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Immune Cell Membrane Protrusions as Sensory Organelles

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Keywords

immune cell protrusions, membrane curvature, actin cytoskeleton, mechanosensing, immune synapse formation, cell migration

Abstract

Immune cells possess a remarkable set of complementary surface protrusions, such as microvilli, podosomes, filopodia, and lamellipodia, which play pivotal roles in the sensing of and responding to varied environmental cues. These dynamic structures maximize the surface area–to–volume ratio of immune cells, which in turn enhances cell–cell and cell–matrix interactions, while generating pulling and pushing forces, allowing immune cells to integrate biochemical and physical cues from their surroundings. This review discusses recent insights into the structures and dynamics of different protrusions, the molecular machinery behind mechanosensing, the differential role of protrusions for different subsets of immune cells, and the cutting-edge technology that has advanced our understanding of those protrusions.

Contents

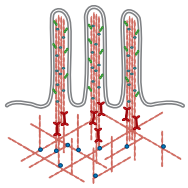
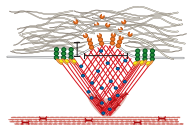
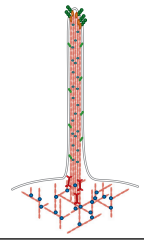
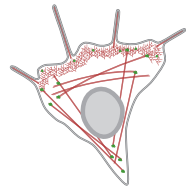
1. STRUCTURE AND DYNAMICS BEHIND MEMBRANE PROTRUSIONS

Immune cells employ a diverse range of highly dynamic, actin-rich membrane protrusions—namely microvilli, podosomes, filopodia, and lamellipodia—to interact with their surroundings and enable cell environmental sensing and migration. Super-resolution and live-cell imaging technology, such as light sheet microscopy (Cai et al. 2017, 2022), revealed not only the nanoscale architecture of these projections but also their ability to rapidly extend and retract in response to various stimuli in a highly dynamic fashion (Chamaraux et al. 2008, Orbach & Su 2020). Their distinct structures and dynamics are key to fulfilling complementary roles in gathering and integrating biochemical and mechanical information. Furbished with various receptors, these protrusions can serve as cell-specific detectors for antigens or bacterial recognition (Cai et al. 2017, Labernadie et al. 2014, Möller et al. 2013, Zhang et al. 2020). The actin cytoskeleton forms a shared core structure in these protrusions, consisting of either branched or bundled actin filaments, that guides their formation, maintenance, and retraction, thereby defining their functionality over time. Actin polymerization can create pushing forces, while actin–myosin contraction can create pulling forces. The dynamic changes in shape, size, and volume have mechanical implications and alter not only membrane area but also membrane curvature and tension, which affects clustering and conformational changes of proteins, influencing intracellular signaling and subsequently immune cell functions (Du et al. 2023, Huse 2017). Sections 1.1–1.4 describe the structural and dynamic particularities of different protrusions (also summarized in **Table 1** and illustrated in **Figure 1**).

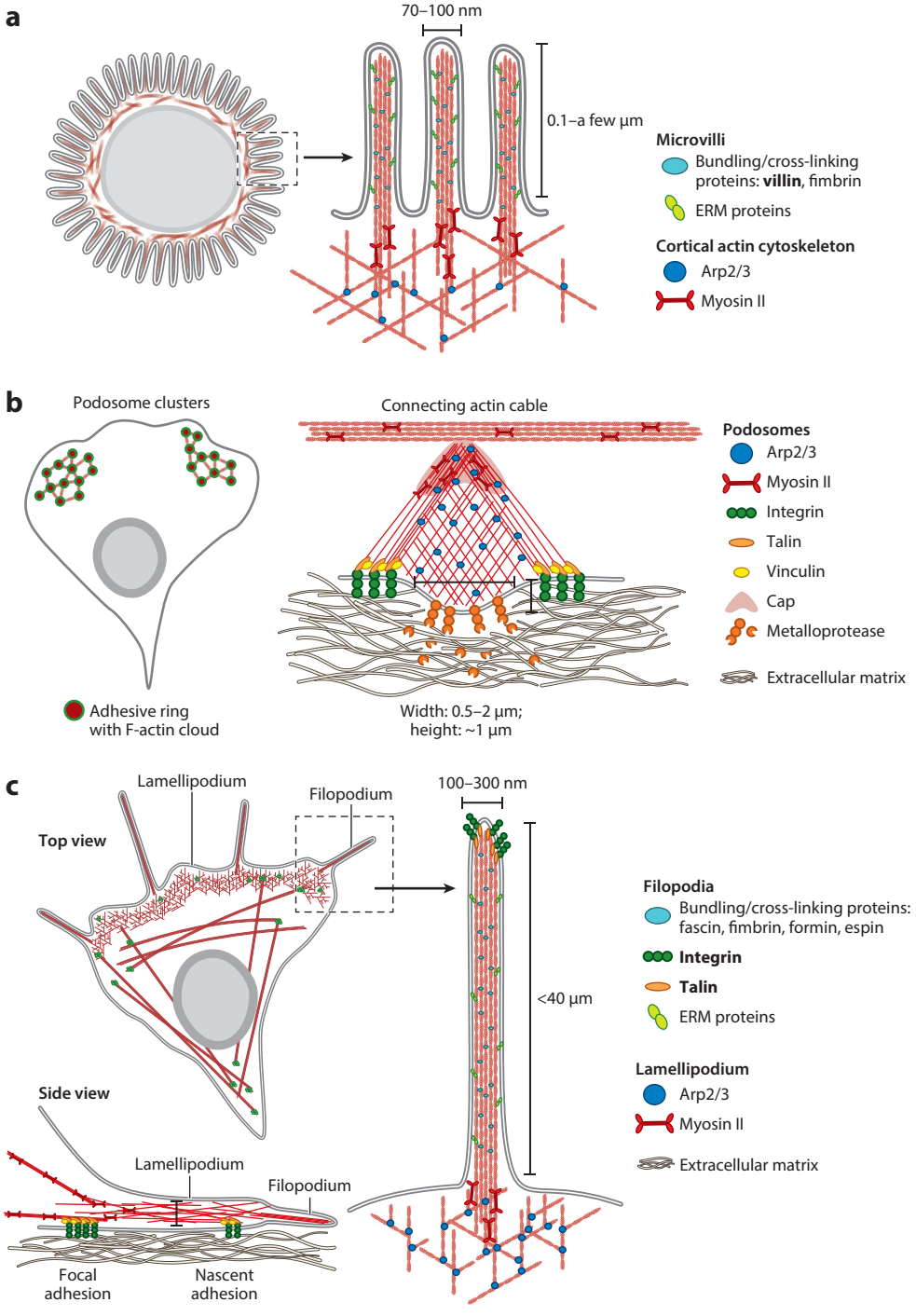
1.1. Microvilli

Microvilli measure typically 70–100 nm in diameter and 0.1 up to a few micrometers in length, and their number per surface area varies depending on cell type, cell function, and cell activation

