



Review

Mechanobiology of Type 1 hypersensitivity: Elucidating the impacts of mechanical forces in allergic reactions

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ABSTRACT

Type 1 hypersensitivity involves an exaggerated immune reaction triggered by allergen exposure, leading to rapid release of inflammatory mediators. Meanwhile, mechanobiology explores how physical forces influence cellular processes, and recent research underscores its relevance in allergic reactions. This review provides a concise overview of Type 1 hypersensitivity, highlighting the pivotal role of mast cells and immunoglobulin E (IgE) antibodies in orchestrating allergic reactions. Recognizing the dynamic nature of cellular responses in allergies, this study subsequently delves into the emerging field of mechanobiology and its significance in understanding the mechanical forces governing immune cell behavior. Furthermore, molecular forces during mast cell activation and degranulation are explored, elucidating the mechanical aspects of IgE binding and cytoskeletal rearrangements. Next, we discuss the intricate interplay between immune cells and the extracellular matrix, emphasizing the impact of matrix stiffness on cellular responses. Additionally, we examine key mechanosensitive signaling pathways, including the mitogen-activated protein kinase (MAPK) pathway, Rho guanosine triphosphatase (GTPase) and integrin-mediated focal adhesion signaling, shedding light on their contributions to hypersensitivity reactions. This interplay of mechanobiology and Type 1 hypersensitivity provides insights into potential therapeutic targets and biomarkers, paving the way for better clinical management of Type 1 hypersensitivity reactions.

1. Introduction

Type 1 hypersensitivity represents a prototypical allergic reaction characterized by an exaggerated immune response to innocuous substances, known as allergens. This hypersensitivity is classified as an immediate or immunoglobulin E (IgE)-mediated hypersensitivity, involving the immediate release of inflammatory mediators upon re-exposure to specific allergens. The sensitization phase begins when the immune system of individuals prone to Type 1 hypersensitivity responds to the first exposure of specific allergens by producing IgE antibodies [1,2]. These IgE antibodies occupy the high-affinity IgE receptors on the surface of mast cells and basophils. Upon subsequent exposure to these specific allergens, the crosslink between allergens and IgE antibodies activate mast cells and basophils, triggering the release of potent mediators such as histamine, leukotrienes, and cytokines (Fig. 1) [1,3–5]. The rapid release of these mediators results in the clinical manifestations of allergy, ranging from mild symptoms like itching and sneezing to severe, life-threatening reactions like anaphylaxis [1,6]. Common allergens implicated in Type 1 hypersensitivity span a broad spectrum, including environmental allergens such as pollen, dust mites and animal dander, as

well as food allergens like nuts, shellfish and eggs. Additionally, insect venom, certain medications and latex are recognized triggers [7]. The role of allergens in Type 1 hypersensitivity is pivotal, as the immune system perceives them as foreign and mounts an immune response, with subsequent exposures leading to heightened sensitivity and escalating allergic reactions [8].

Mechanobiology, an interdisciplinary field at the intersection of biology and physics, investigates how physical forces and mechanical properties influence cellular behavior and function [9]. At its core, mechanobiology encompasses the study of mechanosensation, mechanotransduction, and the cellular responses to mechanical cues. Mechanobiology explores the dynamic interactions between cells and their physical microenvironment. It encompasses a range of processes, including cellular sensing of mechanical forces, transmission of these forces into biochemical signals, and the subsequent cellular responses. Key principles involve understanding how cells perceive and respond to mechanical cues through various molecular mechanisms, including mechanosensitive proteins, cell adhesion molecules, and the cytoskeleton [9,10]. Over the past decades, extensive research has unveiled the critical role of mechanical forces in shaping cellular processes. Studies

