

Review

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Review

Mechanosensitive Ion Channel Piezo1-Mediated Mechanical Sensing in White Blood Cells and Platelets

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Abstract

The mechanosensitive ion channel Piezo1 acts as a crucial molecule for cellular mechanical signal sensing and transduction. It transforms physical mechanical cues in the microenvironment, including matrix stiffness, fluid shear stress, and tissue tension, into intracellular biochemical signals through Ca²⁺ influx-mediated mechanisms. Consequently, it regulates the activation, proliferation, differentiation, migration, and effector functions of blood cells. Herein, we review the research progress of Piezo1 in various white blood cells, with a particular emphasis on its functional regulatory mechanisms in neutrophils, macrophages, platelets, and T and B lymphocytes. We briefly summarize its current functional status in natural killer cells, dendritic cells, plasma cells, platelets, and other cell types. We analyze the integrated effects and multi-cellular cooperative interactions of Piezo1-mediated blood cell mechanotransduction across physiological and pathological contexts. We discuss the potential value of Piezo1 as a mechano-immunotherapeutic target, therapeutic strategies, and challenges facing clinical translation. Finally, we provide perspectives on future research directions, offering theoretical references for deepening the understanding of the molecular mechanisms by which mechanical microenvironments regulate white blood cell function and disease progression and for developing novel therapeutic strategies.

Keywords: Piezo1; blood cells; mechanosensing; immune regulation; signal transduction

1. Introduction

Tissue microenvironment remodeling in disease states is a multidimensional process [1]. Beyond classical biochemical signals such as inflammatory cytokines and chemokines, biophysical cues have emerged as another critical dimension for understanding disease mechanisms [2]. These cues notably include matrix stiffness, fluid shear stress, and interstitial pressure [3]. Such as in solid tumors, uncontrolled proliferation of cancer cells and resident fibroblasts drives extensive extracellular matrix deposition and crosslinking [4]. In fibrotic diseases, persistent fibroblast activation drives excessive collagen deposition. This leads to a marked increase in extracellular matrix stiffness [5]. And in cardiovascular disease, altered hemodynamics generate aberrant shear stress along the vessel wall [6]. These mechanical cues profoundly influence immune cell migration, activation, polarization, and effector functions [7]. Among the mechanosensitive molecules, Piezo1 has emerged as a key ion

channel that directly senses mechanical stimuli and transduces them into intracellular Ca^{2+} signals, thereby regulating a wide range of immune cell behaviors [8].

Piezo1 is widely expressed in diverse blood cell lineages [9]. In neutrophils, Piezo1 contributes to shear-induced neutrophil extracellular trap formation (NETosis) and facilitates the process of trans-endothelial migration [10]. Within macrophages, this mechanosensitive channel drives the polarization toward M1 or M2 phenotypes under different matrix stiffness conditions [11]. In platelets Piezo1 was shown to regulate platelet rolling and adhesion to the growing thrombus [12], also it modulates Ca^{2+} -dependent activation and thrombosis [13]. Besides, Piezo1 regulate megakaryocyte mechanosensing, thus influencing platelet production [14]. Piezo1 pathological activation was recently shown to cause thromboembolic events in patients with hereditary xerocytosis [15], thus predicting its implication in pathological thrombosis. In both T and B lymphocytes, it shapes cellular activation, differentiation programs, and antibody class switching processes [16,17]. Moreover, emerging evidence indicates that Piezo1 also functions in natural killer cells (NKs), dendritic cells (DCs), and plasma cells, suggesting conserved mechanotransduction mechanisms across both innate and adaptive immunity (Figure 1) [18,19].

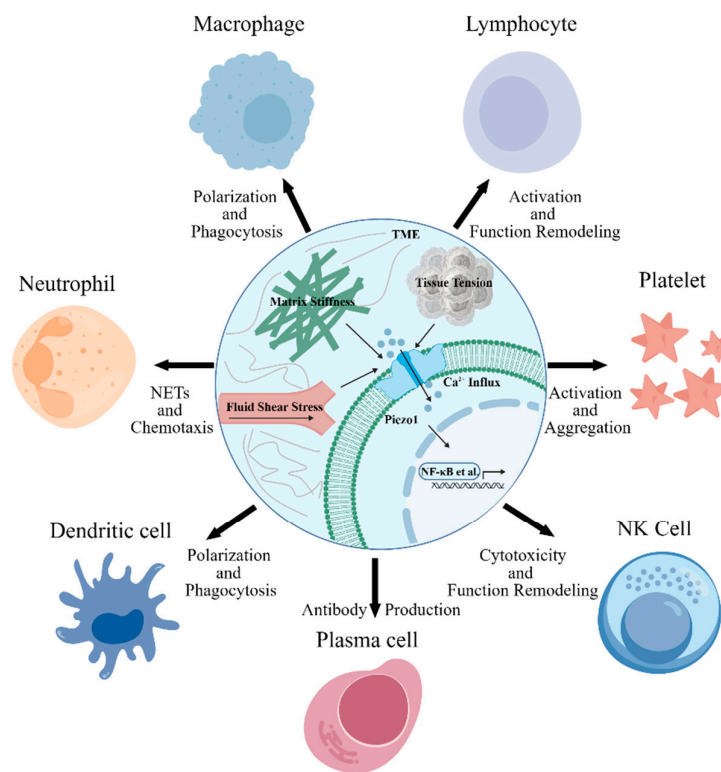


Figure 1. Schematic Diagram of Piezo1-Mediated Mechanosensation in Major Blood Cell Types. NETs, neutrophil extracellular traps; NK cell, natural killer cell.

This review offers a systematic summary of current knowledge regarding Piezo1-mediated mechanotransduction across various blood cell types. We place particular emphasis on neutrophils, macrophages, platelets, and T and B lymphocytes. Available findings on NK cells, dendritic cells, and plasma cells are also briefly consolidated. Beyond describing individual cell responses, we examine how Piezo1 helps coordinate interactions among different immune populations within the mechanical microenvironment. This coordination gives rise to a multi-cellular mechano-immunological network, one that can either restrain or accelerate tumor progression depending on context. We evaluate the potential of Piezo1 as a novel mechano immunotherapeutic target, highlight the challenges for clinical translation, and propose future research directions. This review aims to

provide a theoretical framework for understanding how the mechanical factors regulate influence disease via blood cell modulation and to inspire new therapeutic strategies.