Table 1 Overview of the different membrane protrusions used by leukocytes

Parameter/property	Microvilli	Podosomes	Filopodia	Lamellipodia
				
Cell type	T cells, B cells, NK cells, DCs	Macrophages, DCs, T cells, B cells, NK cells	T cells (migration/ activation), DCs, NK cells, macrophages	T cells, DCs, NK cells (during migration), B cells
Key components	Unidirectional actin filaments, ERM proteins, fimbrin	Actin, Arp2/3, integrins (β2), talin, vinculin, WASP, cortactin	Unidirectional actin filaments, Ena/VASP, formins, fascin, fimbrin, talin	Actin, Arp2/3 complex, WAVE complex, integrins, WASP, talin, vinculin
Stimulating factors	Constitutive in immune cells	Stiffness of ECM, antigen recognition, TCR engagement, immune synapse formation	Cell activation, migration, chemotaxis, TCR engagement	Migration, chemotaxis, cell activation
Structure	Cross-linked actin filament bundle, integrin anchored with ERM proteins, PIP_2 anchored with villin	Actin-rich core surrounded by adhesion proteins (e.g., integrins, talin)	Finger-like projections containing cross-linked actin filament bundle, integrin anchored with ERM proteins	Broad, sheetlike actin network, Arp2/3 complex regulated
Size	Diameter: 70–100 nm Length: 100 nm to a few micrometers	Width: 0.5–2 μm Height: ~1 μm	Diameter: ~0.1–0.3 μm Length: <40 μm	Diameter: 0.1–0.2 μm Width: 2–10 μm Length: depends on migration requirements
Lifetime	Dynamic (lateral movements), more stable than filopodia	Short-lived, ~5–15 min during immune synapse and migration	Highly dynamic, seconds to minutes	Dynamic, continually forming and retracting
Main functions	Increasing surface area, antigen scanning, force generation, immune surveillance	ECM binding and degradation, force generation, mechanosensing	Probing environment, transient ECM binding, guiding migration, signaling, force generation	Cell migration, stable ECM adhesion, force generation, environmental sensing
Cell-specific functions	Enhancing antigen scanning, expanding interaction area	Synapse stability, TCR signaling support, mechanotransduction, ECM degradation	Exploration during migration guidance	Promoting directional migration, synapse formation
Physiological functions	Antigen scanning, immune synapse interaction	APC–T cell contact stabilization, TCR signaling enhancement, ECM degradation	Migration guidance, synapse formation	Migration, adhesion, and directional sensing support
Mechanical force creation	Tensile and pushing forces during antigen scanning, pulling antigens	Actomyosin contraction via integrin engagement with the ECM, myosins	Actin polymerization at leading edge, traction forces	Actin polymerization generates protrusive forces
Associated genetic disorders	Celiac disease, microvillus inclusion disease	Wiskott–Aldrich syndrome (WASP defects)	Wiskott–Aldrich syndrome (affects filopodia formation)	Wiskott–Aldrich syndrome (affects migration and function)

Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; ECM, extracellular matrix; ERM, ezrin, radixin, moesin; NK, natural killer; PIP_2, phosphatidylinositol 4,5-biphosphate; TCR, T cell receptor; WASP, Wiskott–Aldrich syndrome protein.



(*Caption for* ***Figure 1*** *appears on following page*)

Figure 1 (*Figure appears on preceding page*)

Structural features and key components of membrane protrusion. The figure illustrates the structural organization, dimensions, and molecular composition of various membrane protrusions critical for immune cell function; details are summarized in **Table 1**. (*a*) Immune cell with actin-rich microvilli protrusions extending from the cortical actin cytoskeleton. Close-up shows F-actin cores and associated binding proteins within individual microvilli. (*b*) Migrating immune cell displaying podosomes, characterized by adhesive ring structures surrounding F-actin-rich cores (F-actin clouds). Close-up reveals architecture of podosomes and their role in extracellular matrix degradation via metalloproteases. (*c*) Migrating immune cell displaying the branched versus bundled actin cytoskeleton and adhesion sites of the lamellipodium and filopodia extending from the lamellipodium, shown in top and side views. Close-up shows bundled actin cores in filopodia versus the branched actin network in the lamellipodium, along with associated proteins. Abbreviation: ERM, ezrin, radixin, moesin; F-actin; filamentous actin.

stage (Jung et al. 2016, Kim & Jun 2019, Majstoravich et al. 2004). Epithelial cells, for example, often have longer and denser microvilli to maximize absorptive capacity, whereas T cells, B cells, and dendritic cells (DCs) may have shorter and more flexible microvilli suited for antigen scanning on antigen-presenting cells (APCs) (Al-Aghbar et al. 2022, Alexander et al. 1976, Sauvanet et al. 2015).

In microvilli of epithelial cells, villin is a key regulator of bundling, nucleation, capping, and severing of actin filaments (Khurana & George 2008). Via its three phosphatidylinositol 4,5-biphosphate (PIP_2) binding sites, villin anchors the actin filament bundle to the inner side of the plasma membrane (Kim & Jun 2019, Kumar et al. 2004). In leukocytes, the assembly of microvilli is instead regulated by ERM family members (ezrin, radixin, moesin), linking the cortical filamentous actin (F-actin) cytoskeleton to the plasma membrane (García-Ortiz & Serrador 2020) (**Figure 1*a***; **Table 1**). Moreover, cross-linking of the actin filaments by fimbrin makes the structure unipolar, essential for the creation of pushing forces at the tip during actin polymerization (Volkmann et al. 2001). Actin polymerization and depolymerization make the filaments highly dynamic so that they can extend within seconds to millisecond timescales, enabling T cells to explore multiple regions of the APC surface and identify antigens in as little as 5–30 s (Cai et al. 2017). Recent cutting-edge imaging studies traced microvilli dynamics in real time, showing that they exhibit lateral mobility on the plasma membrane that allows them to optimize contact with APCs (Cai et al. 2017, 2022) and enable exertion of small traction forces (Aramesh et al. 2021, Barbieri et al. 2021). Although microvilli are relatively short compared to filopodia (Jung et al. 2016, Mattila & Lappalainen 2008), their high density creates a large overall surface area, increasing the cell's surface area–to–volume ratio (Fisher et al. 2008, Gorelik et al. 2003, Majstoravich et al. 2004, Sauvanet et al. 2015) (see **Table 1**). This expanded surface area is essential for cells that rely on intensive interaction with their environment for optimal function. Together, these characterizations enable the cells to detect both biochemical and physical cues efficiently, enabling a swift and efficient immune response.

1.2. Podosomes

Podosomes, in contrast to microvilli, are larger, more stable structures and are involved in extracellular matrix (ECM) adhesion, degradation, and cell migration (**Figure 1*b***; **Table 1**). Furthermore, they act as sensory platforms, enabling immune cells to probe the mechanical properties of the surrounding ECM (van den Dries et al. 2019). Podosomes are longer-lived than microvilli, persisting for 30 s to 14 min (Destaing et al. 2003). Their actin cores and associated myosin II contractile forces allow immune cells to generate pressure in the center of the integrin ring onto the ECM (see the middle panel in **Figure 1*b***; **Table 1**), sensing its stiffness and other physical characteristics (Linder & Wiesner 2016). This slower, sustained interaction is essential for processes like tissue

remodeling and migration through dense tissue, where the mechanical properties of the substrate guide immune cell behavior (Gaertner et al. 2022, Lee et al. 2022, Linder & Wiesner 2016). While podosomes are more commonly associated with macrophages and DCs (Gaertner et al. 2022, Lee et al. 2022, van den Dries et al. 2019), emerging evidence suggests that Wiskott–Aldrich syndrome protein (WASP)-dependent structures similar to podosomes form transiently in T cells under conditions of confinement, pushing against obstructing barriers and probing cells for antigens (Gaertner et al. 2022, Kumari et al. 2015, Sage et al. 2012). Notably, the probing of flat, stiff substrates for antigens, which constrains podosome formation, still has functional consequences even without the full development of protrusions (Sage et al. 2012).

