Advances in the Study of Macrophage Polarization in Wound Healing

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Abstract: The skin is the largest organ of the human body and the first part to be damaged by external impact and injury. Macrophages, as the main immune cells of the body, are involved in the whole process of trauma inflammation, repair, regeneration, and fibrosis, and with the study of their molecular pathway mechanisms promoting macrophage polarization becoming clearer, it also brings undeniable research progress for molecular targeting therapy in later stages of clinical practice. This review summarizes the molecular mechanisms associated with the typing of macrophages, the various stages of repair during organismal injury, and macrophages, thus bringing new thinking to macrophage polarization for wound healing.

Keywords: Macrophage polarization; Tissue damage; Wound healing; Inflammation

1. Introduction

Wound healing is a process in which the body undergoes mechanical injury or infection, causing tissue damage, and the body repairs to restore homeostasis, mainly through the stages of coagulation, inflammation, decrease in the inflammatory response, tissue fibrosis, vascularization, and epithelial regeneration and remodeling. Macrophages are important players in tissue injury, constantly driving tissue repair and remodeling[1].Macrophages play different roles from killing pathogens, phagocytosis of apoptotic cells, and cellular debris to participating in and promoting the necessary inflammatory response of the body, to initiating and maintaining the tissue regeneration and remodeling process while the inflammation subsides at a later stage. Macrophages are highly plastic and heterogeneous, and after damage to the organism, they constantly adjust their functional phenotype according to the changes in the trauma microenvironment. Macrophages act as masters of body repair, and the correct expression of pro-and anti-inflammatory macrophages and the timely conversion of M1 to M2 types are crucial for the repair of traumatic injury in the body.

2. Differentiation phenotype of macrophages

Human macrophages are divided into resident macrophages derived from the yolk sac or fetal liver, and macrophages recruited from the blood and bone marrow under proliferative inflammatory conditions in the body (such as tissue repair). Macrophages that reside in tissues while the body is in a state of homeostasis maintain the dynamic balance of the body's activities and provide significant nutritional signals.When tissue injury occurs, resident macrophages are not sufficient to exert pro-inflammatory and anti-inflammatory effects to restore tissue homeostasis, so the body recruits a large number of macrophage precursors from bone marrow and blood to the peri-wound area, and they are influenced by the different inflammatory states of the wound microenvironment[2], showing different functional phenotypes to promote wound repair.

According to previous studies, it is customary to classify macrophages according to Th1/Th2, and macrophages can be classified into a "classically activated" pro-inflammatory phenotype (M1) and an "alternatively activated" anti-inflammatory phenotype (M2)[3].Classically activated macrophages induced by damage-associated molecular patterns (DAMPs) or granulocyte-macrophage colony-stimulating factor (GM-CSF) or pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), alone or in concert with cytokines (such as interferon-c (IFNc), tumor necrosis factor-alpha (TNFa)), produce relevant pro-inflammatory mediators such as interleukin and reactive oxygen species (ROS), which play a role in phagocytosis and removal of pathogenic microorganisms, other foreign bodies, and cellular debris.However, the over-activation of M1 macrophages and their massive accumulation in tissues to produce inflammatory cytokines and protein

hydrolases can also be a major persecutor of other healthy tissues[4].M2 macrophages activated alternatively by IL-4 and IL-13 induced by immune complexes such as IL-4 and IL-13 with and transforming growth factor-β (TGF-β)[5], produce anti-inflammatory cytokines such as IL-10, arginase-1 (Agr1), and TGF-β to suppress Th1 immune response in response to Th2 immune response and resistance to parasites.Although anti-inflammatory phenotype macrophages play an irreplaceable role in suppressing inflammation, removing pathogens, and promoting tissue healing, the anti-inflammatory phenotype, due to its lack of cytotoxic effects and its function in providing nutrients to tissues, has instead contributed to the proliferation of cancer.

With the experimental and clinical development, the bipolar classification method of M1 and M2 macrophages seems to be unable to meet the clinical requirements, and the binary classification method is too simplistic for the complex biology of macrophages. It has been suggested that macrophages in trauma are not present in the body as a single M1 or M2 form[6].In another word, the pro-inflammatory and anti-inflammatory phenotypes do not exist singly in the trauma but coexist in the tissue and change in the M1/M2 form as the trauma matures. According to the current study, M2 macrophages can be divided into 4 subtypes: M2a, M2b, M2c, and M2d. It is generally believed that M2a isoforms, mediated by IL-4 or IL-13, play an essential role in inhibiting tissue inflammatory changes and promoting wound healing, and may also have the ability to promote tissue fibrosis[7], M2b macrophages are thought to represent an intermediate between M1 and M2a polarized states[8], which are thought to produce large amounts of anti-inflammatory factors (such as IL-10) while simultaneously secreting small amounts of pro-inflammatory factors (such as TNF-α, IL-6, etc.)[9]and are thought to regulate the balance between pro-inflammatory and anti-inflammatory ; M2c isoforms are activated by IL-10, TGF-β, or glucocorticoids and play important functions in limiting inflammation, suppressing immune responses, tissue repair, and remodeling[10]. It is worth mentioning the M2d subtype, which has been suggested to be a good player in promoting neovascular growth and fighting against traumatic inflammatory response, but also in promoting tumor vascular growth and tumor migration and invasion[11]. This also provides a new direction of thinking from macrophage phenotypic differentiation against tumor growth. Recently, Mosser et al. proposed a new classification of macrophages into three cell populations: host defense, wound healing, and immune regulation, and used these three macrophage functions as a classification triad[7,] on which more macrophage subtypes can be explored according to different activation states of macrophages.

