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Matrix Stiffness Regulation of Macrophage Function

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Abstract: Macrophages are found throughout the body, engulfing microorganisms and cell debris, while coordinating inflammatory responses to maintain tissue homeostasis. As macrophages patrol within different organs and tissues, they are exposed not only to a variety of biochemical cues, but also to mechanical cues, such as tissue stiffness. More and more studies have shown that macrophages can sense changes in microenvironment stiffness, but little is known about the molecular mechanism of how stiffness regulates macrophage function. The 2020 Nobel Prize-winning mechanically-sensitive ion channels the transient receptor potential channel subfamily V member 4 (TRPV4) and Piezo1 are of widespread interest. Research suggests that Piezo1 and TRPV4 on macrophages can sense matrix stiffness in the microenvironment and convert it into biochemical signals to activate specific cellular effector functions. These findings help us better understand how microenvironment stiffness affects macrophage behavior, which may be associated with diseases in which tissue stiffness is altered, and may enhance our understanding of disease mechanisms.

1. Introduction

Macrophages are a kind of extremely important innate immune cells which exist in almost all tissues, like microglia in brain, alveolar macrophages in lung, osteoclasts in bone, Kupffer cells in liver, etc [1]. When a pathogen or foreign body invades, it is the first to arrive and secrete cytokines to recruit monocytes from the blood, which then differentiate into macrophages in the tissue and fight the pathogen together. Because of this patrolling nature of macrophages, macrophages are not only exposed to a variety of biochemical signals, but also to physiological or disease-dependent dynamic external forces, including tissue stiffness.

Many in vitro studies have shown that macrophages respond to mechanical stimulation, and tissue stiffness can regulate macrophage phenotype and function. In spite of this, the molecular mechanism by which extracellular matrix stiffness regulates macrophages' mechanical signaling under physiological and pathological conditions remains unclear. But it is speculated that key mechano-signal transducers are mechano-force-sensitive, so mechano-sensitive ion channels, such as TRPV4 and Piezo1, which won the 2020 Nobel Prize, are of widespread interest to researchers for their role in the sense of mechanical forces in macrophages[2]. The study of the regulation of macrophage

function by the mechanosensitive ion channel TRPV4 and piezo1 may provide a theoretical basis for many clinical diseases in which tissue stiffness is altered, such as tumors and pulmonary fibrosis. In this review, the studies on matrix stiffness and macrophages are first discussed, and then the related mechanical and molecular mechanisms of TRPV4 and Piezo1 on macrophages are discussed.

2. Matrix stiffness

Stiffness is the inherent material property of tissues, which can be used as an indicator to measure the softness and rigidity of tissues[3]. It mainly depends on the extracellular matrix (ECM), whose main components are collagen and elastin[4]. In the human body, cells are surrounded by a rich extracellular matrix that provides a variety of biochemical and biophysical cues to guide cell behavior. Macrophages experience a wide variety of tissue stiffness due to their diverse distribution. For example, microglia residing in the human brain are exposed to a shear modulus of 0.5-1kpa[5-7], alveolar macrophages in the lung had a Young's modulus of 2 kPa[8], the macrophages in liver had a 1.8-2.8kPa Young's modulus [9], the macrophages in dermal tissue had a shear modulus of 7-130 kPa[10], and the osteoclasts had a Young's modulus in the GPa range[11]. In addition, pathological diseases such as tumor[12, 13] or tissue fibrosis[8] can also advance changes in the range of stiffness encountered by these and other immune cells.

In general, hydrogels are ideal for simulating hardness[14] and include degraded natural proteins such as collagen, laminin, hyaluronic acid (HA), Matrigel™, fibrin, and polysaccharides (alginate, chitosan)[15-17]; And precisely tuned synthetic substrates such as polyacrylamide[18], polycaprolactone (PCL)[19], polyethylene glycol (PEG)[20], and composite substrates[15].

Stiffness affects macrophage morphology. In vitro studies have shown that the morphological parameters of macrophages vary according to the hardness of the medium used, including diffusion area, roundness and membrane morphology. For example, macrophages on hard substrates generally exhibit larger and flatter morphology and increased adhesion compared to macrophages on soft substrates [21-24].