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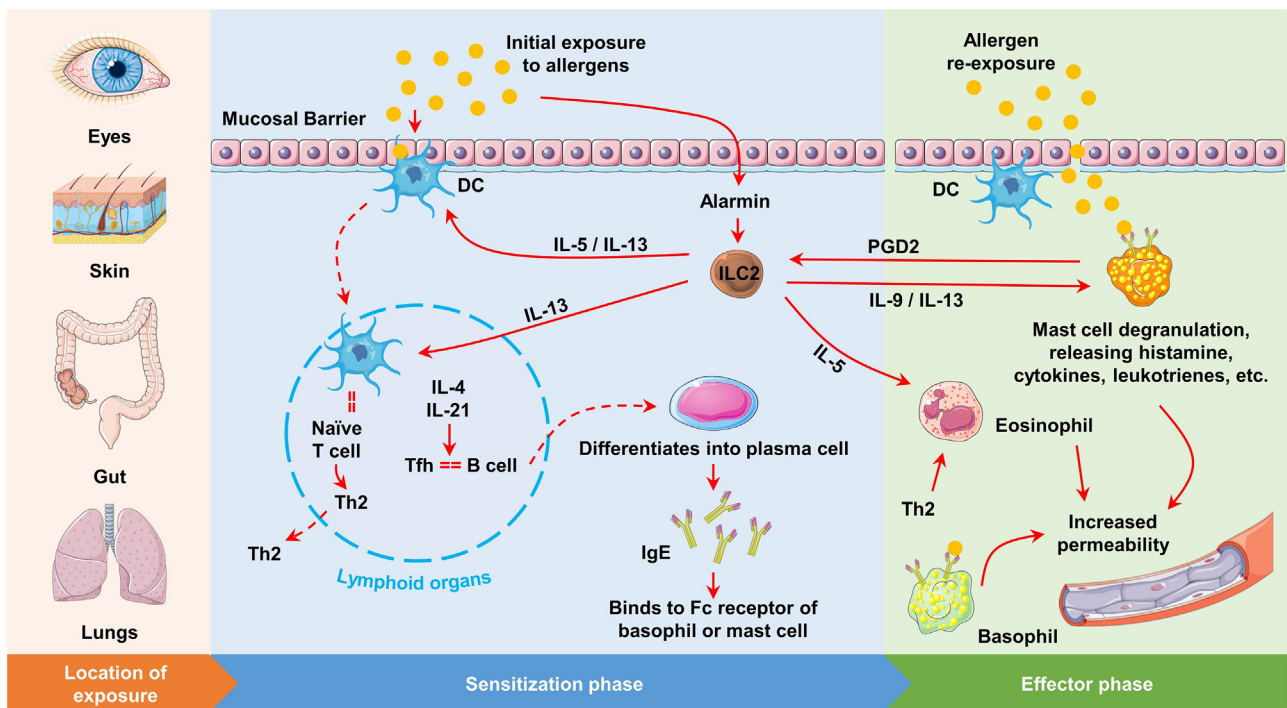


Fig. 1. Immune cascades in Type 1 hypersensitivity reaction. An individual is first sensitized to an allergen. During initial exposure, the allergen is captured by antigen-presenting cells (APCs), such as dendritic cells. APCs process the allergen and present it to T-helper (Th) cells, specifically Th2 cells. Th2 cells become activated and release cytokines, particularly interleukin-4 (IL-4) and IL-13. These cytokines stimulate B cells to differentiate into plasma cells, which then produce large amounts of IgE antibodies specific to the allergen. IgE antibodies are released into the bloodstream and bind to the surface of mast cells and basophils, which are effector cells involved in the immune response. IgE antibodies on the surface of mast cells and basophils serve as receptors for the specific allergen. The sensitized mast cells and basophils are now primed and ready for subsequent exposure to the allergen. Upon re-exposure to the allergen, it binds to the specific IgE antibodies on the surface of mast cells and basophils. The cross-linking of IgE antibodies on mast cells and basophils triggers a signaling cascade that leads to the release of pre-formed inflammatory mediators stored in granules. These mediators include histamine, leukotrienes, and prostaglandins. Released mediators cause various physiological effects, including increased vascular permeability, leading to edema and fluid leakage. (DC = dendritic cell; IgE = immunoglobulin E; IL = interleukin; ILC2 = type 2 innate lymphoid cell; PGD2 = prostaglandin D2; Tfh = T follicular helper; Th2 = T helper 2).

have demonstrated that mechanical cues influence cell morphology, migration, proliferation, and differentiation [11–13]. Notably, investigations into cellular responses to substrate stiffness, fluid shear stress, and cyclic stretch have provided valuable insights into the impact of mechanical stimuli on cell behavior [14,15]. These studies have underscored the intricate interplay between mechanical forces and biochemical signaling pathways, revealing the multifaceted nature of mechanobiological regulation.

The rationale for delving into mechanobiology in the context of Type 1 hypersensitivity stems from the growing awareness that allergic reactions are not solely mediated by biochemical signals. Rather, mechanical forces within the cellular microenvironment may play a crucial role in modulating immune cell responses during hypersensitivity reactions [16–19]. Investigating the mechanobiological aspects of mast cell activation, IgE binding, and cytokine release can provide a more comprehensive understanding of the intricate processes underlying Type 1 hypersensitivity. Unraveling these mechanistic details may open new avenues for targeted therapeutic interventions, potentially offering innovative strategies for managing allergic conditions based on a deeper comprehension of the mechanical forces at play in hypersensitivity reactions. In this manuscript, we aim to comprehensively discuss the role of mechanical forces in Type 1 hypersensitivity reactions and the potential clinical implications of modulating cellular mechanobiology to manage Type 1 hypersensitivity.

2. Cellular components involved in Type 1 hypersensitivity

2.1. Mast cells

Mast cells are specialized cells distributed throughout connective tissues. Structurally, they possess large cytoplasmic granules containing

an array of bioactive molecules, including histamine, cytokines, and proteases [20,21]. These granules play a pivotal role in the rapid release of inflammatory mediators during immune responses. Functionally, mast cells are key players in both innate and adaptive immunity [21]. Upon encountering antigens, particularly in the context of allergic reactions, mast cells unleash a cascade of immune responses [20]. The release of histamine contributes to vasodilation and increased vascular permeability, fostering an environment conducive to the influx of immune cells [22–24]. Furthermore, mast cells secrete cytokines that orchestrate inflammation, influencing the recruitment and activation of various immune cells [21,25,26].