2. Mechanoresponsive and Functional Regulatory Roles of Piezo1 in Major White Blood Cells

2.1. Piezo1-Mediated Regulation of Neutrophil Activation and Functional Reprogramming

Neutrophils, as core constituents of innate immunity, represent the earliest infiltrating immune cells within the mechanical microenvironment, and their activation status, functional output, and survival duration directly influence inflammatory homeostasis and tumor progression dynamics [20,21]. Mechanical microenvironment such as tumor microenvironment contains multiple mechanical cues. These cues include interstitial fluid shear stress, blood flow shear stress, abnormally increased matrix stiffness, changed tissue tension, and intercellular mechanical contacts. Neutrophils can accurately detect these mechanical cues through the mechanosensitive ion channel Piezo1. This detection process further triggers a series of intracellular signal transduction cascades. These cascades can comprehensively regulate multiple biological processes of neutrophils. The processes include neutrophil activation, adhesion, migration, effector functions, and apoptosis [17,22]. While Piezo1-mediated Ca^{2+} influx serves as the central hub for mechanical force-regulated neutrophil functional modulation [8], Piezo1 also exhibits multifaceted regulatory mechanisms in this process. While Piezo1-mediated Ca^{2+} influx serves as the central hub for mechanical force-regulated neutrophil functional modulation, this mechanosensitive ion channel also operates through multifaceted regulatory mechanisms [23]. Under varying levels of shear stress (4–80 dyne/cm²), Ca^{2+} influx through Piezo1 activates the calcium-dependent calpain protease pathway, triggering cytoskeletal reorganization and thereby promoting canonical neutrophil extracellular trap formation (NETosis). The resulting NETs function as a scaffold for platelet adhesion and aggregation, generating a self-amplifying feedback loop of NET-mediated platelet recruitment and platelet-driven NETosis that propagates immunothrombosis [10,24,25]. In an atherosclerosis model, low shear stress (5 dyne/cm²) at arterial bifurcations and other sites leads to downregulation of Piezo1 expression. This, in turn, induces NETs through the histone deacetylase 2 (HDAC2)–reactive oxygen species (ROS) axis, promoting endothelial cell injury and plaque formation [26]. Furthermore, in an influenza virus infection model, mechanical signals were shown to integrate magnesium ion signaling via Piezo1, thereby promoting neutrophil NETs formation through the Sirtuin 2 (SIRT2)–hypoxia-inducible factor-1 α (HIF-1 α) pathway. Subsequent uptake of NET-derived DNA by macrophages drives classical macrophage activation (M1 polarization) through the Toll-like receptor 9 (TLR9) pathway. This process also involves the cyclic GMP-AMP synthase and stimulator of interferon genes (cGAS-STING) pathway, further amplifying local inflammatory responses [22].

Piezo1 is also deeply involved in the regulation of neutrophil migration, adhesion, and functional reprogramming [27,28]. During transendothelial migration, plasma membrane tension activates Piezo1 as neutrophils traverse interendothelial gaps, eliciting transient Ca^{2+} influx. This calcium signal subsequently stabilizes hypoxia-inducible factor-1 α (HIF-1 α) and upregulates nicotinamide adenine dinucleotide phosphate oxidase 4 (NOX4), thereby markedly enhancing reactive oxygen species (ROS) production and bactericidal capacity [29,30]. This mechanically driven functional activation mechanism indicates that neutrophil effector functions are already enhanced during the process of transendothelial migration, representing an efficient pre-adaptive strategy [23]. In pulmonary microvessels, capillaries with diameters less than 5 μm impose physical constraints on neutrophils, inducing repetitive cellular deformation that activates Piezo1 and reprograms their transcriptome via the extracellular signal-regulated kinase (ERK)/nuclear factor-kappa B (NF- κB) pathway. This mechanotransduction event confers pro-angiogenic functionality upon neutrophils, upregulating effector molecules including vascular endothelial growth factor A (VEGFA), interleukin-1 beta (IL-1 β), and C-X-C motif chemokine ligand 1/2 (CXCL1/2), while simultaneously modulating their retention time and migratory behavior within pulmonary vasculature [31].

Under pathological mechanical microenvironments, Piezo1 exerts more significant regulatory effects on neutrophils. In an ankylosing spondylitis model, mechanical strain initiates a multistep cascade by first acting upon syndecan-1-positive (SDC1⁺) sheath fibroblasts, driving their differentiation through SOX5-mediated transcriptional regulation. These differentiated fibroblasts subsequently secrete high levels of C-X-C motif chemokine ligand 5 (CXCL5), which recruits C-X-C chemokine receptor type 4-positive (CXCR4⁺) neutrophils and promotes their NETosis, ultimately exacerbating enthesitis and new bone formation. This reveals that mechanical forces can remotely regulate neutrophil function through an indirect crosstalk mechanism between stromal cells and neutrophils [32]. From the hematopoietic origin, upon inflammation-induced mobilization of hematopoietic stem cells (HSCs) into circulation, blood flow shear stress activates two parallel pathways through Piezo1. The junctional adhesion molecule 3 (JAM3) pathway regulating cell homing and transendothelial migration, and the calpain 2 (CAPN2) pathway driving myeloid-biased differentiation (Figure 2). This dual-pathway activation promotes neutrophil generation at the source level and accelerates inflammatory aging processes [33]. Collectively, these findings demonstrate that therapeutic strategies targeting Piezo1 hold promise for disrupting this mechanically-immunologically coupled vicious cycle, offering novel targets for tumor immunotherapy [34].