It is becoming clear that macrophages respond markedly to mechanical signals, but although considerable efforts have been made to understand how the hardness of the microenvironment affects macrophage phenotype and function, the data remain inconclusive. Studies have shown that harder substrates can up-regulate the pro-inflammatory response of macrophages, leading them to differentiate into M1 phenotype. For example, Previtera et al. showed that bone marrow-derived macrophages(BMDMs)was exposed to polyacrylamide gel at 0.3 to 230 kPa, and higher concentrations of secretory IL-1β, TNF-α, and NO were detected on harder substrates after LPS treatment[25]. Furthermore, the expression and translocation of various signaling molecules in macrophages grown on hard substrates are higher than those grown on soft substrates[25]. Blakney et al. showed that macrophages exhibited a classic activation phenotype when stimulated with LPS, with increased expressions of TNF-α, IL-1β, and IL-6, and stimulated macrophages had an increase in cytokine production with an increase in substrate stiffness. However, in the absence of stimulus, macrophages do not respond to substrate hardness[22]. Sridharan et al. also reported that THP-1-derived macrophages were cultured on polyacrylamide gel coated with collagen of different stiffness (11-323 kPa). They found that hard matrix (323 kPa) pushed macrophages to the proinflammatory phenotype, and macrophage phagocytosis was damaged, while soft (11 kPa) and medium (88 kPa) matrix differentiated cells to the anti-inflammatory and high phagocytosis phenotype[26].

Other studies have shown that more softer materials enhance the pro-inflammatory behavior of macrophages. Escolano et al. reported that compared with 33.1kPa hydrogel, BMDM on 0.2kPa polyacrylamide matrix up-regulated its proinflammatory response. Although no significant changes in proinflammatory gene expression were observed, they detected elevated levels of IL-6 and IL-1β

secretion on the most compliant hydrogels under LPS primers and niuricin stimulation[27]. Cultured mouse BMDMs and RAW264.7 cells on a polyacrylamide gel coated with fiber-binding protein with a certain stiffness (1, 20, and 150 kpa), Gruber et al found secretion of the pro-inflammatory cytokine, TNFα, in response to stimulation of TLR4 and TLR9 was increased in macrophages grown on soft gels versus more rigid gels, particularly for BMDMs[24]. In addition, several studies have suggested that higher stiffness will facilitate the transition from M1 to M2-like phenotypes. The effect of different PDL-coated polyacrylamide gels in the phenotype of BMDMs was tested, with higher levels of M1-like genes detected on 1 kPa of gel and M2-like genes detected on 50 kPa of material[28,29].

In several experiments, stiffness induced double phase reactions in macrophages. Morphology and cytokine production of RAW264.7 cells in response to LPS of BMDMs were similar on soft gels (1 kPa) and hard gels (150 kPa), but different from those observed on medium hardness gels (20 kPa)[24]. A similar biphasic phenomenon has been reported in human THP-1 cells treated with phosphomyrisate, with maximum IL-8 release when the cells were grown on an interpenetrating polymer network with a hardness of 9.9 kPa and a hardness of 1 or 389 kPa[30]. Sridharan et al. also observed that in THP-1-derived macrophages the influence of material stiffness on phagocytosis and several M1 genes and cytokines followed a biphasic response[26]. One possible explanation is that the response of macrophages to inflammatory stimuli is optimal at "average" tissue hardness (e.g. 20 kPa PA gel). Thus, conditions that increase hardness or reduce hardness can modulate the response of macrophages. Therefore, the non-linear relationship between substrate stiffness and macrophage behavior cannot be determined until more data is collected.

The differences in macrophage response between studies may be due to the selection of different cell lines, adhesive proteins, their coating density, or the type of stimulation excitation. It is clear that further research is needed to dissect how matrix stiffness regulates the behavior of macrophages and how this affects their ability to induce an inflammatory response.

3. Mechanical transduction mechanism

Mechanically sensitive ion channels play an important role in mechanical signal transmission. It can adapt to the changes of mechanical stress on the cell membrane by making rapid changes, so as to convert the mechanical stimulation received by the cell membrane into bioelectrical signals or biochemical signals, which has an important influence on the cell response to external changes. At present, mechanosensitive ion channels mainly include Piezo protein, transient receptor potential channel, two-pore potassium channel and degenerative protein. One of the two mechanically sensitive ion channels, Piezo1 and TRPV4, which won the Nobel Prize in 2020, are at the center of the intrigue.