Mast cell activation is a tightly regulated process, typically initiated by the cross-linking of IgE antibodies bound to the mast cell surface. Sensitization precedes this process, during which IgE antibodies specific to a particular antigen attach to mast cell receptors. Upon subsequent exposure to the same antigen, the cross-linking of IgE molecules triggers a series of intracellular signaling events [1,27]. Activation pathways involve the phosphorylation of key signaling molecules, such as tyrosine kinases, leading to the mobilization of calcium ions and activation of phospholipase enzymes [28,29]. These events culminate in the degranulation of mast cells, with the release of preformed mediators like histamine and newly synthesized cytokines. Additionally, mast cells contribute to the immune response by generating lipid-derived mediators, including prostaglandins and leukotrienes [20].

2.2. IgE antibodies

IgE antibodies represent a critical component of the adaptive immune system and play a central role in allergic reactions. Unlike other antibody classes, IgE is primarily associated with responses to parasitic infections

and allergies [30,31]. In the context of allergies, the role of IgE is pivotal in mediating hypersensitivity reactions upon exposure to specific allergens. Upon initial exposure to an allergen, the immune system triggers a specific immune response that includes the production of IgE antibodies by plasma cells. These IgE antibodies have a high affinity for Fc receptors present on the surface of mast cells and basophils. This sensitization phase primes the immune system for subsequent encounters with the same allergen. Upon re-exposure, the allergen binds to the IgE antibodies on the surface of sensitized mast cells, initiating a cascade of events leading to the release of potent mediators [32,33].

The binding of IgE antibodies to mast cells is a crucial step in the initiation of allergic responses. Mast cells express a specific type of Fc receptor, known as FcεRI, which selectively binds to the Fc region of IgE antibodies [3,34]. The high affinity between IgE antibodies and FcεRI ensures that even low concentrations of allergen can lead to the cross-linking of IgE molecules on adjacent receptors. Upon allergen binding, the cross-linking of IgE–FcεRI complexes triggers a series of intracellular signaling events within the mast cell [34]. The ultimate result is the degranulation of mast cells, releasing a multitude of bioactive substances, including histamine, prostaglandins, and cytokines. This release of mediators initiates the inflammatory response characteristic of allergic reactions [3,27,35].

Among other molecular determinants, Interleukin-21 (IL-21) emerges as a significant player in modulating IgE responses. IL-21, a cytokine belonging to the type I cytokine family, is known for its broad immunomodulatory effects impacting a variety of immune cells including T, B, and natural killer cells. IL-21 is predominantly produced by CD4⁺ T cells, particularly T follicular helper (T_{fh}) cells, and exerts a significant influence on the immune response. Its receptor, IL-21R, is expressed on various immune cells, allowing IL-21 to modulate growth, differentiation, and function. The relationship between IL-21 and IgE production has been a subject of considerable interest. Studies have shown that IL-21 can modulate IgE synthesis in various ways. Hiromura et al. (2007) demonstrated that administration of IL-21 in a murine model of allergic rhinitis significantly reduced symptoms and serum concentrations of ovalbumin (OVA)-specific IgE, indicating a suppressive effect of IL-21 on IgE synthesis. This was a pivotal finding, linking IL-21 directly to the suppression of IgE [36]. Further, Jen et al. (2015) showed that IL-21 inhibits IgE secretion from B cells stimulated by the combination of CD40 ligand and IL-4. This negative regulatory role of IL-21 in IgE production suggests its potential utility in therapeutic interventions for allergic diseases [37]. The modulation of B cell function by IL-21 is a critical factor in its regulation of IgE levels. B cells undergo class switch recombination (CSR) to produce IgE, and IL-21 directly influences this process (Fig. 1). Kishida et al. (2007) found that treatment with IL-21 in anaphylactic mice models suppressed IgE CSR in splenic B cells, resulting in a significant decrease in serum concentrations of both total and allergen-specific IgE. These findings underscore the importance of IL-21 in regulating B cell function and, consequently, IgE production in allergic responses [38]. Additionally, the interplay between IL-21 and T cells is significant in the context of allergic diseases. IL-21 influences the differentiation and function of T_{fh} cells, which are integral to B cell activation and subsequent IgE production. Fröhlich et al. (2007) highlighted the role of IL-21R signaling in Th2 immune responses. Given that Th2 responses are closely associated with allergic reactions and IgE production, this finding suggests that IL-21's action on T cells has an indirect yet significant impact on IgE regulation in allergic responses [39].

2.3. Other immune cells involved in Type 1 hypersensitivity

Basophils and eosinophils emerge as crucial contributors, amplifying and modulating the allergic response [33]. Basophils, akin to mast cells, possess high-affinity IgE receptors (FcεRI) on their surface. Upon allergen exposure, cross-linking of IgE antibodies on basophils triggers a cascade of events leading to degranulation. Basophils release histamine, leukotrienes, and other inflammatory mediators, intensifying the overall

hypersensitivity reaction. Additionally, basophils contribute to the recruitment and activation of other immune cells, shaping the magnitude and duration of the allergic response [33,40,41]. Whilst, activation of eosinophils is mediated by IgE antibodies and other factors, leading to the release of cytotoxic granule proteins and inflammatory mediators. Eosinophils also participate in tissue remodeling and repair, contributing to the chronicity of allergic conditions [33,42,43]. Their involvement in Type 1 hypersensitivity extends beyond the immediate response, influencing the overall pathology of allergic diseases.