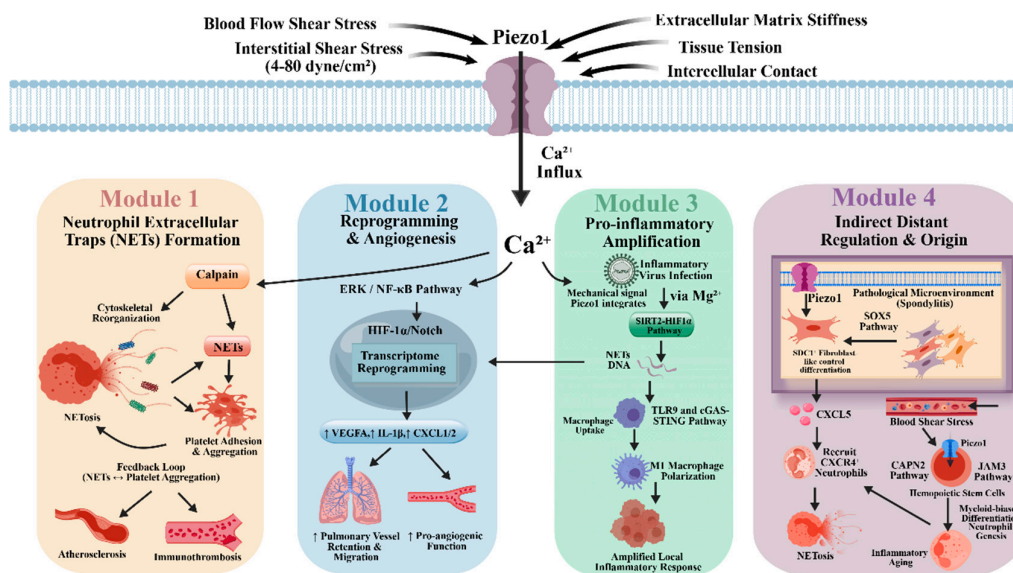


Figure 2. Mechanistic Diagram of Piezo1-Induced Neutrophil Activation and Functional Reprogramming. NETs, neutrophil extracellular traps; NETosis, neutrophil extracellular trap cell death; Calpain, calcium-dependent cysteine protease. ERK, extracellular signal-regulated kinase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; HIF-1 α , hypoxia-inducible factor 1-alpha; VEGFA, vascular endothelial growth factor A; IL-1 β , interleukin-1 beta; CXCL1/2, C-X-C motif chemokine ligand 1/2. Mg²⁺, magnesium ion; SIRT2, sirtuin 2; DNA, deoxyribonucleic acid; TLR9, toll-like receptor 9; cGAS, cyclic GMP-AMP synthase; STING, stimulator of interferon genes; M1, classically activated macrophage. SDC1, syndecan-1; CXCL5, C-X-C motif chemokine ligand 5; CXCR4, C-X-C chemokine receptor type 4; CAPN2, calpain 2; JAM3, junctional adhesion molecule 3.

2.2. Piezo1-Dependent Mechanical Signal Regulation of Macrophage Polarization and Inflammatory Phenotype Specialization

Macrophages are key immune cells that participate in immune regulation in the tissue mechanical microenvironment. Their polarization direction and inflammatory phenotype directly affect immune surveillance. They also directly affect the remodeling of the mechanical microenvironment. Extensive studies have confirmed that mechanical cues in the mechanical

microenvironment, including matrix stiffness, fluid shear stress, and tissue tension are transduced into intracellular biochemical signals via the mechanosensitive ion channel Piezo1, thereby regulating macrophage polarization toward either the M1 phenotype or the alternatively activated macrophage (M2) phenotype, ultimately determining their inflammatory and functional outputs [11,35,36]. Under matrix stiffness stimulation, Piezo1 mediates Ca^{2+} influx and activates Yes-associated protein/transcriptional coactivator with PDZ-binding motif (YAP/TAZ) nuclear translocation, thereby directly regulating the expression of macrophage polarization-related genes and completing phenotypic switching [37]. Simultaneously, under conditions of appropriate mechanical stretching intensity, Piezo1-mediated M2 polarization further promotes the secretion and activation of transforming growth factor-beta 1 (TGF- β 1), thereby promoting osteogenic differentiation and bone formation of bone marrow mesenchymal stem cells (BMSCs) [38]. In a sepsis-induced myocardial injury model, macrophage-specific Piezo1 knockout activates the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) signaling pathway and upregulates secreted phosphoprotein 1 (SPP1) expression, driving macrophage polarization toward the anti-inflammatory M2 phenotype, significantly reducing myocardial inflammation levels and improving cardiac function [39]. Additionally, fluid shear stress can directly activate the Piezo1 channel, promoting inflammasome activation through the Ca^{2+} -NOD-like receptor family pyrin domain-containing 3 (NLRP3)-cysteine-aspartic acid protease-1 (Caspase-1) signaling axis, thereby enhancing the inflammatory response capacity of macrophages [40].

In pathological mechanical microenvironments, Piezo1 plays a particularly critical regulatory role in macrophages. Fibrotic tissues can produce sustained mechanical tension. This tension activates Piezo1 in macrophages. Activated Piezo1 further promotes the activation of hepatic stellate cells. This process relies on inflammatory responses and paracrine signaling mediated by macrophages. It ultimately aggravates the progression of tissue fibrosis. In contrast, specific knockout of Piezo1 in macrophages can significantly alleviate tissue damage and inflammatory reactions [41]. The elastic mechanical signaling of nanomaterials can similarly reprogram the phenotype of tumor-associated macrophages via Piezo1, thereby ameliorating the local immunosuppressive state within the mechanical microenvironment [42]. Intercellular mechanical contact can couple and activate Piezo1 through $\alpha_v\beta_3$ integrin, thereby amplifying profibrotic signaling [43]. Extrinsic mechanical stimuli, such as ultrasound and mechanical vibration, can also directionally regulate macrophage polarization via Piezo1, participating in tissue repair and osteogenic activities [44,45]. During atherosclerotic plaque progression, the abnormally stiffened mechanical microenvironment resulting from significantly increased vascular wall matrix stiffness can activate macrophage Piezo1, promoting inflammasome activation through the Ca^{2+} -NF- κ B signaling axis and driving macrophage polarization toward the pro-inflammatory M1 phenotype, thereby accelerating plaque destabilization and rupture [11]. Furthermore, during the ischemia/reperfusion pathological process of acute kidney injury (AKI), aberrant fluid shear stress resulting from hemodynamic disturbances in peritubular capillaries and localized tissue hypoxia can activate macrophage Piezo1, driving macrophage polarization toward the pro-inflammatory M1 phenotype through the Ca^{2+} -calpain-HIF-1 α /Neurogenic locus notch homolog protein (Notch) signaling axis, thereby exacerbating renal inflammatory injury and the fibrotic process (Figure 3) [46].