1.3. Filopodia

Filopodia extend farther out than microvilli and are specialized for long-range environmental exploration. These slender, finger-like projections, typically extending from the lamellipodial and lamellar actin networks, are found on the surface of various cell types, including macrophages and DCs (**Figure 1*c***; **Table 1**). They range in size, typically measuring 0.1–0.3 μm in diameter and extending up to 40 μm in length, allowing immune cells to efficiently survey large areas (Mattila & Lappalainen 2008). To maintain stability of these slender structures, the actin filaments in filopodia are cross-linked by proteins such as fascin, espin, fimbrin, and formin, creating a unipolar actin bundle (Mellor 2010, Schirenbeck et al. 2005, Vignjevic et al. 2003, Volkmann et al. 2001). Rapid extension and retraction of these dynamic structures, allow immune cells to rapidly adjust their interactions with the ECM and other cells, facilitating processes like antigen capture, migration, and immune synapse formation (Mattila & Lappalainen 2008). Once a contact is created, the lifetime of the filopodium is increased by tensile forces generated by the cortical actin network as the cell tries to retract the filopodium (Bornschlögl et al. 2013, Möller et al. 2013). Furthermore, these stabilized interactions with the ECM via integrin and talin allow immune cells to exert small traction forces to test physical properties of the ECM (Jacquemet et al. 2015, Miihkinen et al. 2021, Tu et al. 2022), guiding directional movement through adhesive contacts at their tips (Jacquemet et al. 2015, Möller et al. 2013).

1.4. Lamellipodia

Lamellipodia are broad, sheetlike extensions of the cell membrane (0.1–0.2 μm thick) (Abercrombie et al. 1971) primarily made up of dense, branched networks of actin filaments just beneath the cell surface. Lamellipodia are commonly found in motile cells, such as fibroblasts, epithelial cells, and immune cells. They play a vital role in migration, adhesion, and environmental sensing (Case & Waterman 2015). They form through continuous assembly and disassembly of actin, known as treadmilling. Actin polymerization at the leading edge pushes the membrane forward, while nascent adhesion sites limit retrograde flow (Krause & Gautreau 2014, Pollard & Borisy 2003). These adhesions anchor the actin cytoskeleton of the lamellipodium to the ECM through integrins and via adaptor proteins like talin and vinculin (Vicente-Manzanares et al. 2009). Maturation of these adhesion sites into stable focal adhesions provides the traction necessary for the cell to pull its body forward (**Figure 1*c***; **Table 1**).

The rapid and adaptable nature of lamellipodia and the filopodia protruding from them enables cells to sense and respond to physical and biochemical cues in their environment (Krause & Gautreau 2014, Mastrogiovanni et al. 2020). They direct migration and allow the cells to navigate through complex tissue through continuous surface interactions, for example, for extravasation and tissue invasion during immune surveillance (Gaertner et al. 2022, Song et al. 2014).

2. SCALING LAWS FOR IMMUNE CELL SENSING VIA SURFACE PROTRUSIONS

As immune cells exploit different types of surface protrusions—all of which differ in diameter, length, and dynamics—to gather critical biochemical and mechanical information, it is important to quantitatively learn how they function individually and cooperate with each other. Designing biomimetic systems that replicate these interactions requires a deep understanding of how different physical forces and effects scale at the size of immune cells, which typically have a radius less than 25 μm. This scaling affects how immune cells gather, process, and respond to information (Discher et al. 2005, Vogel & Sheetz 2006). A higher surface area–to–volume ratio is essential for optimizing their ability to sample and interact with their environment. For example, surface protrusions, such as microvilli on T cells, enhance this ratio by providing a greater surface area without significantly increasing cellular volume. These structures allow T cells to maximize their contact points with APCs and scan a larger area for potential antigenic information at low energy costs while maintaining minimal metabolic activity and resource demands until antigen encounter (Buck et al. 2015, Cai et al. 2017, Fritzsche et al. 2017).

While universal physical forces apply to all objects, their relative influence changes significantly at the cellular scale. Forces such as mass, inertia, and heat capacity scale with volume (L^3, where L is the characteristic length), whereas surface forces, fluid drag, and friction scale with surface area (L^2). Consequently, the surface area–to–volume ratio becomes crucial for immune cells, dramatically increasing as their size decreases to the cellular level (Safran 2018). The Reynolds number—which scales with L and represents the ratio of inertial to viscous forces—further helps define how immune cells experience fluid dynamics. Due to their small size, immune cells operate at low Reynolds numbers, where viscous forces dominate (Rapp 2017). Under these flow conditions, immune cells must adapt by exerting greater forces to overcome fluid drag forces, for example, while initiating and stabilizing adhesive interactions during extravasation. Surface protrusions, such as microvilli, enable cells to probe for ligands and establish stable adhesions even under viscous flow forces by increasing their surface area, enhancing ligand scanning along the endothelium, and distributing forces across multiple adhesion points to resist fluid drag (Harrison et al. 2019).

Additionally, these structures enable cells to generate frictional forces for efficient crawling and adhesion in crowded tissues. Protrusions, with their high surface area–to–volume ratio, optimize sensory capabilities and adhesion while minimizing energy expenditure, crucial for rapid and effective immune responses (Discher et al. 2005, Yi et al. 2012, Zhang et al. 2020) as well as their metabolism (Buck et al. 2015, O'Neill et al. 2016, Schuster et al. 2021).

3. MECHANOSENSORY TOOLBOX

3.1. Mechanosensing

Mechanosensing, or mechanotransduction, is a process by which cells detect and convert mechanical cues, like pressure or stiffness, into biochemical signals regulating their behavior. Immune cells rely on mechanosensing to navigate tissues, detect antigens, and coordinate responses. For instance, T cells use mechanical forces to engage their receptors and initiate activation (Jenkins et al. 2023, Suzuki et al. 2007) (**Figure 2*a***), while other immune cells, such as macrophages, sense tissue stiffness to guide the immune response (Meli et al. 2020).

Key players in mechanosensing include adhesion molecules, ion channels, and cytoskeletal components, which work together to interpret physical signals and adjust cellular functions. This ability is critical for immune defense and maintaining health, as highlighted by studies of cellular force sensing and cytoskeletal dynamics (Case & Waterman 2015, Discher et al. 2005, Jeffreys et al. 2024, Vogel & Sheetz 2006, Zhang et al. 2020).