Various immune cells, such as T lymphocytes and macrophages, also contribute significantly to the orchestration of Type 1 hypersensitivity reactions. T-helper 2 (Th2) cells play a crucial role in initiating and perpetuating allergic responses by releasing cytokines that promote class switching to IgE and activation of eosinophils [44,45]. Macrophages contribute to the inflammatory milieu through the release of cytokines and participation in antigen presentation [46,47]. Complement components (e.g., C3a and C5a) can further amplify allergic reactions by promoting vasodilation, smooth muscle contraction, and recruitment of immune cells [48–50]. Additionally, chemokines and adhesion molecules facilitate the migration of immune cells to the site of allergen exposure, influencing the intensity and duration of the hypersensitivity reaction [51].

3. Molecular forces in Type 1 hypersensitivity

3.1. Forces exerted during mast cell activation

In Type 1 hypersensitivity reactions, the activation of mast cells is a pivotal event driven by complex molecular forces, beginning with the mechanical aspects of IgE binding. Sensitization, the initial phase of hypersensitivity, involves the binding of allergen-specific IgE antibodies to the high-affinity FcεRI receptors on the surface of mast cells [33,52]. This interaction has profound mechanical implications, as it initiates a series of conformational changes in both IgE and FcεRI. The binding of IgE antibodies to FcεRI induces a transition from a low-affinity to a high-affinity state, enhancing the stability of the complex. This change is associated with alterations in the quaternary structure of IgE, involving bending and straightening of the IgE molecules [52,53]. The mechanical forces exerted during this process are critical for the formation of stable IgE–FcεRI complexes, priming mast cells for subsequent activation upon allergen exposure. Moreover, the mechanical force exerted during IgE binding is not uniform across all receptor–ligand interactions. The strength and duration of IgE binding can vary depending on factors such as allergen size and affinity for IgE [53].

Following IgE binding (Fig. 2), the molecular forces during mast cell activation extend to cytoskeletal rearrangements, orchestrated by the dynamic interplay of actin filaments, microtubules, and other cytoskeletal components. This process is integral for the morphological changes associated with mast cell degranulation and the release of inflammatory mediators [54,55]. Actin, a major cytoskeletal protein, undergoes rapid rearrangements upon mast cell activation. The activation of FcεRI induces the polymerization of actin filaments, leading to the formation of membrane protrusions and lamellipodia [54,56]. These structural changes facilitate the movement of secretory granules towards the cell membrane, a crucial step in the degranulation process. Simultaneously, microtubules, composed of tubulin subunits, undergo reorganization to support the transport of secretory granules within the cell. The cytoskeletal architecture is modified to create microtubule tracks that guide the movement of granules towards the plasma membrane. Microtubule reorganization is essential for the efficient release of granule contents during mast cell degranulation. The coordination of actin and microtubule dynamics is finely tuned during mast cell activation, highlighting the importance of molecular forces in orchestrating hypersensitivity reactions. These cytoskeletal rearrangements not only facilitate the mechanical processes of granule movement but also contribute to the overall structural changes associated with mast cell activation [54,55].

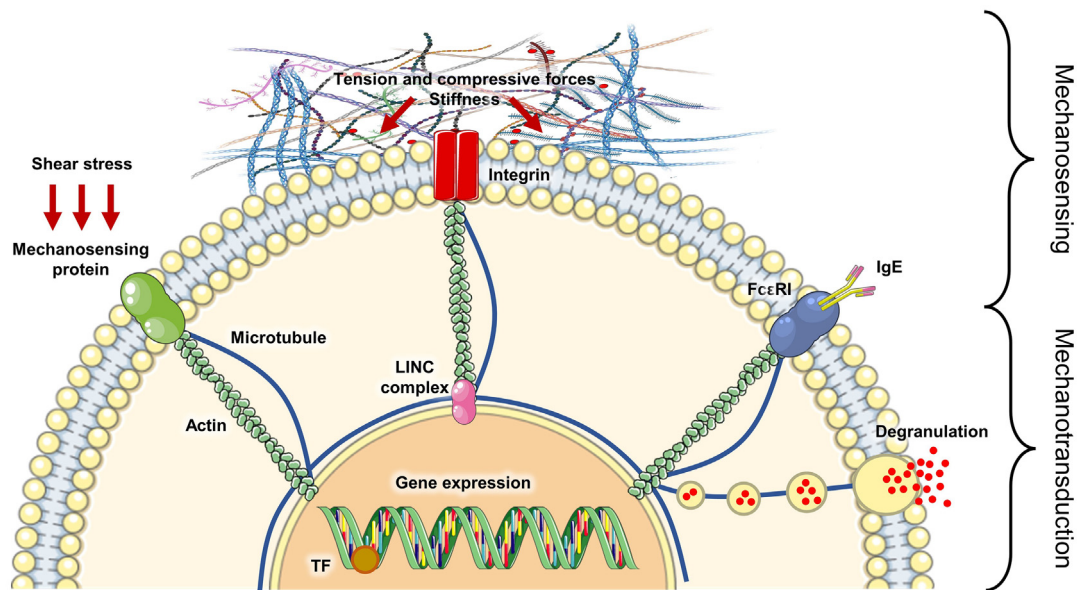


Fig. 2. Mechanobiology of mast cell activation and degranulation. Mechanical forces trigger the activation of mechanosensing proteins, integrins, and other mechanosensitive channels, resulting in rapid rearrangements of actin and microtubules. Simultaneously, exposure to presensitized allergens activates FcεRI, leading to mast cell degranulation. Furthermore, the mechanotransduction process can alter gene expression, thereby modulating the production of inflammatory cytokines. (IgE = immunoglobulin E; LINC = linker of nucleoskeleton and cytoskeleton; TF = transcription factor).