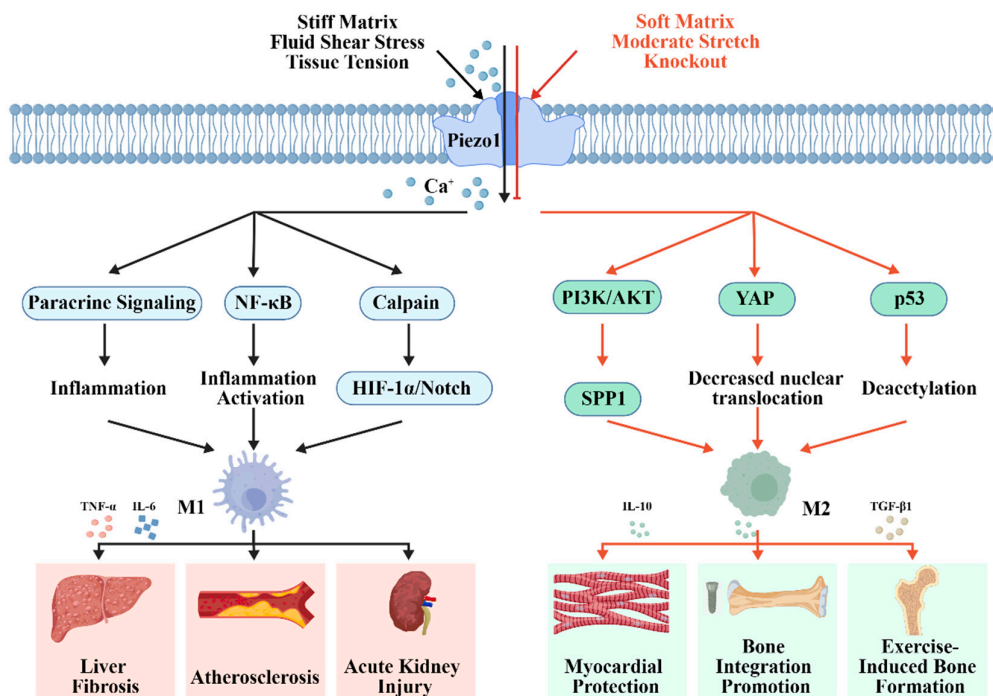


Figure 3. Mechanistic Diagram of Piezo1-Induced Macrophage Polarization. NF- κ B, Nuclear factor kappa-light-chain-enhancer of activated B cells; Calpain, Calcium-dependent cysteine protease; HIF-1 α , Hypoxia-inducible factor 1-alpha; TNF- α , Tumor necrosis factor-alpha; IL-6, Interleukin-6; M1, Classically activated macrophage; PI3K/AKT, Phosphatidylinositol 3-kinase/Protein kinase B. YAP, Yes-associated protein; p53, Tumor protein p53; SPP1, Secreted phosphoprotein 1; IL-10, Interleukin-10; M2, Alternatively activated macrophage; TGF- β 1, Transforming growth factor-beta 1.

In summary, Piezo1 serves as a critical mechanosensor in macrophages for perceiving diverse pathological mechanical signals. By mediating distinct intracellular signaling axes, it orchestrates macrophage polarization and functional phenotypes, playing a central regulatory role in various pathological processes including tumorigenesis, fibrosis, atherosclerosis, and acute kidney injury. Piezo1 thus represents a pivotal molecular hub linking the mechanical microenvironment to macrophage-mediated inflammation and tissue injury.

2.3. Piezo1-Dependent Mechanical Signal Regulation of Platelet Mechanosensing and Coagulation Function

Platelets are a vital type of blood cell. They are involved in coagulation, thrombosis, and immune regulation. When carrying out these functions, platelets rely heavily on the precise sensing of mechanical cues. These cues come from the tissue mechanical microenvironment, including tumor microenvironment. Starting with the study of Ilkan et al. in 2017, which demonstrated Piezo1 functioning in platelets, as well as in the megakaryocytes [12], it was proposed that Piezo1 serves as the core platelet mechanosensor [13]. However, a platelet's capabilities of direct membrane tension sensing are limited due to its small size and discoid shape. The recent review of Mammadova-Bach et al. [47] proposes platelet main glycoproteins, GPIb and GPIIb/IIIa (integrin α _{IIb} β ₃) as the shear stress sensors. On the other hand, plasma membrane swelling was reported to activate Piezo1 [48], therefore it is possible, that rolling platelets "sense" shear stress by their swelling. For platelets and red blood cells the impact of Piezo1 is elevated by its direct coupling with the scramblase transmembrane

protein 16F (TMEM16F) [49,50], thus promoting phosphatidylserine (PS) exposure by these cells, followed by the induction of blood coagulation [51].

Mechanical stimuli prevalent in the tumor microenvironment, including elevated matrix stiffness [52], aberrant blood flow shear stress [53], and mechanical contact triggered by vascular endothelial injury [54], can directly activate the Piezo1 channel on the platelet surface, thereby mediating Ca^{2+} ion influx [12]. This calcium signal triggers a cascade amplification reaction intracellularly. On one hand, it activates downstream signaling pathways including the Calpain-Talin1 axis [13,55] and Ras homolog family member A (RhoA)/rho-associated coiled-coil containing protein kinase ROCK [56], thereby driving cytoskeletal reorganization and enhancing integrin $\alpha_n\beta_3$ activation, which significantly augments platelet adhesion to vascular endothelium, tumor cells, and the extracellular matrix, thus establishing the foundation for platelet aggregation and microthrombus formation [57]. Additionally, Piezo1-mediated Ca^{2+} influx facilitates platelet degranulation, promoting the release of bioactive molecules including platelet-derived growth factor (PDGF), TGF- β , and platelet factor 4 (PF4). These molecules promote tumor cell proliferation, invasion, and angiogenesis, while concurrently recruiting immune cells such as macrophages and neutrophils, thereby fostering a pro-tumorigenic microenvironment [58]. Concurrently, Piezo1 inhibition diminishes heterotypic adhesion between tumor cells and platelets, suggesting that Piezo1 serves as a pivotal regulatory molecule linking platelet mechanosensation, coagulation function, and tumor progression [59].

In the pathological progression of tumors, Piezo1-mediated mechanosensation and functional dysregulation of platelets constitute critical regulatory factors for cancer-associated thrombosis and metastasis. Elevated shear stress within the tumor stroma activates Piezo1, thereby facilitating platelet hyperactivation and inducing aberrant platelet aggregation to form tumor-associated microthrombi. These microthrombi may occlude tumor vasculature, resulting in hypoxia and metabolic dysregulation that can further drive malignant progression [60,61]. Simultaneously, activated platelets and their secreted factors can coat circulating tumor cells (CTCs), thereby attenuating immune surveillance and establishing a protective shield for tumor cell distant colonization (Figure 4) [62].