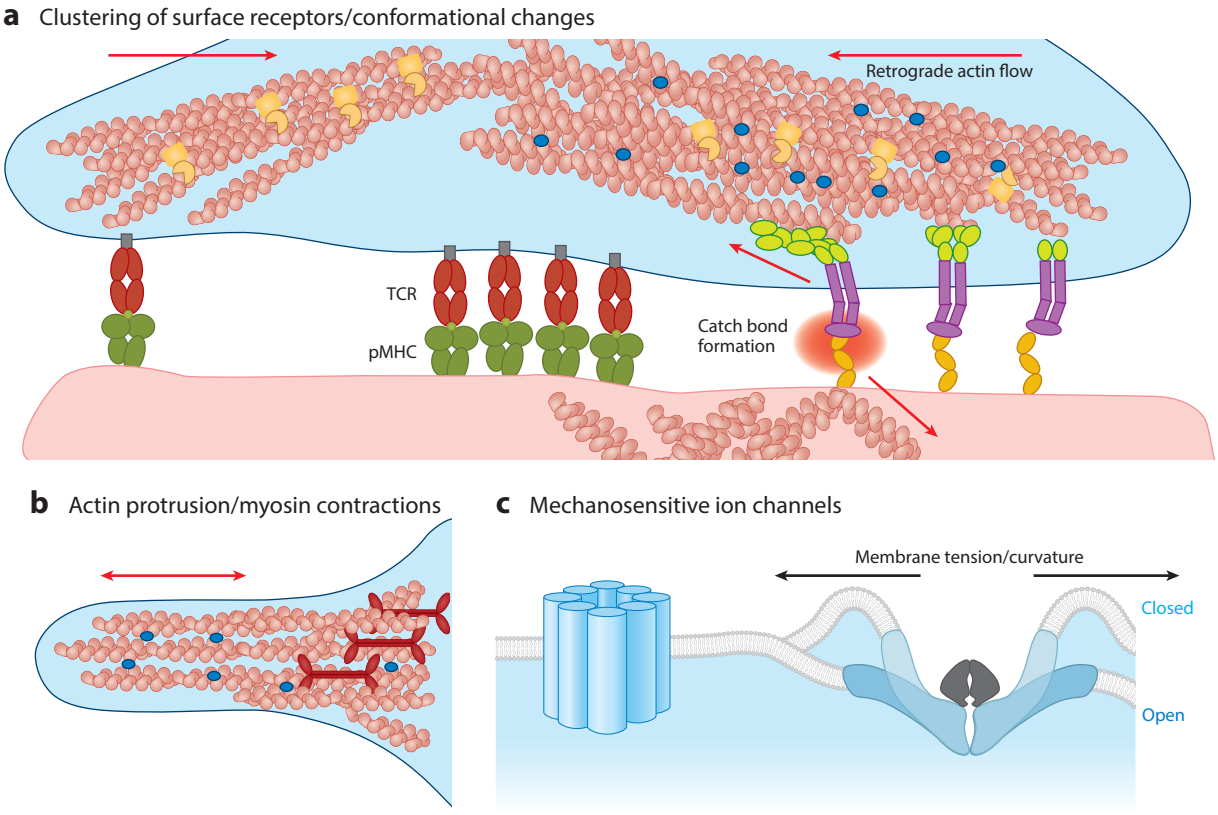


Figure 2

Mechanotransduction in immune cells through surface protrusions and force-dependent mechanisms. (*a*) Clustering of surface receptors and force-regulated conformational changes. Clustering of receptors such as T cell receptors (TCRs) during interactions with peptide–major histocompatibility complexes (pMHCs) facilitates T cell signaling. Retrograde actin flow generates mechanical forces that stabilize receptor–ligand interactions through catch bond formation. This process is reinforced by the counterpart of the antigen-presenting cell's (APC) cytoskeleton, enhancing TCR signaling and improving antigen discrimination. (*b*) Actin protrusions and myosin contractions. Protrusive forces generated by actin polymerization and retraction forces from myosin II–mediated contraction enable immune cells to probe and engage with their environment dynamically. These forces are critical for antigen scanning, immune synapse formation, and migration. (*c*) Mechanosensitive ion channels. Membrane tension and curvature activate mechanosensitive ion channels, such as Piezo channels, which convert mechanical stimuli into biochemical signals. This activation allows cells to sense mechanical changes in their environment and modulate intracellular responses.

For leukocytes, mechanosensing in tissues via protrusions such as lamellipodia and podosomes is driven largely by integrins on the immune cell surface that transmit mechanical signals to the actin cytoskeleton upon binding to ECM proteins like fibronectin and collagen (van den Dries et al. 2019). Integrin-mediated mechanotransduction is essential for sensing ECM stiffness, connecting external forces to internal pathways that control adhesion, migration, and ECM remodeling (Engler et al. 2006, Vogel & Sheetz 2006). Force is generated by myosin II and actin retrograde flow coupled to the ECM through adhesion complexes. Under force, talin, a mechanosensitive adaptor protein that links integrins to the actin cytoskeleton, stretches, exposing vinculin binding sites that stabilize the integrin–actin linkage, reinforcing the adhesion (Elosegui-Artola et al. 2018, Sun et al. 2016). Phosphorylation by the focal adhesion kinase (FAK) further connects mechanical cues to downstream signaling pathways that support cell survival, migration, and ECM degradation (Sun et al. 2016).

Immune cells, such as T cells, rely on actin remodeling regulated by proteins like WASP, the Arp2/3 complex, and filamin (an actin cross-linking protein) to generate and stabilize membrane protrusions, which are essential for adhesion, force generation, and cell migration (Gaertner et al. 2022) (**Figure 2*b***). WASP, although not necessary for microvilli formation in T cells, plays a critical role during migration through confined environments, where it helps structure the actin network and generates mechanical forces pushing against the constraining environment (Gaertner et al. 2022, Sage et al. 2012, Shah et al. 2021). As immune cells protect their nuclei during migration through confined spaces by forming a protective actin cloud around the nucleus (Shen et al. 2024), the F-actin network minimizes nuclear deformation and reduces DNA damage as cells navigate through tight environments. Furthermore, Arp2/3 facilitates actin branching, while filamin stabilizes the actin network under mechanical strain, enabling immune cells to resist deformation (Gaertner et al. 2022).

During T cell activation, the rearrangement of actin within membrane protrusions is vital for forming the immunological synapse, stabilizing the interaction with APCs, and maintaining T cell receptor (TCR) signaling (Dustin 2014; Kumari et al. 2014, 2015; Valitutti et al. 1995). During this process, invadosome-like actin-driven structures help lymphocytes apply mechanical forces that sustain synaptic contacts and improve antigen recognition (Fritzsche et al. 2017, Razvag et al. 2019, Sage et al. 2012). Additionally, cytoskeletal tension regulated by actin and integrin activity stabilizes adhesions and enhances immune responses (**Figure 2*a***) (Burkhardt et al. 2008, Leithner et al. 2021, Negulescu et al. 1996, Yi et al. 2012).

3.2. Membrane Curvature and Protein Clustering

Localized membrane curvature and transient protein clustering enhance leukocyte signaling and adhesion by organizing receptors, adhesion molecules, and signaling complexes, thereby enabling rapid immune responses (Al-Aghbar et al. 2022, Jung et al. 2016, Zhu et al. 2019). Proteins involved in these processes often feature specialized domains that bind to curved membranes containing specific lipids, allowing them to detect and stabilize membrane curvature, organize actin networks, and facilitate receptor clustering during immune activation.