3.2. Role of molecular forces in degranulation

Degranulation involves the release of preformed mediators stored in granules, such as histamine, proteases, and various cytokines, leading to the characteristic symptoms of allergies [57]. The mechanical aspects of molecular forces play a critical role in regulating the efficiency and dynamics of granule release during hypersensitivity reactions [52]. The actin cytoskeleton is a key player in the mechanical orchestration of granule release. Upon mast cell activation, there is a rapid reorganization of actin filaments, creating a dynamic network that facilitates the movement of granules towards the cell membrane. This actin-based cytoskeletal rearrangement is crucial for the efficient fusion of granules with the plasma membrane, enabling the release of their contents into the extracellular space [54,55]. Microtubules, another component of the cellular cytoskeleton, contribute significantly to the mechanical forces driving granule release. They serve as tracks for intracellular transport, guiding the movement of granules towards the cell periphery. The reorganization of microtubules is essential for positioning secretory granules at the plasma membrane, ensuring a timely and precise release of mediators upon allergen exposure [54,58]. The process of granule exocytosis, where the granule membrane fuses with the plasma membrane, involves intricate mechanical events. Molecular forces generated by the actin cytoskeleton and microtubules facilitate the docking and priming of granules at the plasma membrane, culminating in the fusion event. This fusion allows for the controlled release of granule contents into the extracellular milieu, contributing to the inflammatory cascade characterizing hypersensitivity reactions [55,59,60].

Beyond granule release, molecular forces also play a vital role in modulating cytokine production during Type 1 hypersensitivity. Cytokines are key signaling molecules that orchestrate immune responses and contribute to the amplification and persistence of allergic reactions [61]. The mechanical forces exerted during mast cell activation impact signaling pathways involved in cytokine production. For instance, the activation of mechanosensitive receptors, such as integrins and IgE receptors, initiates intracellular signaling cascades that converge on pathways regulating cytokine gene expression [62,63]. The mechanical cues from the microenvironment influence the activation of transcription factors, such as NF-κB and AP-1, modulating the synthesis and secretion

of cytokines [64]. Cytoskeletal dynamics, particularly the reorganization of actin filaments, also contribute to cytokine secretion. Actin filaments are involved in the movement of cytokine-containing vesicles towards the cell membrane for exocytosis. The coordination of actin polymerization and depolymerization is crucial for the trafficking of cytokine vesicles, ensuring their timely release [54,55].

4. Extracellular matrix (ECM) remodeling in Type 1 hypersensitivity

4.1. ECM components involved in allergic reactions

Several key extracellular matrix (ECM) components, including collagen, fibronectin, and laminin, emerge as central players in orchestrating cellular interactions and signaling events associated with hypersensitivity reactions [65,66]. Collagen, a structural protein abundant in the ECM, contributes to the mechanical integrity of tissues and serves as a scaffold for cell adhesion. In allergic reactions, collagen can act as a ligand for integrins on immune cells, influencing their migration and activation [67–69]. Additionally, changes in collagen density and organization within the ECM can impact the biomechanical properties of tissues, influencing the behavior of immune cells during hypersensitivity responses [70]. Moreover, increased collagen deposition and cross-linking can occur, influencing tissue stiffness and creating a more restrictive microenvironment. This altered collagen composition can impact the mechanical cues perceived by immune cells, influencing their activation and migratory behavior during allergic responses [71].

Fibronectin is a multifunctional glycoprotein that mediates cell adhesion and participates in various cellular processes. Changes in fibronectin expression and organization also occur in allergic reactions. Increased fibronectin levels can enhance immune cell adhesion and migration, contributing to the infiltration of inflammatory cells into tissues. Additionally, proteolytic cleavage of fibronectin can generate bioactive fragments that modulate immune cell function and exacerbate hypersensitivity responses [72]. During allergic reactions, fibronectin interacts with integrins on immune cells, facilitating their adhesion to the ECM. This interaction not only influences immune cell migration but also modulates intracellular signaling pathways [62,69]. Fibronectin is also

involved in the formation of immune synapses, specialized structures that facilitate communication between immune cells and contribute to hypersensitivity responses [73,74].