3.1 TRPV4

In 2000 Strotmann et al.[31] and Liedtke et al.[32] first described TRPV4 cationic channels, which belong to a large family of transient receptor potential (TRP) channels. The TRP family consists of 30 proteins, divided into 6 subgroups: TRPC (canonical), TRPM (melastatin), TRPV (vanilloid), TRPA (ankyrin), TRPML (mucolipin), and TRPP (polycystin) [33, 34]. TRP channels, all six-transmembrane proteins, are weakly voltage-sensitive cation-selective channels that are gated differently by temperature, mechanical forces, electrophiles, ligands, and internal cues (such as membrane composition and pH) that contribute to immune and inflammatory responses. Studies have shown that macrophages express TRPV4, TRPV2, TRPA1, TRPC6, TRPM2, TRPM7, TRPML1, etc., and they play a role in cell proliferation, inflammatory activation, polarization, phagocytosis, adhesion and migration[35]. However, until now, only TRPV4 activity was affected by the mechanical environment of macrophages, including matrix hardness, shear stress, and tensile force[36].

The mechanosensitivity of macrophages is attributed to transient receptor potential vaniline-like

type 4 (TRPV4), as the absence or inhibition of this mechanosensitive calcium channel eliminates the observed effect of substrate hardness on macrophage behavior. Scheraga et al. showed that compared with cells on soft substrates, BMDMs cultured on hard substrates showed increased intracellular calcium influx and phagocytosis mediated by LPS, and pharmacological inhibition or decreased expression of TRPV4 would lead to decreased phagocytosis of BMDMs cultured on hard substrates[37]. Scheraga's group further investigated the downstream molecular effects of TrPV4-mediated phagocytosis on LPs-stimulated phagocytosis, showing that TRPV4 controls a MAPK molecular switch from the activation of the major c-Jun N-terminal kinase JNK to the activation of p38. Phagocytosis and cytokine secretion are mediated in a matrix stiffness-dependent manner[38]. Data from these two studies suggest that in Gram-negative bacterial infections such as E. coli and Pseudomonas aeruginosa, TRPV4 signaling triggered by changes in the hardness of the extracellular matrix during infection acts synergistically with LPs-induced signaling to promote host defense and relief of lung damage. In addition, Dutta et al. demonstrated in a mouse skin fibrosis model established by blemycin that hard substrates (50kPa) increased macrophage M1 marker expression in a Trpv4-dependent manner and further enhanced this response by adding soluble factors. This did not occur in soft substrates (1 kPa)[39]. This provides insights into stroma-macrophage interactions that may aid in the development of bioactive implants and therapies.

3.2 Piezo1

Piezo1[40] was first identified in mouse neuroblastoma in 2010. Piezo1, one of two members of the Piezo family, is an evolutionally-conserved large membrane protein[40]. The cryo-electron microscope structure of Piezo1 for mice[41]has been obtained, in a homologous trimer propeller-like structure. Piezo1 is widely available in mammals and is important for the mechanical conduction of blood vessels (such as the regulation of blood pressure), urinary osmal pressure, mechanical cartilage transduction, bone diseases, neuronal physiology of dorsal root ganglia, peripheral trigeminal nerve receptors, and other pathophysiological conditions[42]. Piezo1, a novel mechanosensitive ion channel protein closely related to mechanical stress stimulation signals, translates mechanical stimulation into electrical and biochemical signals within milliseconds and is the molecular basis for the perception and response of cells to mechanical forces. One of these, Piezo1, has recently been shown to be highly expressed in macrophages, sensing and transducing other biological forces, including stiffness, such as tension, shear and periodic hydrostatic pressure, in addition to regulating macrophage inflammation and healing responses and phagocytosis[43-46].