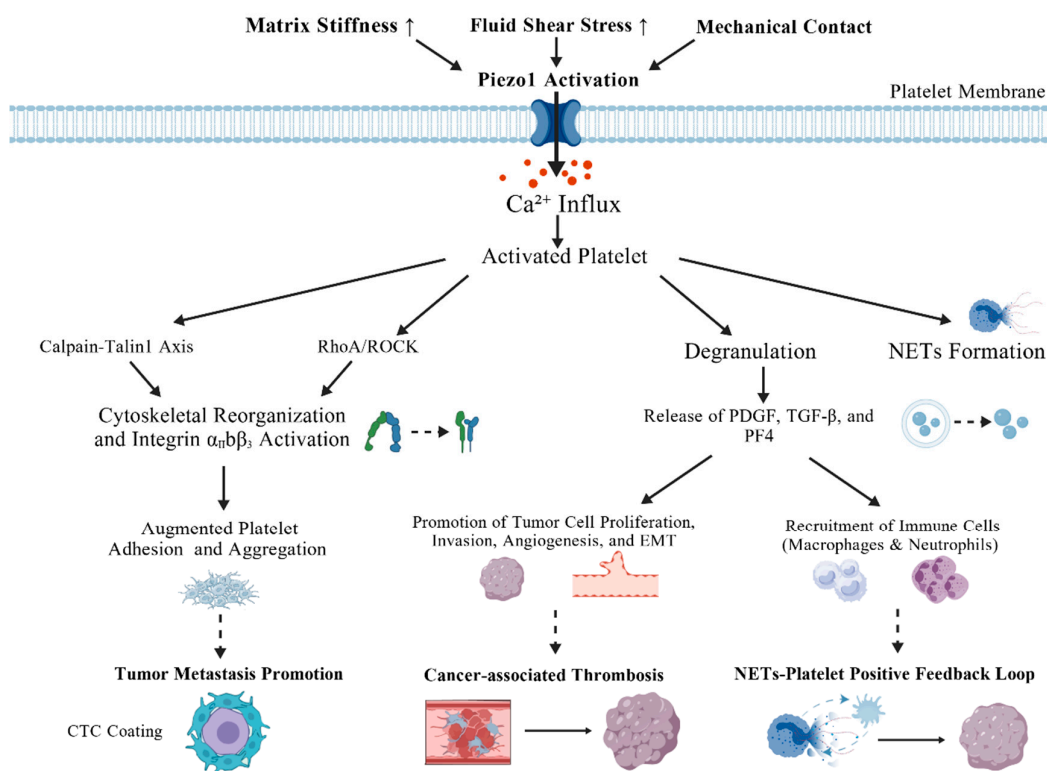


Figure 4. Mechanistic Diagram of Piezo1-Induced Platelets Mechanosensation and Coagulation Function. NETs, neutrophil extracellular traps; PDGF, platelet-derived growth factor; PF4, platelet factor 4; RhoA, Ras homolog family member A; ROCK, Rho-associated protein kinase; TGF- β , transforming growth factor beta.

The process of platelet formation in the bone marrow, called megakaryopoiesis, is known to be crucially dependent on the mechanistic stimuli, and thus could be Piezo1-dependent. Indeed, in the early steps Piezo1 was shown to have an inhibitory effect [63]. While it was recently demonstrated, that pharmacological Piezo1 stimulation promotes pro-platelet formation at the later stages of megakaryopoiesis [14]. Upon induction of Piezo1 in this model a phenotype resembling myelofibrosis occurred, and knockout of janus kinase 2 (*JAK2*) prevented this, thus suggesting possible role of Piezo1 in hematological malignancies.

In addition to its direct effects, Piezo1 serves as an important mediator in the intercellular communication between platelets and neutrophils [10]. Activated platelets significantly promote the recruitment and local adhesion of neutrophils within the microenvironment through the release of soluble mediators and surface interactions [64]. Upon adhesion to platelets and damaged extracellular matrix via integrins, neutrophils undergo cytoskeletal remodeling and generate intracellular mechanical tension. These mechanical signals are sensed by mechanosensitive ion channels such as Piezo1, leading to Ca^{2+} ion influx. Elevated intracellular Ca^{2+} levels facilitate neutrophil activation and promote the formation of NETs. As a reciprocal regulatory mechanism, the reticulated NETs are capable of capturing and intercepting circulating platelets, providing a natural scaffold for the physical reinforcement of microthrombi [65]. This pathological positive feedback loop of platelet activation, NETs release, and thrombus stabilization continuously amplifies local pro-tumorigenic inflammatory signals. It also establishes a protective barrier for the survival and targeted colonization of circulating tumor cells, ultimately exacerbating the risk of tumor metastasis [66].

2.4. Piezo1-Dependent Mechanical Signal Regulation of Lymphocyte Immune Activation and Differentiation

Lymphocytes, as the core components of adaptive immunity, undergo regulation of their activation, proliferation, differentiation, and functional execution by mechanical signals within the mechanical microenvironment. Piezo1 serves as a critical mechanotransducer. It plays a central role in lymphocyte mechanosignaling. It directly participates in their immune activation and phenotypic differentiation. Through these actions, Piezo1 modulates the magnitude and direction of anti-tumor immune responses [17]. Piezo1 can precisely sense mechanical signals within the tissue remodeling microenvironment and regulate lymphocyte functions by mediating Ca^{2+} influx and activating downstream signaling pathways. In T lymphocytes, upon activation by mechanical stimuli, Piezo1 mediates early and rapid Ca^{2+} influx, primarily modulating rapid cytoskeletal responses such as microtubule-organizing center (MTOC) reorientation [67]. In addition, chronic mechanical stress induces T cell exhaustion through Piezo1 [68], whereas inhibition of Piezo1 enhances their cytotoxic capacity [69]. The activation and antibody secretion of B lymphocytes are likewise regulated by Piezo1. The response of B cells to membrane-bound antigens is entirely dependent on the mechanotransduction function of Piezo1. When Piezo1 is inhibited or knocked down, B cells fail to effectively form immune synapses, undergo Ca^{2+} influx and execute proliferation and antibody secretion [16]. The Piezo1 signaling pathway exhibits specificity in regulating B cell antibody class switching. Studies have revealed that Piezo1 activation selectively enhances TGF- β 1-induced Smad3 phosphorylation, thereby specifically promoting IgA class switching and secretion, which holds significant implications for mucosal immunity [70]. During chemokine-induced T cell migration, Piezo1 serves as a critical component of the “outside-in” signal transduction machinery. After chemokine receptor activation and, closely following the activation of focal adhesion kinase, Piezo1 senses increased membrane tension and mediates the recruitment of the integrin lymphocyte function-associated antigen-1 (LFA-1) at the leading edge of the cell, thereby driving efficient chemotactic movement [71].