Key proteins involved in curvature sensing, such as IRSp53, TOCA1, CDC42 interaction protein 4 (CIP4) (Snider et al. 2021), and fibrin binding protein 1 (FNBP1) (Wang et al. 2022), include domains that detect, stabilize, and induce curvature such as Bin/Amphiphysin/Rvs (BAR), I-BAR, and F-BAR domains. These proteins act as scaffolds for actin polymerization at protrusion edges, promoting the formation and dynamics of filopodia and lamellipodia (Fricke et al. 2010, Liu et al. 2015, Tsai et al. 2022). Furthermore PIP_2 binding can recruit proteins such as WASP and N-WASP to curved membrane domains to facilitate actin remodeling during immune synapse formation and antigen engagement (Blumenthal & Burkhardt 2020, Tsai et al. 2022). Proteins with pleckstrin homology domains, such as Sos1 or Vav1 (Powis et al. 2023), interact with phosphatidylinositol lipids enriched in curved membrane regions, promoting localized signaling cascades critical for T cell activation (Sezgin et al. 2017). Annexins, which bind curved membranes in a calcium-dependent manner, play roles in membrane stabilization and vesicle trafficking during synapse formation (Gerke et al. 2024, Seaton 1996). Similarly, epsin, an ENTH domain protein, contributes to membrane invagination during receptor recycling (Charpentier & King 2021, Ford et al. 2002). In addition, clathrin- and endosomal sorting complexes required for transport (ESCRT)-dependent membrane budding during receptor recycling and downregulation are facilitated by hepatocyte growth factor-regulated tyrosine kinase substrate (HRS), which recruits ESCRT components to promote vesicle formation (Kvalvaag et al. 2023). Complementarily, lipid mediators such as diacylglycerol have been implicated in vesicle budding, underscoring the multifaceted regulation of membrane dynamics (Kvalvaag et al. 2023, Stinchcombe et al. 2023).

Membrane curvature also enhances the spatial confinement of integrins to the tip of filopodia and microvilli (Jung et al. 2016, Miihkinen et al. 2021), increasing their local density and promoting ligand binding. Furthermore, the phosphatase CD45 has been reported to be more densely concentrated farther away from microvilli tips, facilitating TCR triggering (Ghosh et al. 2020, Jung et al. 2021). In contrast, TCR molecules are randomly distributed on the microvilli and the cell body (Cai et al. 2022, Rossboth et al. 2018). Moreover, in contrast to the TCR clusters shown by Cai et al. (2022), the TCR complexes are proposed to be predominantly monomeric and randomly diffusing until engaged (James et al. 2011, Rossboth et al. 2018). However, distinguishing true clustering from natural fluctuations resulting from diffusion statistics in super-resolution data is challenging (Baumgart et al. 2016). Advanced imaging and biophysical techniques continue to unravel the intricate roles of these proteins in modulating leukocyte function, highlighting the synergistic interplay between membrane curvature and cellular signaling.

3.3. Receptor Dynamics

Receptor dynamics in immune cells allow them to respond to mechanical forces such as stretch, shear stress, and compression. Mechanosensitive receptors undergo conformational changes under mechanical stimuli, altering binding affinity and triggering intracellular signaling (Hope et al. 2022, Yang et al. 2022). Integrins and selectins, particularly LFA-1 and L-selectins in leukocytes, strengthen adhesion under force, for example, during antigen recognition and synapse formation or during immune cell migration and adhesion to vascular endothelium, through catch bonds that enhance bond stability under tension and facilitate tissue infiltration under flow conditions (Ivetic et al. 2019, Springer & Dustin 2012, Sundd et al. 2013).

Mechanosensitive ion channels, including Piezo1 and some TRP channels, further support mechanotransduction by responding to shear stress, membrane tension (Sitarska & Diz-Muñoz 2020), and compression. Piezo1, activated by membrane stretch, permits calcium influx, an essential signal in leukocyte activation and migration (Cahalan & Chandy 2009, Coste et al. 2010, Kwak et al. 2023, Liu et al. 2024) (see **Figure 2*c***). Similarly, TRPV4 channels respond to osmotic and mechanical stress, mediating calcium signaling during migration of leukocytes into tissue and inflammation (Majhi et al. 2015, Michalick & Kuebler 2020).

Another class of receptors, adhesive G protein–coupled receptors (GPCRs), traditionally linked to chemical signaling, also responds to mechanical stimuli by adjusting intracellular signaling output (Lala & Hall 2022). Together, integrins, Piezo channels, TRP channels, and mechanosensitive GPCRs enable leukocytes to process mechanical and biochemical information from their environment, crucial for guiding immune cell responses during migration, adhesion, and antigen recognition (Atcha et al. 2021, Luo et al. 2007, Nonomura et al. 2018).

4. HOW IMMUNE CELLS EXPLOIT THEIR MECHANOSENSORY TOOLBOX

4.1. T Cells and NK Cells

T cell activation is initiated by recognizing foreign antigenic peptides presented by a major histocompatibility complex (MHC) on APCs through TCRs (see **Figure 3*a***). This triggers together with costimulatory signals a cascade of events, leading to T cell proliferation, differentiation, and effector function. T cells encounter varied environmental conditions, such as different stiffnesses and viscoelastic properties, that influence TCR signaling and activation (Jeffreys et al. 2024, Lei et al. 2021, Rushdi et al. 2020). Microvilli are essential to the initiation of T cell signaling by increasing surface area and sampling speed (Cai et al. 2017, 2022; Pullen & Abel 2019). Membrane protrusions inherently provide several advantageous features. First, the high membrane curvature