Like TRPV4, Piezo1 is important for matrix stiffness dependent activation of macrophages. The research suggests that Piezo1 regulates the perception of stiffness in macrophages in vitro and the inflammatory response of foreign bodies in rigid implants in vivo. Atcha et al showed that the expression of iNOS or ARG1 in macrophages cultured on harder substrates (280 Kpa) was the highest when stimulated by IFN-γ/LPS or IL4/IL13, indicating that stiffness regulates the inflammatory/healing response of macrophages[43]. On this basis, they found that Piezo1 is highly expressed in bone-marine-derived macrophages, and that its activity enhances IFN-γ /LPS and inhibits IL4/ IL13-induced activation by increasing NFκB and decreasing STAT6. Its activity enhances IFN-γ /LPS and inhibits il4 / il13 induced activation by increasing NFκB and decreasing stat6 activation[43], which suggests that Piezo1 is involved in stiffness-mediated macrophage activation. Mechanical mismatches between surgical implants and natural tissue are common and manifest as severe foreign body reactions, especially as hard materials have been shown to promote inflammation more than soft materials. Atcha et al [43] implanted Piezo1fl/+ and Piezo1ΔLysM prefabricated soft (1kpa) and hard (140kpa) PEGDA-400 hydrogels subcutaneously into PIEZO1FL /+ and PIEZO1δLysM mice. In a control group, Piezo1fl/+ mice, they found that the hard implant

significantly increased the invasion of immune cells and caused a more serious foreign body reaction, as shown by the formation of thicker fibrous capsules, than the soft implant. In contrast, in Piezo1 absent mice, the stiffened foreign body inflammatory response is mitigated. The research suggests that the expression of Piezo1 in myeloid cells influences the response of the host to implants of different hardness materials. Another study on titanium alloy implants with different stiffness also confirmed this view. Tang et al[47] showed that compared with traditional Ti6Al4V alloy (high stiffness), the number of M2 macrophages around the new titanium alloy (low stiffness) significantly increased and could better regulate the remodeling response after the material implantation. They further suggest that the implant influences angiogenesis and osteoblast differentiation through the Piezo1 / YAP signaling axis, which regulates macrophage polarization and related cytokine secretion[47]. This provides a strong theoretical supplement for the future application of implants in surgery.

The phagocytosis and bactericidal activity of macrophages require appropriate extracellular matrix stiffness, and Piezo1 plays an important role in the transduction of mechanical signals from the matrix to intracellular signals. Geng et al reported that phagocytosis events (that is, the number of viable bacteria in cells at 0 time point) of BMDMs cultured on rigid substrates (35kpa or glass) were much more numerous than on soft substrates (5 kPa), and that the Piezo1 defects affect the phagocytosis and scavenging of BMDMS cultured on rigid substrates [48]. Yoda1 treatment enhanced bacterial phagocytosis and macrophage clearance [48]. Thus, the matrix stiffness, together with Piezo1, helps both bacterial clearance and host defense.

4. Conclusion

There is no doubt that physical cues in the microenvironment (such as matrix stiffness) regulate macrophage phenotype and function, and that the ability of macrophages to sense and respond to mechanical forces is critical to their function. However, knowledge of how macrophages respond to these biophysical changes remains limited[49]. Knowledge in the public domain is primarily based on biomaterial studies aimed at controlling macrophage behavior and regulating foreign body responses by regulating the biophysical properties of substrates or scaffolds. In the context of surgical implants, a deeper understanding of the mechanobiology of macrophages will also contribute to the development of better immunomodulatory therapies and the design of high-quality biomaterials for implantable medical devices.

Mechanical cues are altered during the development and progression of many pathological conditions in which macrophages are involved, including various forms of cancer, cardiovascular disease, and fibrosis[50]. The hardness and structure of ECM become a hallmark of tissue infection or cancer. Primary tumors are often associated with higher than healthy tissue hardness. For example, in human brain tumors, the elastic modulus can be increased from several hundred Pa in non-cancerous tissues to 13.5 kPa[6] in advanced glioblastoma. Targeted regulation of tissue hardness provides a new pathway for inflammatory and fibrotic diseases by directly promoting favorable macrophage function and indirectly improving disease outcomes through macrophage-mediated activity. TRPV4 inhibitor, GSK2798745 (GSK), has been developed and clinically evaluated for potential benefit in the treatment of a variety of diseases, including cardiogenic pulmonary edema, chronic cough, and LPS-induced lung injury[51-53]. However, the scientific basis of these experiments is mainly to inhibit the role of TRPV4 in vasodilation and vascular permeability. But further analysis of the mechanisms by which matrix hardness regulates the behavior of macrophages, and how they sense and respond to mechanical tissue signals, such as TRPV4 and Piezo1, may offer potential therapeutic opportunities for clinical diseases.

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