MTOC, microtubule organizing center; TIM-3, T-cell immunoglobulin and mucin domain-containing protein 3; PD-1, Programmed cell death protein 1; CD4⁺ T-cell, cluster of differentiation 4-positive T cell; T_{reg}, regulatory T cell; Th1, T helper type 1 cell; Th17, T helper type 17 cell; IFN- γ , interferon-gamma; IL-17, interleukin-17; BCR, B cell receptor; TGF- β 1, Transforming Growth Factor-beta 1; SMAD3, Mothers Against Decapentaplegic Homolog 3; IgA, Immunoglobulin A.

Different lymphocyte subtypes exhibit distinct responses to mechanical signals, and Piezo1 maintains immune homeostasis through precise regulation of these differential responses. In CD4⁺ T cells, Piezo1 demonstrates differential regulatory effects on helper T cell subset differentiation. Studies have shown that Piezo1-deficient CD4⁺ T cells exhibit significantly increased production of interferon-gamma (IFN- γ) and interleukin-17 (IL-17) under in vitro T helper 1 (Th1) and T helper 17 (Th17) polarization conditions, indicating an intrinsic function of Piezo1 in suppressing excessive inflammatory responses [72]. In regulatory T cells (T_{reg}s), Piezo1-mediated mechanical signals influence their suppressive function. Although Piezo1 deficiency does not affect T_{reg} suppressive capacity in vitro, its absence leads to significant expansion of the T_{reg} cell population in chronic inflammatory models such as experimental autoimmune encephalomyelitis, thereby ameliorating disease severity. This suggests that Piezo1 specifically upregulates T_{reg} responses in vivo to maintain immune tolerance [73]. Aberrant Piezo1 activation may disrupt the balance between T_{reg} cells and effector T cells, facilitating tumor immune evasion (Figure 5). Piezo1 functional deficiency directly compromises humoral immune responses, particularly at mucosal barrier defense sites [74]. Both genetic ablation and persistent overactivation of Piezo1 disrupt the coupling between mechanical cues and metabolic rewiring in CAR-T cells, leading to impaired cytotoxic function; in contrast, transient, moderate Piezo1 signaling coordinates synaptic mechanics, calcium transients, and ATP production to maintain peak effector activity [75]. Collectively, these findings establish Piezo1 as a core mediator of lymphocyte mechanotransduction and a critical target for regulating tumor immunity and intervening in immune evasion.

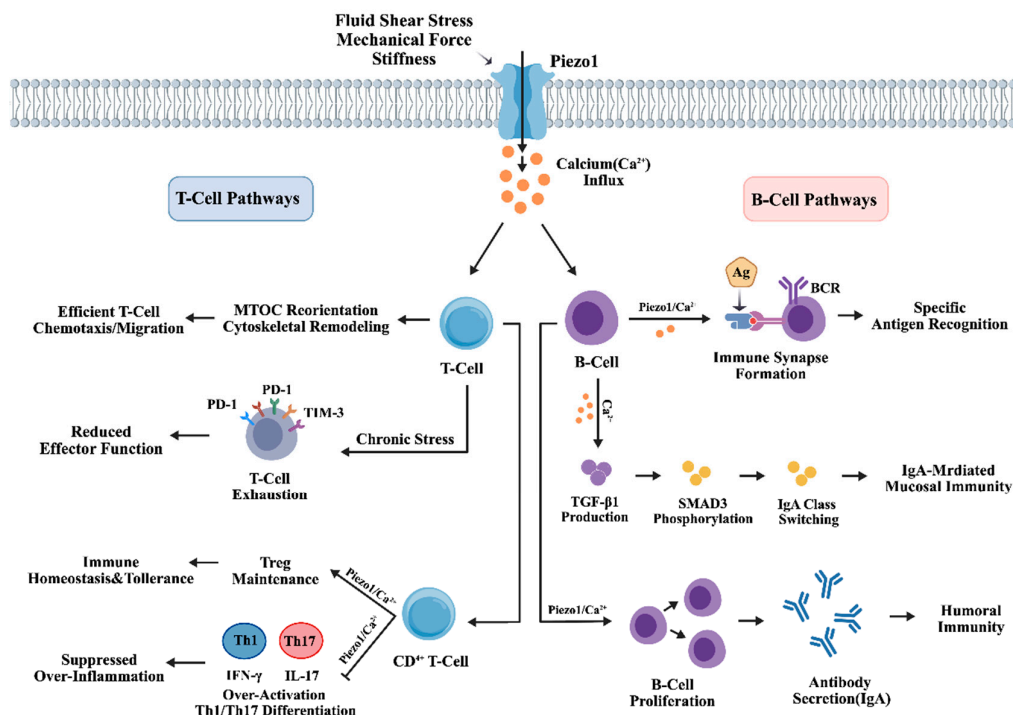


Figure 5. Mechanistic Diagram of Piezo1-Induced Lymphocytes Phenotypic Alterations.

2.5. Piezo1 and Other White Blood Cells

In addition to macrophages, NKs, DCs, and plasma cells can also sense mechanical cues in the mechanical microenvironment via the Piezo1 channel, thereby completing functional specialization and immune effector output. As critical cytotoxic cells of innate immunity, NKs recognize matrix stiffness and target cell mechanical properties through Piezo1, which mediates Ca^{2+} influx and regulates immunological synapse assembly. Increased matrix stiffness significantly enhances NK cytotoxic activity, while Piezo1 inhibition markedly impairs their migration and killing capacity within solid tissues [18]. Dendritic cell function is similarly regulated by mechanical signals. Studies have shown that increased matrix stiffness has a specific effect. It promotes the polarization of dendritic cells toward a pro-inflammatory phenotype. This shift enhances their maturation. It also boosts their antigen presentation and phagocytic capabilities [76]. Matrix stiffness and inflammatory signals activate Piezo1 in DCs, triggering Ca^{2+} influx and influencing cytokine secretion patterns through the Piezo1– Ca^{2+} –nuclear factor of activated T cells (NFAT) pathway, thereby regulating the $\text{T}_\text{H}1/\text{T}_\text{reg}$ balance and participating in the construction of the tumor immune microenvironment [19]. Under non-tumor, ous or acute infection conditions, Piezo1 activation may enhance DC type I interferon production, thereby activating NKs and cytotoxic T lymphocytes (CTLs), demonstrating the context-dependent nature of its function [77]. B cells and plasma cells can sense plasma membrane tension and matrix mechanical alterations via Piezo1, regulating TGF- β 1-mediated IgA class switching and influencing antibody synthesis and secretion efficiency. Piezo1 functional deficiency directly compromises systemic humoral immune response levels [70,77]. Beyond direct regulation of immune cell function through calcium ion signaling, Piezo1 can also synergize with integrin signaling pathways to transduce extracellular matrix mechanical stimuli into intracellular biochemical signals [78]. Studies have shown that Piezo1 activation or deficiency in DCs affects their interaction with the extracellular matrix (ECM), thereby modulating immune cell migration and antigen-specific T cell activation [19]. This synergistic signaling mechanism plays a critical role in mediating inflammatory responses during both physiological and pathological processes [79]. As a central hub, Piezo1 integrates mechanical signals to coordinate immune cell migration, synapse formation, and effector molecule release, thereby playing a pivotal role in the coordinated response between innate and adaptive immunity [80].