Laminin, a glycoprotein with structural and signaling roles, is a crucial component of the ECM. It forms the basis of basement membranes, providing structural support to tissues. Laminin interacts with cell surface receptors, including integrins, influencing cell adhesion, migration, and differentiation [69]. Modifications in laminin composition and distribution further contribute to the altered ECM landscape during hypersensitivity reactions. These changes can impact the integrity of tissue barriers, influencing the entry of allergens and immune cells into target tissues. Disruptions in laminin-mediated signaling can also affect immune cell behavior, contributing to the perpetuation of allergic responses [75,76].

4.2. Impact of ECM stiffness on cellular responses

ECM is not merely a structural scaffold; its mechanical properties, particularly stiffness, profoundly influence cellular behavior across diverse physiological processes. In the context of allergic reactions and Type 1 hypersensitivity, the stiffness of the ECM exerts a decisive impact on various cell types, modulating their behavior and functionality [77]. ECM stiffness acts as a regulator of cell adhesion and migration. Cells, including immune cells involved in hypersensitivity reactions, sense and respond to the mechanical properties of their microenvironment. As ECM stiffness increases, cells often exhibit enhanced adhesion and slower migration [78,79]. This altered behavior can influence the recruitment and retention of immune cells at sites of allergic inflammation, contributing to the perpetuation of hypersensitivity responses [79]. Cellular responses to allergens and inflammatory cues are further influenced by ECM stiffness. Studies have demonstrated that changes in substrate stiffness can impact the proliferation and differentiation of immune cells [19]. For example, increased ECM stiffness has been associated with enhanced T cell activation and proliferation, potentially contributing to the amplification of immune responses in allergic reactions [80]. Persistent alterations in ECM stiffness can drive tissue remodeling and fibrosis, hallmark features of chronic allergic diseases. In conditions such as asthma, prolonged exposure to allergens can induce ECM remodeling, leading to increased tissue stiffness. This altered mechanical microenvironment can drive aberrant wound healing responses, contributing to the development of fibrosis and structural changes in affected tissues [77,81,82].

The stiffness of the ECM influences various aspects of immune cell behavior, shaping the dynamics of hypersensitivity reactions. Mast cells are highly responsive to changes in ECM stiffness. Studies have shown that alterations in substrate stiffness can modulate mast cell activation and degranulation [79,83]. Increased stiffness has been associated with heightened mast cell responses, leading to enhanced release of inflammatory mediators such as histamine [84]. T cells, central orchestrators of immune responses, are also influenced by ECM stiffness. The formation of immune synapses is sensitive to the mechanical properties of the microenvironment. Changes in ECM stiffness impact the stability and dynamics of immune synapse formation, influencing T cell activation and cytokine production during hypersensitivity reactions [85]. Macrophages, with their diverse functions in inflammation and tissue repair, are sensitive to ECM stiffness cues. Stiffer matrices can induce a pro-inflammatory phenotype in macrophages, influencing their cytokine secretion and tissue remodeling activities. The altered behavior of macrophages in response to changes in ECM stiffness contributes to the complex immunological milieu in allergic diseases [86–88].

5. Specific mechanosensitive pathways in Type 1 hypersensitivity

Type 1 hypersensitivity reactions, orchestrated by intricate immune responses, are now being recognized as dynamic processes influenced by

mechanosensitive pathways. The mechanobiological aspects of hypersensitivity involve the activation of specific signaling cascades, including the Mitogen-Activated Protein Kinase (MAPK) pathway, Rho GTPases, and Integrins with focal adhesion signaling.

The MAPK pathway, an evolutionarily conserved intracellular signaling cascade, plays a pivotal role in translating extracellular mechanical signals into cellular responses during Type 1 hypersensitivity [89,90]. Upon allergen exposure, the activation of mechanosensitive receptors, such as integrins, triggers the activation of MAPK signaling components. The MAPK pathway comprises three main kinases: extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK [9,91,92]. These kinases modulate cellular functions by phosphorylating downstream targets, influencing gene expression, and regulating cellular responses. In the context of Type 1 hypersensitivity, the MAPK pathway can amplify immune responses, leading to enhanced degranulation of mast cells and the release of pro-inflammatory mediators [93–96].

Rho GTPases, a family of small G proteins, act as molecular switches in cellular processes such as cytoskeletal dynamics, cell migration, and vesicle trafficking [9,97]. In Type 1 hypersensitivity, Rho GTPases contribute to the mechanotransduction process by responding to mechanical cues [98]. Upon allergen exposure, the activation of receptors on the cell surface, including IgE receptors and integrins, can stimulate Rho GTPases. Rho GTPases, particularly RhoA, Rac1, and Cdc42, modulate the organization of the actin cytoskeleton and influence cell morphology and motility [98,99]. In the context of hypersensitivity reactions, the activation of Rho GTPases can enhance the migratory capacity of immune cells, facilitating their recruitment to the site of allergen exposure [100]. Moreover, Rho proteins can regulate mast cell activation and degranulation through cytoskeletal remodeling required for granule exocytosis [101].