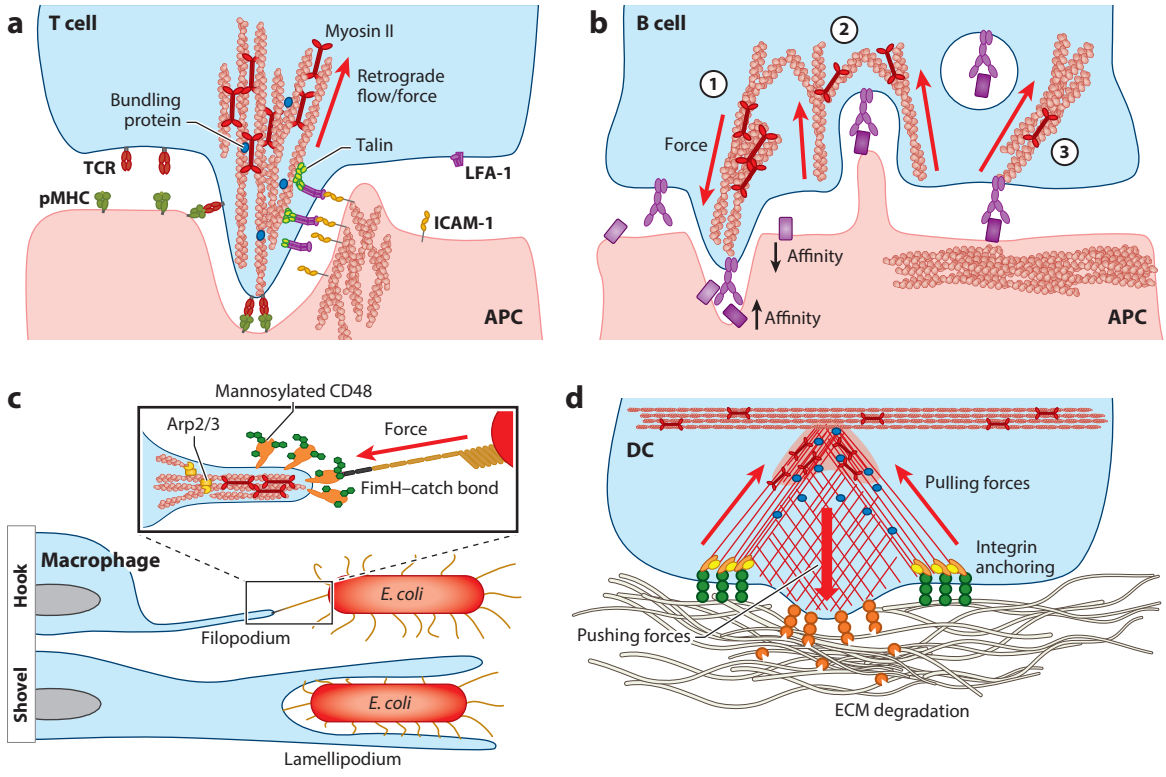


Figure 3

Immune cell interactions. (*a*) T cell immune synapse and force generation. T cells utilize microvilli and actin-driven structures to interact with APCs. The retrograde actin flow, mediated by bundling proteins and myosin II, generates tensile forces that stabilize the TCR–pMHC interaction, enhancing antigen discrimination. Integrins like LFA-1 bind to ICAM-1 on DCs, reinforcing the immune synapse. (*b*) B cell antigen extraction and affinity discrimination. B cells use mechanical forces to engage and extract antigens from APCs. (①) Initial probing involves actin-based forces that test antigen affinity. (②) High-affinity antigens are preferentially extracted through sustained force application, aided by receptor clustering. (③) Clathrin-mediated endocytosis completes the process, internalizing antigens and associated membrane fragments for processing. (*c*) Macrophages deploy filopodia and lamellipodia to detect and capture pathogens like *Escherichia coli*. Filopodia act as hooks, engaging bacterial adhesins like FimH via catch bonds, while lamellipodia function as shovels, engulfing bacteria for phagocytosis. The inset highlights actin remodeling at the tip of filopodia, driven by Arp2/3 and force-sensitive molecular interactions. Panel adapted from Möller et al. (2013). (*d*) DC podosomes and ECM degradation. DCs form podosomes, actin-rich protrusions anchored by integrins, to degrade the ECM. These structures utilize Arp2/3-mediated actin networks and generate localized forces for tissue remodeling and invasion. Pulling forces are applied through integrins to simultaneously generate pushing forces to the center of the podosome. Abbreviations: APC, antigen-presenting cell; DC, dendritic cell; ECM, extracellular matrix; pMHC, peptide–major histocompatibility complex; TCR, T cell receptor.

provided by microvilli helps organize signaling proteins and lipids such as PIP_2 (Al-Aghbar et al. 2022, Epand et al. 2015, Orbach & Su 2020). Key signaling proteins like L-selectin and TCR are more densely concentrated closer to microvilli tips (Jung et al. 2016, 2021), whereas enzymes like CD45 concentrate farther away (Ghosh et al. 2020, Jung et al. 2021), creating a favorable environment for TCR signaling (Al-Aghbar et al. 2022, Davis & van der Merwe 2006). However, there has also been some controversy over these observations, shown by the free diffusion of TCR clusters independent of microvilli tips (Cai et al. 2022). Second, mechanical forces play a crucial role in T cell activation, from early antigen engagement to T cell signaling (Blumenthal & Burkhardt 2020, Leithner et al. 2021, Sage et al. 2012). Microvilli generate pushing forces to overcome the glycocalyx barrier on APCs to position TCRs closer to peptide-MHCs (pMHCs),

enabling rapid and stable bond formation (Jenkins et al. 2023). Furthermore, the TCR seems to be linked to the actin cytoskeleton within the microvilli by phosphorylated proteins of the ERM family, as shown by the colocalization of the TCRαβ with ERM proteins as well as with actin filaments (Ghosh et al. 2020). Moreover, tensile forces enhance kinetic proofreading by modulating TCR–pMHC bond lifetimes, enabling the discrimination between high- and low-affinity ligands (Allard et al. 2012, Kim et al. 2009, Klotzsch & Schütz 2013, McKeithan 1995, Zhu et al. 2019). Single-molecule Förster resonance energy transfer assays (Göhring et al. 2021) show that TCR–pMHC unbinding rates in the dynamic environment of the immunological synapse where cellular movements and forces disrupt the interactions are increased compared with unbinding rates in solution (Huppa et al. 2010). Furthermore, mechanical experiments by biomembrane force probing and in vitro experiments confirm that both catch bonds (Liu et al. 2014) and slip bonds (Limozin et al. 2019) contribute to the antigen discrimination process. Integrin-mediated signals, like those from LFA-1, lower the activation threshold and heighten T cell responsiveness (Springer & Dustin 2012), while cytoskeletal tension maintains immune synapse stability (Comrie et al. 2015, Kumari et al. 2020, Leithner et al. 2021, Suzuki et al. 2007). Disruptions in this system, as seen in Arp2/3-deficient T cells, result in impaired cell spreading and cytokine secretion (Colin-York et al. 2019).

In both natural killer (NK) cells and cytotoxic T lymphocytes, surface protrusions contribute to the sensing and responding to mechanical cues, which are critical for efficient tissue migration and the targeted elimination of infected or transformed cells (Ben-Shmuel et al. 2021, Tamzalit et al. 2019). Actin remodeling plays a central role not only in immune synapse formation but also in cytotoxic granule secretion (Rak et al. 2011). Polarization of the microtubule-organizing center allows cytolytic granules, containing perforin and granzymes, to be directed toward the immunological synapse (Butler & Cooper 2009). This ensures the precise delivery of cytotoxic molecules, inducing target cell lysis while minimizing collateral damage to neighboring cells (Ham et al. 2022, Orange 2008, Rak et al. 2011).

Both NK cells and cytotoxic T lymphocytes adapt their cytotoxic activity based on the stiffness and viscoelasticity of target cells and ECM (Friedman et al. 2021, Lei et al. 2021). Stiffer opposing substrates, as shown by acrylamide gels and beads, enhanced immune synapse formation and degranulation of NK cells, regulated by mechanosensitive integrins such as LFA-1 (Friedman et al. 2021). These integrins transmit mechanical signals to the actin cytoskeleton, enabling fine-tuned activation of cytotoxic functions.

Over the last decade, important milestones have been reached toward advancing cellular therapies, such as chimeric antigen receptor (CAR) T cell therapies (Albelda 2024, Khan et al. 2024). In CAR T cell therapy, microvilli help stabilize or even hyperstabilize the contact between immune cells and cancer cells, depending on antigen abundance and CAR–ligand affinity, thereby enhancing the targeting and elimination of cancer cells (Beppler et al. 2023). Understanding the underlying biology of microvilli-targeted cell contacts is crucial for advancing cellular immunotherapies.

4.2. B Cells (Affinity Maturation and T Cell Help)

As for T cells, membrane protrusions in B cells are crucial for immune synapse formation and furthermore help in antigen extraction and affinity maturation (Kwak et al. 2018, Liu et al. 2020). Advances in imaging and biophysical techniques have highlighted the importance of ligand mobility, density, stiffness, and topography in influencing B cell receptor (BCR) signaling (Natkanski et al. 2013, Nowosad et al. 2016).