3. Integrated Effects of Piezo1-Mediated Blood Cell Mechanotransduction in Disease Mechanical Microenvironments

3.1. Interactive Regulation Between Disease Mechanical Microenvironment Mechanical Signals and Blood Cell Functions

The mechanical characteristics of the mechanical microenvironment are critical physical signals. They regulate blood cell function. Solid tumors universally show mechanical alterations. These alterations include elevated matrix stiffness. They also include enhanced interstitial fluid shear stress. In addition, they include dysregulated tissue tension [81,82]. These mechanical cues are sensed by tumor-infiltrating immune cells via the mechanosensitive ion channel Piezo1 and subsequently transduced into intracellular biochemical signals, thereby regulating immune cell activation, migration, and effector functions [23]. Upon activation by mechanical cues, Piezo1 primarily mediates Ca^{2+} influx [83], initiating downstream calcium-dependent signaling cascades, including activation of the nuclear factor of activated T cells (NFAT) and Yes-associated protein (YAP) transcriptional axes that broadly regulate the functional phenotypes of neutrophils, platelets, NKs, dendritic cells, and plasma cells, driving immune cell reprogramming toward pro-tumorigenic phenotypes [84]. Concurrently, activated blood cells can further exacerbate matrix stiffening and collagen cross-linking through the release of inflammatory factors, matrix metalloproteinases, and pro-coagulant molecules [85], establishing a positive feedback loop of mechanical abnormality–blood cell activation–tumor progression. Throughout this process, Piezo1 functions as the principal

mechanotransducer, serving as the critical molecular nexus that couples mechanical microenvironmental cues with immune regulatory programs.

3.2. Mechanical Synergism Among Different Blood Cells Mediated by Piezo1

The diverse blood cells in the TME do not function as independent mechanical signaling units. Instead, these blood cells form a complex multi-cellular mechano-immunological synergistic network. This network centers on the Piezo1 channel [86]. Individual cells first perform local primary mechanical sensing. This sensing process is gradually amplified into systematic cascading responses. These responses cover both innate immunity and adaptive immunity.

During the early phase of tumor infiltration, mechanical interplay between neutrophils and platelets constitutes the initiating step for pro-inflammatory and pro-metastatic responses, with both cell types acutely sensing aberrant shear stress and vascular matrix stiffness. Upon mechanical stimulation, neutrophils are robustly activated via the Piezo1–Ca²⁺–calpain signaling pathway, resulting in massive release of NETs [10]. These reticular structures provide a robust physical scaffold for platelet adhesion and aggregation. They also further amplify platelet activation levels, establishing a positive feedback loop of mechanical stimulation, NET release, and the deterioration of the thrombotic microenvironment, which synergistically constructs a pro-inflammatory and pro-metastatic environment. NKs synchronously participating in immune surveillance are similarly highly dependent on this channel [18]. NKs can perceive three-dimensional matrix stiffness and target cell rigidity alterations through Piezo1, transducing these mechanical cues into intrinsic signals that regulate immunological synapse formation and granule exocytosis. Aberrant Piezo1 function or excessive matrix stiffening significantly impairs NK cell infiltration capacity and cytotoxic killing efficiency, enabling tumors to readily breach innate immune surveillance defenses [87].

At the adaptive immunity level, DCs, as critical antigen-presenting cells, exhibit highly multifaceted responses to microenvironmental mechanical cues. On one hand, DCs can perceive matrix stiffness through activation of intracellular YAP/TAZ signaling pathways, thereby upregulating glycolytic metabolism and promoting the secretion of pro-inflammatory factors such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) [76]. However, within the complex mechanical microenvironment, the direction of T cell polarization guided by DCs is likewise under the surveillance of the core mechanosensory channel Piezo1. High-stiffness microenvironmental stimulation of DCs triggers Piezo1-mediated Ca²⁺ influx, which not only activates the Ca²⁺–NFAT pathway but also integrates the Sirtuin 1 (SIRT1)–HIF-1 α metabolic reprogramming pathway, thereby modulating the cytokine secretion profile (e.g., suppressing interleukin-12 (IL-12) while promoting TGF- β 1 secretion), ultimately priming DCs to promote the differentiation of immunosuppressive T_{reg}s [19]. This interplay and signal integration between distinct mechanosensors (YAP/TAZ and Piezo1) ultimately determines the trajectory of local adaptive immunity within tumors. Furthermore, when B cells and plasma cells sense antigen-presenting cell membrane tension and lymph node matrix mechanical signals, Piezo1 may participate in regulating their antibody class switching and secretion efficiency, constituting an important complement to the mechanical regulation of humoral immunity [70].

Piezo1 on the macrophage surface acts as a critical mechano-immunological switch that determines phenotypic polarization, determining phenotypic polarization. Under general mechanoresponsive conditions, high-stiffness matrices typically activate the Piezo1–YAP axis and drive macrophage polarization toward the classically activated M1 phenotype [37]. However, during tumor progression, microenvironmental signals may induce downregulation or functional suppression or functional suppression of Piezo1 expression on tumor-associated macrophage (TAM) surfaces to evade immune surveillance. This inactivation of the core mechanosensor blocks normal pro-inflammatory signal transduction, thereby promoting macrophage polarization toward the pro-tumorigenic alternatively activated M2 phenotype [39,88]. These M2-polarized TAMs subsequently secrete substantial anti-inflammatory factors and exosomes, directly suppressing local CD8⁺ T cell cytotoxic function, thereby constructing a deeply immunosuppressive microenvironment [89,90].

Piezo1 is not merely the molecular basis for individual blood cells to perceive mechanical signals but also serves as an important hub mediating collaborative interactions among multiple blood cell types. By transducing mechanical signals across cells and amplifying immune effects, it regulates tumor inflammation, immune suppression, and malignant progression, highlighting its potential as a theoretical foundations for immunotherapeutic strategies targeting the tumor mechanical microenvironment.