Integrins, cell surface receptors that mediate adhesion to the ECM, are crucial players in mechanosensing during Type 1 hypersensitivity (Fig. 2) [62,102]. These receptors form focal adhesions, dynamic structures that link the ECM to the actin cytoskeleton, thereby transmitting mechanical signals into the cell. Upon allergen-induced cross-linking of IgE antibodies and subsequent activation of mast cells, integrins participate in focal adhesion signaling [62,103]. This activation triggers a cascade of events, including the recruitment of focal adhesion kinase (FAK) and the assembly of focal adhesion complexes. FAK, in turn, phosphorylates downstream effectors, contributing to cytoskeletal rearrangements and the activation of signaling pathways such as MAPK [104]. The integrin-mediated focal adhesion signaling not only influences the immediate degranulation of mast cells but also contributes to the modulation of immune cell behavior, including migration and cytokine release [105,106]. Integrins serve as crucial hubs in the mechanosensitive network during hypersensitivity reactions, translating mechanical cues from the microenvironment into biochemical responses.

Basophils share similarities with mast cells, including the expression of FcεRI and the ability to release histamine. The mechanosensitive pathways of basophils, however, has been less studied. Recent findings suggested that like mast cells, basophils might also possess mechanosensitive channels that contribute to their activation and degranulation during allergic responses [107]. Meanwhile, the mechanosensitivity of eosinophils, particularly in the context of migration through the extracellular matrix in tissues, is an area of ongoing research. Studies suggest that eosinophils can respond to mechanical cues in their environment, which may influence their behavior during an allergic response [108]. In addition to mast cells, basophils and eosinophils, other immune cells such as T cells and dendritic cells also exhibit mechanosensitive behaviors that can influence the allergic response. T cells, for instance, can modulate their response based on the stiffness of the antigen-presenting cells they interact with. Dendritic cells, which present allergens to T cells, also respond to mechanical cues in their environment, which can affect their maturation and antigen-presenting capabilities [108].

6. Potential experimental models and techniques

6.1. Experimental models for studying mechanobiology in Type 1 hypersensitivity

Experimental models play a crucial role in unraveling the biomechanical dynamics underlying allergic reactions, offering insights that transcend conventional immunological approaches. *In vitro* cell culture models form the cornerstone of mechanobiological investigations, providing a controlled environment for studying cellular responses to mechanical cues. Cultured mast cells, primary immune cells, and cell lines representing key players in hypersensitivity reactions offer a platform for dissecting the impact of mechanical forces on cellular behavior. These models enable the manipulation of substrate stiffness, allowing researchers to mimic the physiological range of tissue mechanics and study how variations influence mast cell activation, degranulation, and cytokine production [109,110]. Next, moving beyond traditional two-dimensional cell cultures, three-dimensional (3D) models provide a more realistic representation of tissue architecture and mechanics. 3D culture systems, such as spheroids and organoids, allow the examination of immune cell responses within a microenvironment that better recapitulates the *in vivo* setting. These models enable the exploration of ECM remodeling, cell–cell interactions, and the impact of mechanical forces on mast cell behavior in a more physiologically relevant context [111–114].

Engineered tissue models provide a sophisticated platform for studying mechanobiology in a controlled and customizable environment. Incorporating mast cells, immune cells, and relevant ECM components, these models enable the recreation of specific aspects of allergic reactions. Biomechanical parameters, such as tissue stiffness and elasticity, can be precisely tuned to mimic pathological conditions. Engineered tissue models allow researchers to explore the mechanosensitive aspects of mast cell activation, degranulation, and immune cell interactions within a more biomimetic setting [115].

Animal models, particularly rodents, remain invaluable for studying Type 1 hypersensitivity and offer a more holistic view of the immune response. Allergen-challenge models involve the sensitization and subsequent exposure of animals to allergens, leading to hypersensitivity reactions. Incorporating biomechanical assessments, such as measuring lung tissue stiffness or analyzing airway mechanics, enhances these models. This approach allows researchers to investigate how changes in tissue mechanics contribute to the progression and severity of allergic responses [110,116]. Additionally, advancements in *in vivo* imaging techniques, such as intravital microscopy, facilitate the real-time visualization of cellular dynamics within living organisms. These approaches provide a window into the mechanobiological events occurring during Type 1 hypersensitivity reactions in intact tissues. *In vivo* imaging allows the tracking of immune cell migration, interactions, and responses to mechanical forces in real-time, offering dynamic insights into the spatiotemporal aspects of allergic reactions [117–119].

6.2. *In vitro* systems and tools for assessing cellular forces

Confocal microscopy is a powerful imaging technique that allows for high-resolution visualization of cellular structures and dynamics. In the context of Type 1 hypersensitivity, confocal microscopy can be employed to study the spatial distribution of immune cells, the dynamics of mast cell degranulation, and the interaction between cells and the ECM [120, 121]. Fluorescent labeling of specific cellular components provides detailed insights into the mechanosensitive events at the subcellular level [122,123]. Multiphoton microscopy extends the capabilities of traditional fluorescence microscopy, enabling deep tissue imaging with reduced photodamage. This technique is particularly valuable for studying immune cell behavior in 3D environments, such as engineered tissues or microfluidic systems. Multiphoton microscopy allows researchers to visualize cellular responses to mechanical forces in more physiologically relevant contexts, providing a dynamic understanding of

allergic reactions [124,125]. Atomic force microscopy (AFM) is a versatile tool that combines high-resolution imaging with force measurement capabilities. It allows the mapping of mechanical properties of cells and tissues, offering insights into stiffness, adhesion, and deformability. AFM can be applied to study the mechanical changes in mast cells, assess the impact of allergen exposure on cell elasticity, and investigate the interactions between immune cells and ECM components [114].