Upon antigen binding, BCR cross-linking triggers receptor aggregation into microclusters and recruitment of signaling intermediates such as CD19, initiating downstream signaling pathways

(Harwood & Batista 2009). Actin cytoskeletal reorganization supports rapid cell spreading over the APC surface, enhancing antigen recognition and synapse stabilization (Tolar 2017). Actin filaments also regulate BCR diffusion, membrane organization, and access to costimulatory and inhibitory molecules, thereby modulating signaling thresholds (Gasparrini et al. 2016). Dense actin networks slow BCR mobility, while actin depolymerization promotes microcluster formation (Keppler et al. 2015, Treanor et al. 2010).

In conditions like Wiskott–Aldrich syndrome (WAS), cytoskeletal defects disrupt actin polymerization and impair B cell activation, leading to autoimmunity and infection susceptibility (Thrasher & Burns 2010). Arp2/3- and formin-mediated actin branching generates lamellipodia and podosome-like structures that drive antigen extraction and immune synapse formation (Bovellan et al. 2014, Fritzsche et al. 2016). Germinal center B cells further refine antigen discrimination by applying localized forces via myosin IIa–mediated contractility (Nowosad et al. 2016) (see **Figure 3*b***). During this process, known as affinity maturation, B cells exert strong mechanical forces through their BCRs to extract antigens tethered to stiff APC membranes. High-affinity BCRs facilitate the internalization of the antigen bound to the receptor, whereas low-affinity BCRs are more likely to dissociate from the antigen under force. Conversely, during the activation of naive B cells only weak forces are required for antigen capture from soft APC membranes through clathrin-mediated endocytosis, often internalizing portions of the APC membrane (Spillane & Tolar 2017). These processes underscore the role of membrane protrusions and actin dynamics in sensing mechanical cues and optimizing antigen acquisition.

4.3. Macrophages

Macrophages are professional phagocytes of the immune system, equipped with specialized cellular protrusions to facilitate the detection and engulfment of pathogens, as well as cell and nonbiological debris. These protrusions, which include filopodia, lamellipodia, and podosomes, serve as mechanosensitive structures that guide the macrophage's interactions with their environment and help in the initiation and resolution of immune responses (Linder & Wiesner 2016, Ni et al. 2023).

Macrophages extend their protrusions to explore their surroundings. The dynamics formation of these protrusions, regulated by key signaling molecules such as Rac1 and Cdc42, allows macrophages to sense chemical gradients (chemotaxis) and physical barriers, guiding them toward sites of infection or injury (Allen et al. 1998, Chen et al. 2000). Filopodia, reaching much farther than podosomes or lamellipodia, are particularly well-suited to make first contact with foreign objects. Formation of an adhesive contact between the tip of a filopodium and an object leads to the stabilization of the filopodium (Bornschlögl et al. 2013, Möller et al. 2012, Schuerle et al. 2017). To strengthen the adhesion, the initial adhesive contact between a macrophage and *Escherichia coli* involves mannosylated proteins on the macrophage's filopodia forming a catch bond with FimH on the bacterial fimbria (Möller et al. 2013, Thomas et al. 2006). Premature bond breakage and potential loss of prey are further prevented by the quick recruitment of adhesion receptors to the interaction site (Sun et al. 2021).

For pathogen capture, macrophages use, in fact, a specialized hook and shovel mechanism to first hold on to a distant object via a filopodium forming a hook, followed by redirecting actin polymerization toward the hook. As bacteria typically form adhesive contacts with the surfaces to which they adhere, podosome-like structures of macrophages, known to assemble at the leading lamella (Evans et al. 2003), are needed to break these adhesive surface bonds. This breakage finally allows the macrophage to pull a bacterium on top of the lamellipodium while the bacterium is still on the filopodium hook, allowing the initiation of its phagocytosis (Möller et al. 2013) (see **Figure 3*c***).

The phagocytic process, by which macrophages engulf and digest microbes and all kinds of extracellular particles, is one of the most essential features of macrophages (Chen et al. 2023). The engagement with particles or pathogens leads to the activation of phagocytic receptors—such as Fc receptors and complement receptors—triggering the recruitment of the actin machinery to the site of particle contact (May & Machesky 2001). To form the phagocytic cup, macrophages wrap their lamellipodium around the target material, regulated by proteins such as WASP, Arp2/3, and formin. Mechanical forces applied through integrin junctions facilitate the closure of the phagocytic cup and aid in the internalization of large particles (Krendel & Gauthier 2022). Macrophages can detect differences in the stiffness and shape of target particles and adapt their phagocytic response accordingly (Beningo & Wang 2002, Möller et al. 2012, Wang et al. 2024). Stiff particles induce the typical rapid formation of a phagocytic cup, whereas soft particles lead to a slower response, characterized by F-actin protrusions and frequent stalling. This mechanical switch in the phagocytic process is largely mediated by β2 integrins, which are crucial for actin dynamics at the contact site (Settle et al. 2024). Mechanosensation by the lamellipodium thus plays a significant role in regulating macrophage phagocytosis itself.

The activation and differentiation of macrophages are also influenced by the mechanical properties of the ECM, and by spatial and fluidic aspects of their niche, which can modulate their polarization into proinflammatory (M1) or anti-inflammatory (M2) phenotypes. Proinflammatory activation enhances actin polymerization, which in turn leads to the release of the nuclear transcription factor MRTFa from G-actin, enhancing the upregulation of proinflammatory cytokine release. Consequently, the proinflammatory response of macrophages is significantly downregulated upon spatial confinement of their lamellipodium and, therefore, limits actin polymerization (Jain & Vogel 2018), further confirmed by partial confinement by adhesion to stripes that stabilized the anti-inflammatory M2-like phenotype (Jain et al. 2019, Li et al. 2022). Furthermore, on softer substrates, impaired stiffness sensing and reduced YAP nuclear translocation lead to a diminished immune response characteristic for M2 macrophages, whereas M1 activation is generally promoted on stiffer substrates (Meli et al. 2020). Similarly, macrophages are sensitive to interstitial flow via β1 integrins and FAK, enhancing an M2-like phenotype (Li et al. 2018). Therefore, the dynamic reorganization of the actin cytoskeleton is key for macrophage function.

This process highlights how macrophages use coordinated surface protrusions to detect and engulf bacteria, with lamellipodia enabling the formation of a phagocytic cup. Conversely, viral pathogens like HIV-1 exploit the dynamic nature of macrophage podosomes to facilitate viral entry into host cells (Li et al. 2021).

4.4. Dendritic Cells

DCs, as professional APCs, play a crucial role in initiating and regulating immune responses by capturing and presenting antigens to T and B cells. Depending on their activation state, these cells are differentially equipped with various membrane protrusions, such as microvilli, filopodia, lamellipodia, podosomes, and membrane ruffles (large sheetlike protrusions), which are essential for probing the extracellular environment, migrating to the lymph node, and interacting with other immune cells.

Immature DCs employ filopodia, lamellipodia, and podosomes, allowing anchoring in the ECM, directing migration through the tissues, and helping to sample their environment for antigens (Baranov et al. 2014). These structures, especially the podosomes, interact strongly with the ECM via integrins and other mechanosensitive proteins linking the cell's actin cytoskeleton to the ECM (see **Figure 3*d***). This enables them to respond to stiffness and mechanical properties of the ECM and tissue microenvironments, which influences matrix degradation and directs

migration, allowing the DCs to penetrate tissues and access antigens hidden within the ECM (van den Dries et al. 2013).

