused on TRPV4 channels, with less research addressing Piezo channels and their downstream effects. This requires further in-depth analysis.

Mechanical channels have been found in many immune cells other than macrophages and neutrophils, including monocytes and eosinophils, although the properties of the mechanical channels in these cells have not been fully clarified. The Piezo1 channel has also been found in the mucosal immune system. This reveals a potential therapeutic approach to activating mucosal immunity, by specifically activating the Piezo1 channel in fibroblast reticular cells, which can in turn promote immune-cell aggregation in Peyer's patches.

Eukaryotic cells also exhibit other mechanically activated ion channels [49]; these include TREK-1/2 and TRAAK from the two-pore potassium channel (K2P) family [50], the mechano-electrical transduction (MET) channels TMC1/2 [51], and the OSCA/TMEM63 channels [52]. Limited research has been conducted on their functions in immune cells and their associations with disease. A pan-cancer analysis revealed that Piezo2 is associated with T-cell dysfunction and the secretion of immune-related factors, with the precise mechanism requiring further clarification [53].

The recent discoveries of Piezo and other mechanical channels, summarized in Fig. 1, have provided new directions for advancing the mechanistic understanding of immune cells and of the immune system, thus generating potential treatment options for diseases related to mechanical force. Although further research is required to clarify how Piezo and other mechanosensory channels impact the immune system, there is substantial recent evidence suggesting that they play important roles in the immune system. Activation of Piezo, which are expressed by many types of immune cells, can affect the function of these cells. These findings reviewed here provide a foundation for future research to examine how Piezo activation or deficiency in immune cells affect diseases such as cancer, hypertension, and pulmonary hypertension, and how these diseases can be treated by targeting Piezo.

## Ethics statement

Review and approval by an ethics committee was not needed for this study because this was a literature review and no new data were collected and analysed. For the same reason, informed consent was not required.

## Data availability statement

No data was used for the research described in the article.

## Additional information

No additional information is available for this paper.

## CRediT authorship contribution statement

**Kexin Xia:** Writing – review & editing, Writing – original draft. **Xiaolin Chen:** Writing – review & editing, Conceptualization. **Wenyan Wang:** Writing – review & editing, Writing – original draft. **Qianwen Liu:** Writing – review & editing, Writing – original draft. **Mai Zhao:** Writing – review & editing, Resources. **Jiacheng Ma:** Software. **Hao Jia:** Writing – review & editing, Writing – original draft, Conceptualization.

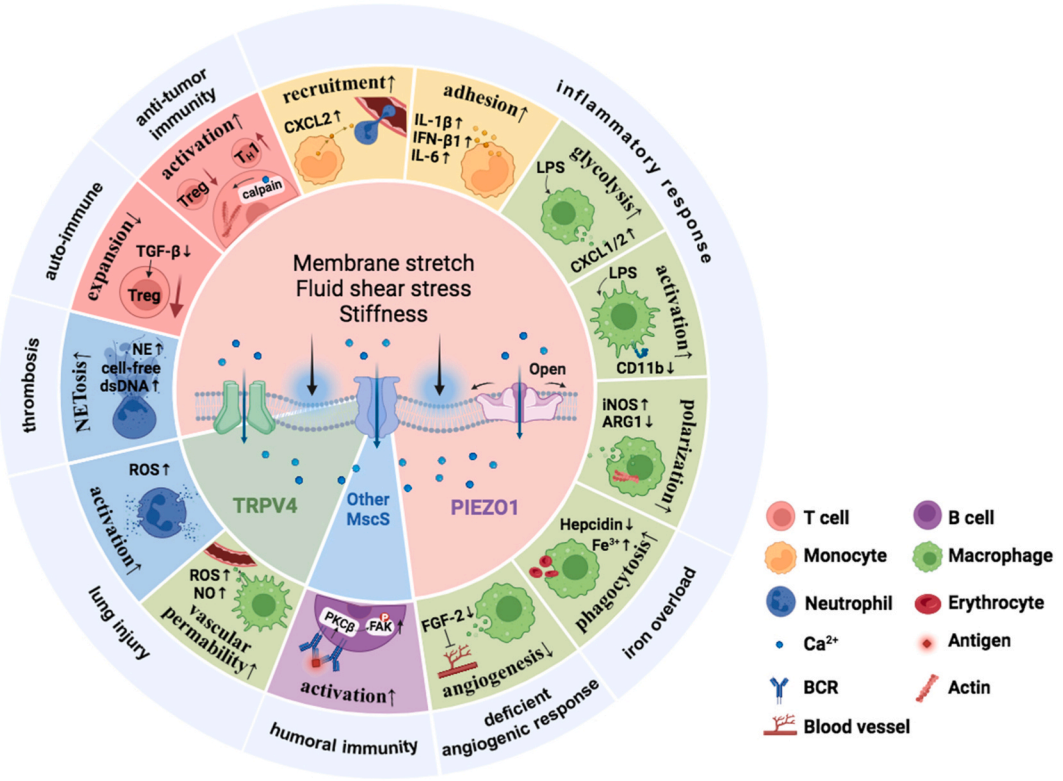


**Fig. 1.** This diagram shows the involvement of piezoelectric channels and other mechanical channels in regulating immune cell function.

## Declaration of competing interest

The 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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