Magnetic tweezers utilize magnetic fields to apply controlled forces to paramagnetic beads bound to cells. This technique allows researchers to exert precise mechanical forces on immune cells and investigate their responses. In Type 1 hypersensitivity studies, magnetic tweezers can be employed to simulate the mechanical aspects of allergen binding to immune cells, providing insights into the force-dependent activation of mast cells and other immune cell types [114]. Microfabricated devices equipped with biosensors offer a platform for assessing cellular forces in a controlled environment. These devices can be designed to measure forces exerted by immune cells during processes such as adhesion, migration, and degranulation. By integrating biosensors with microfabricated systems, researchers can gain real-time, quantitative information on the mechanical aspects of immune cell responses in Type 1 hypersensitivity [126]. Optical tweezers utilize highly focused laser beams to trap and manipulate microscopic objects, including cells. In the context of hypersensitivity reactions, optical tweezers can be employed to exert controlled forces on individual cells or cellular components. This approach enables the investigation of force-dependent processes, such as the mechanical aspects of allergen-antibody interactions and the impact of mechanical forces on immune cell activation [114,127].

7. Clinical promises of understanding the mechanobiology of Type 1 hypersensitivity

Understanding mechanobiological pathways in Type 1 hypersensitivity has opened new frontiers for therapeutic interventions. Targeting these pathways holds promise for developing precision therapies that address the biomechanical aspects of allergic responses. For instance, inhibitors of specific mechanosensitive receptors, such as integrins or receptors involved in mast cell activation, may emerge as novel therapeutics [128,129]. Modulating the mechanical microenvironment, either by altering ECM stiffness or manipulating cellular forces, represents another avenue for intervention. Strategies targeting downstream signaling cascades influenced by mechanobiological cues may also hold potential. By designing therapies that account for the dynamic interplay between mechanics and immune responses, the field is poised to revolutionize allergy treatment with more effective and targeted approaches.

Identifying robust biomarkers is critical for monitoring and predicting allergic responses, and mechanobiology research provides a rich source of potential candidates. Biomarkers that reflect alterations in cellular forces, such as changes in cell stiffness or adhesion properties, could offer insights into the severity and progression of allergic reactions [130]. Additionally, monitoring the expression and activation of mechanosensitive receptors on immune cells may serve as indicative biomarkers. As our understanding of the mechanobiological landscape deepens, the identification and validation of such biomarkers will play a pivotal role in developing diagnostic tools for more precise and personalized allergy management.

While the potential for translating mechanobiology research into clinical applications is immense, several challenges must be addressed to realize these promises. First, translating findings from controlled *in vitro* settings to the complex *in vivo* environment poses challenges. The intricate interactions within tissues, the influence of systemic factors, and the dynamic nature of immune responses in living organisms present hurdles that require innovative solutions. Second, establishing standardized methods for assessing mechanobiological parameters is crucial for robust and reproducible research. Variability in experimental setups, measurement techniques, and data analysis can hinder the comparability of results across studies. Third, successful translation necessitates the collaboration of researchers from diverse disciplines, including immunology,

biomechanics, and clinical medicine. Integrating these perspectives is essential for developing comprehensive approaches that address the multifaceted nature of allergic reactions. Fourth, interventions targeting mechanobiological pathways should be pursued with rigorous ethical considerations and safety assessments. Ensuring the well-being of patients and minimizing potential risks associated with manipulating cellular forces or the ECM is paramount. Fifth, conducting longitudinal studies and clinical trials that span diverse patient populations is essential for validating mechanobiology-based interventions. Understanding the long-term effects, patient variability, and the impact on disease outcomes will be crucial for establishing the clinical efficacy of these approaches. Finally, identifying patient subgroups based on mechanobiological profiles and developing personalized treatment approaches is a complex task. It requires the integration of molecular, cellular, and biomechanical data to tailor interventions to individual patient needs.

8. Summary

Recent mechanobiological studies in Type 1 hypersensitivity have unearthed critical insights into the interplay between cellular forces and immune responses. Investigations employing advanced *in vitro* systems, microscopy techniques, and force measurement methods have elucidated the dynamic mechanics of mast cell activation, immune cell interactions, and the impact of extracellular matrix stiffness. Key findings include the role of mechanosensitive receptors, such as integrins, in orchestrating allergic reactions, and the influence of ECM alterations on cellular behavior. Additionally, force-dependent processes like mast cell degranulation and cytokine production have been illuminated, shedding light on the biomechanical intricacies of hypersensitivity responses. These mechanobiological insights offer transformative implications for understanding and treating Type 1 hypersensitivity. With a multidisciplinary approach, the field of mechanobiology in allergy beckons researchers to unravel more secrets, translate discoveries into clinical applications, and sculpt the future of allergy management.

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Ethical statement

This study does not contain any studies with human or animal subjects performed by any of the authors.

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During the preparation of this work the author used ChatGPT version 3.5 in order to improve readability and language. After using this tool/service, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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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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