To sample the surrounding antigens from the environment, immature DCs use various mechanisms such as receptor-mediated endocytosis, phagocytosis, and macropinocytosis. Overall, the dynamics of the actin cytoskeleton and the resulting protrusions are crucial to the ability of DCs to efficiently capture antigens (Garrett et al. 2000). Upon antigen capture, DCs mature and undergo significant cytoskeletal rearrangements (Comrie et al. 2015) necessary for the migration to the draining lymph node and for antigen presentation to T and B cells. These changes involve the downregulation of podosomes, which reduces adhesion to the ECM, allowing the DCs to migrate at higher speed (Yamakita et al. 2011). Furthermore, the cells produce membrane ruffles, which massively increases their surface area (Verdijk et al. 2004), ensuring efficient presentation of the antigenic peptides, enabling the DCs to capture T and B cells (Benvenuti et al. 2004). The ruffles on human DCs guide T and B cells to a domain of microvilli, where pMHCs and costimulatory molecules are clustered for an efficient synapse formation (Fisher et al. 2008). The critical role of actin polymerization in the effectiveness of the immunological synapse between DCs and T cells was further demonstrated by Leithner et al. (2021) (see **Figure 3*a***). In their study, inhibition of actin polymerization in DCs using MycB resulted in impaired T cell activation. Unlike the central supramolecular activation cluster observed in T cell–B cell interactions, the polarization of the actin cytoskeleton in DCs facilitates the formation of a multifocal synapse (Cai et al. 2017, 2022; Comrie et al. 2015; Fisher et al. 2008; Leithner et al. 2021).

5. EMERGING TECHNOLOGIES, FUTURE DIRECTIONS, AND INTERFACING WITH T CELLS

Advancements in imaging technologies, such as single-molecule and super-resolution imaging, as well as cryo-electron microscopy, have the potential to significantly enhance our understanding of the dynamics of immune cell surface protrusions (Aramesh et al. 2021, Cai et al. 2017, Jung et al. 2016, Ke et al. 2022, Rossy et al. 2013, van den Dries et al. 2013). These techniques offer unprecedented resolution, capturing nanoscale movements and interactions of membrane projections in real time. Super-resolution techniques and advanced low-toxicity live microscopy, such as structured illumination microscopy and lattice light-sheet microscopy, enable the study of 3D versus 2D interactions between immune cells and their environment. These tools provide insights into how immune cells use surface protrusions to gather information across different spatial contexts (Cai et al. 2022, Jung et al. 2016, Rossy et al. 2013, van den Dries et al. 2013).

Understanding these dynamics, especially in confined and complex environments, is crucial for elucidating immune cell behavior and identifying potential therapeutic targets. For example, studies of actin dynamics under confined conditions, such as the redistribution of F-actin regulated by DOCK8, are important for understanding how immune cells maintain their integrity and functionality in tight, challenging environments (Shen et al. 2024). Novel experimental approaches such as optogenetics, microfluidic systems, and 3D biomaterials are powerful tools for manipulating and observing protrusion dynamics in real time. These systems can mimic complex physiological conditions of tissues, including tissue stiffness, fluid dynamics, or confined spaces, providing controlled environments for studying immune cell behavior during migration and antigen recognition (Torisawa et al. 2016). Microfluidic platforms, for example, can simulate the physical properties of tissues, blood vessels, and lymphatic vessels, including flow conditions and oxygen tension, helping to model T cell–tissue interfaces in a controlled manner (Jung 2023, Lee et al. 2022). Furthermore, 3D biomaterials with tunable internal architectures allow for the replication of tissue microenvironments, bridging the gap between in vitro experiments and in vivo complexity.

Force microscopy techniques, such as traction force microscopy, molecular force microscopy, and atomic force microscopy, provide essential insights into how immune cells generate and respond to mechanical forces via their surface protrusions (Choi et al. 2023). These mechanical forces are key in processes like T cell activation, pathogen clearance, and immune cell migration through dense tissue environments (Tabdanov et al. 2021). Mechanical sensing through these protrusions allows immune cells to adapt to their physical surroundings, and advances in this area will help clarify how mechanical forces influence immune responses.

Another promising area of research is the development of spatiotemporally resolved proteomics of membrane protrusions, providing insights into the dynamic protein composition of these structures. Such studies could reveal how immune cells reorganize their signaling complexes in response to external stimuli during activation, migration, and synapse formation. These molecular-level insights are vital for understanding how immune cells integrate biochemical and mechanical cues to make decisions at the single-cell level (Lundberg & Borner 2019).

Finally, the creation of novel fluorescence sensors to detect membrane properties such as curvature, charge, clustering, and membrane tension offers new opportunities to study how immune cells sense and respond to mechanical cues in their environment (Li et al. 2024, Ma et al. 2017). These novel sensors can help reveal how different cell protrusions, like microvilli and podosomes, detect and respond to physical and biochemical stimuli. Combining such advancements with continuous progress in high-resolution imaging and force measurement techniques will allow researchers to further uncover the molecular mechanisms governing membrane protrusion dynamics and their consequences in both health and disease.

Combining advanced imaging, mechanical manipulation, and biochemical stimulation will pave the way for the next generation of immune cell research, optimizing therapeutic applications and enhancing our understanding of immune cell behavior in health and disease (Brameshuber et al. 2022).

6. CONCLUSION

In conclusion, a diversity of immune cell surface projections represent intricate structures, each type with its own functionality that plays vital synergistic roles in environmental sensing and immune responses. These dynamic protrusions, such as microvilli, filopodia, lamellipodia, and podosomes, are essential for immune cell function, facilitating processes like antigen recognition, migration, and cell–cell communication. Understanding the dynamics and molecular mechanisms behind these structures is especially critical in disease models such as cancer and autoimmune disorders.

In cancer, immune cells often struggle to navigate the physical and immunological barriers presented by the tumor microenvironment. T cells and NK cells rely on surface projections to infiltrate tumors and form effective immune synapses with cancer cells. This knowledge is critical for improving immunotherapies such as CAR T cell therapy and immune checkpoint inhibitors, which depend on effective immune cell–tumor cell interactions for successful outcomes (June & Sadelain 2018, June et al. 2018, Li et al. 2024, Maude et al. 2018). By studying the role of immune cell surface projections in the tumor microenvironment, it is possible to refine these therapies to overcome barriers that limit immune cell infiltration and function in solid tumors (Wagner & Klotzsch 2022).

In autoimmune diseases such as WAS, defects in WASP affect immune cell surface projections, disrupting key functions such as cell migration and immune synapse formation. Research into how these defects alter immune cell dynamics and signaling is crucial for designing therapies that can restore immune function or mitigate autoimmune complications (Recher et al. 2012, Rey-Suarez et al. 2020, Tolar 2017). WASP's role in maintaining proper immune cell architecture

highlights the importance of these protrusions in both primary immunodeficiencies and broader autoimmune conditions.

Future research should continue to integrate cutting-edge technologies like super-resolution microscopy, force measurement tools, and spatial proteomics to explore how these surface projections operate in health and disease. This will advance our understanding of immune cell behavior and pave the way for new, targeted therapies in cancer and autoimmune disorders.

DISCLOSURE STATEMENT

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