4. Potential and Challenges of Piezo1 as a Therapeutic Target in Diseases Associated with Tissue Stiffening

4.1. Therapeutic Strategies Targeting Piezo1-Mediated Blood Cell Functional Regulation

Piezo1 plays a critical mediating role between the mechanical microenvironment and immune cell function. Based on this role, targeted Piezo1 modulation has emerged as a potential therapeutic strategy. This strategy aims to reshape the mechanical microenvironment. It also aims to block immune suppression mediated by tissue abnormalities. Small-molecule agonists or inhibitors can precisely regulate Piezo1 activity. This precise regulation can reverse the aberrant shaping of immune cells by mechanical cues in various mechanical microenvironments. In macrophage-targeted interventions, Piezo1 inhibition can block matrix stiffness-induced alternatively activated M2 polarization, reduce pro-inflammatory factor release, and simultaneously enhance pro-inflammatory macrophage antigen presentation and inflammatory clearance capacities, thereby dismantling the immunosuppressive environment caused by tissue matrix alterations [91]. For NKs and cytotoxic T lymphocytes, moderate Piezo1 activation can enhance their infiltration efficiency and cytotoxic activity within dense tumor matrices, strengthening immune surveillance against solid tumors [18]. Concurrently, Piezo1 targeting can also regulate aberrant neutrophil and platelet activation, reduce NETosis and thrombosis-associated microenvironment establishment, and decrease tumor invasion and distant metastasis risk. Piezo1-targeted therapy has a core advantage. It can precisely interface with the mechanical characteristics of the mechanical microenvironment. Through this interface, it achieves synergistic regulation of multiple blood cell functions. Conventional immunotherapeutic approaches cannot offer this unique value. Combination of immune checkpoint inhibitors with Piezo1 modulators holds promise for further enhancing immunotherapeutic response rates and overcoming mechanically-mediated therapeutic resistance.

4.2. Challenges and Optimization Directions in Clinical Translation

Piezo1 plays a key role in regulating the mechanical microenvironment and modulating blood cell function, making it a promising target for diseases associated with tissue stiffening and fibrosis. However, its clinical application presents several challenges. Piezo1-targeted therapy offers a unique advantage by interacting with the mechanical properties of various diseased tissues and regulating multiple blood cell functions. This approach differs from traditional therapies that typically target a single cell type. Piezo1 modulators can influence various blood cells, including macrophages, neutrophils, lymphocytes, and platelets, enhancing immune activation and inhibiting factors such as M2 polarization and platelet activation. This creates a multi-dimensional therapeutic effect by addressing inflammation, immune activation, and tissue remodeling.

However, Piezo1's widespread presence in normal tissues, such as vascular endothelium and neural cells, raises safety concerns, as non-specific inhibition can lead to off-target effects in these systems. Additionally, Piezo1's function varies across different cell types, with pro-tumorigenic effects in some immune cells and enhanced anti-tumor responses in others. Therefore, precise regulation including optimal dosing, timing, and combination strategies is necessary to avoid therapeutic failure.

The heterogeneity of mechanical microenvironments, such as variations in matrix stiffness, hydrostatic pressure, and shear stress across different diseases, complicates the prediction of Piezo1-mediated effects. Future research should focus on developing immune cell-specific delivery systems,

individualized dosing protocols, and allosteric modulators with reduced side effects. Combining mechanical microenvironment interventions with other therapeutic approaches, such as immunotherapy or anti-fibrotic treatments, may further enhance efficacy.

In conclusion, Piezo1 offers a novel approach to mechano-immunotherapy in diseases associated with tissue stiffening and fibrosis. However, challenges related to specificity, safety, and tissue heterogeneity must be addressed for effective clinical translation. Intensive investigation into these issues is crucial for realizing Piezo1's potential as a therapeutic target.

5. Summary and Perspectives

This review summarizes the current understanding of Piezo1, a mechanosensitive ion channel crucial for mechanotransduction in blood cells. It focuses on its role in various immune cells such as neutrophils, macrophages, platelets, lymphocytes, NK cells, dendritic cells, and plasma cells, examining how Piezo1 regulates their functions within the mechanical microenvironment. Piezo1 plays a pivotal role in converting mechanical signals (e.g., matrix stiffness, shear stress, and tissue tension) into biochemical signals via Ca^{2+} influx, which influences cell behavior including activation, proliferation, differentiation, migration, and effector functions. This allows Piezo1 to link the mechanical microenvironment to systemic immune responses, acting as a core molecular hub.

In neutrophils, Piezo1 triggers NETs formation, pro-inflammatory factor release, and migration via calpain protease and NF- κ B signaling, aggravating inflammation and metastasis. In macrophages, it regulates M1/M2 polarization and inflammatory phenotypes through YAP/TAZ, NLRP3-Caspase-1 pathways, contributing to an immunosuppressive tumor microenvironment. In platelets, Piezo1 modulates adhesion, aggregation, and thrombosis, promoting tumor-associated thrombogenesis. In lymphocytes, it affects T cell activation, B cell antibody secretion, and T_{reg} function, helping maintain immune homeostasis and regulating tumor immune evasion. Piezo1's role extends to NKs, DCs, and plasma cells, where it integrates mechanical cues to fine tune innate and adaptive immunity.

Piezo1-mediated mechanotransduction in the tissue mechanical microenvironment operates within a multicellular network, where blood cells interact to form feedback loops that accelerate tumor growth and immune modulation. These interactions reshape the mechanical and immune landscapes of tumors, enhancing malignant progression. Thus, Piezo1 emerges as a promising therapeutic target for mechano-immunotherapy, where small-molecule modulators could restore anti-tumor immune responses and complement immune checkpoint inhibitors for improved treatment outcomes.

However, Piezo1's clinical translation faces challenges, primarily due to its widespread expression in normal tissues, which may lead to off-target effects in the cardiovascular, hematopoietic, and nervous systems. Furthermore, its role in immune cells and tumors can be paradoxical, suppressing tumor-promoting activity in immune cells while supporting tumor growth. Variability in tumor mechanical properties across types and stages complicates Piezo1's immunoregulatory effects. Future research should focus on targeted delivery systems for immune cells, selective modulators to reduce off-target effects, and tailoring treatments based on tumor type and disease stage. Additionally, understanding how Piezo1 functions across different cell types and its synergy with other therapies will be essential for its clinical application.

As research deepens, breakthroughs in Piezo1-targeted interventions may open new avenues for the treatment of various diseases. These interventions hold promising mechano immunological strategies, particularly with significant potential in addressing tissue stiffness and fibrosis related diseases.

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