3. The role of macrophages in all phases of wound healing

3.1. Role of macrophages in the inflammatory phase of trauma

When the body is attacked by pathogens, histogenic resident macrophages play the role of sentinels and are the first to blow the body's Th1 immune response. When the tissue-resident macrophages are not sufficient to play a defensive role against bacteria and viruses, the body recruits reinforcements to play the role of a mainstay, i.e., a large number of macrophage precursors (neutrophils and monocytes) are recruited from the bone marrow and blood to the peri-wound area, and chemokines such as thrombin, (TGF-β), platelet-derived growth factor (PDGF) and vascular endothelial growth factor (VEGF) are released in the local tissue microenvironment[12]. The change in the osmotic pressure of the body's blood vessels and the increase in its permeability cause macrophages to polarize to the pro-inflammatory phenotype (M1 type) or to the pro-inflammatory phenotype of macrophages induced by NADPH oxidases 1 and 2 (NOX1 and NOX2)[13], giving full play to the role of pro-inflammatory macrophage scavengers and phagocytosis of dead cell fragments, pathogenic microorganisms, neutrophils and other decaying cells due to pathology or physiology after tissue injury[14].M1-type macrophages themselves also secrete pro-inflammatory factors such as TNF-α, interleukin-1β (IL-1β), chemokines, and matrix metalloproteinases (MMPs), which together participate in the body's defense. In a study by Yukiteru Nakayama, a long-stranded non-coding RNA was found to help macrophages promote wound repair, and it was suggested that the pro-inflammatory phase is essential in the early wound repair process[15].In other words, M1-type macrophages remove traumatic pathogens and necrotic tissues at the early stage of wound recovery to open a fast pathway for later tissue repair and reconstruction. Of course, if the pro-inflammatory phenotype does not transition smoothly to the anti-inflammatory phenotype, pro-inflammatory macrophages accumulate in large numbers on the wounded surface and stimulate the wounded tissue to release more factors that promote the spread of inflammation on the wounded surface or chemotactic mediators, forming a vicious cycle of inflammation[16], which not only aggravates the tissue inflammatory response but also becomes a persecutor of healthy host cells, leading to chronic inflammation or ulceration of the tissue and difficult

recovery.

3.2. Role of macrophages in the proliferative phase of trauma

As the traumatic inflammation gradually decreases, the body's demand for pro-inflammatory cells decreases and the pro-inflammatory cells become apoptotic, necrotic, or are removed by the "Endocytosis and Cell vomiting" of macrophages[17]. The M1/M2 ratio gradually decreases as the trauma continues to mature, and macrophages of the M2 repair phenotype dominate the wound healing. During this proliferative phase, the tissue undergoes fibrous proliferation, epidermal regeneration, wound contraction, and angiogenic germination[12]. We generally believe that external damage invasion agitates tissue dying cells to release cytokines (such as IL-25 and IL-33), which activate Th2 helper T cells and secrete cytokines such as IL-4 and IL-13, and that M2 macrophages are activated by IL-4 and IL-13 stimulation[18]. Activated anti-inflammatory macrophages secrete anti-inflammatory mediators, such as IL-10, TGF-β, and other tissue remodeling growth factors to promote the repair of body damage and the maintenance of body homeostasis, and up-regulate anti-inflammatory mediators and down-regulate inflammatory mediators to promote tissue repair.TGF-β1 is considered to be a growth factor that has a role in regulating proliferation, migration, differentiation, and reducing the degradation of extracellular matrix (ECM) by fibroblasts during the repair process of the body, and as a mainstay in suppressing excessive inflammation[19]. Martin suggested that this protein factor can stimulate mesenchymal and fibroblasts to promote trauma fibrosis[17], and it can also directly stimulate collagen synthesis. TGF-β can be divided into four isoforms, which are TGF-β1, TGF-β2, TGF-β3, and TGF-β1β2, and play an irreplaceable role in the recovery of traumatic surfaces. According to the study, overexpression of TGF-β1 on traumatic surfaces leads to excessive tissue scarring and keloid formation, while TGF-β3 reduces traumatic fibrosis and may even promote scar-free growth under sterile conditions[20]. Therefore, it is worthwhile to investigate whether there is overexpression of TGF-β1 or suppression of TGF-β3 in the keloid population and whether knocking out TGF-β1 or increasing the concentration of TGF-β3 on the wound surface during the healing process will reduce tissue scar proliferation.

Fibroblasts are also pivotal in wound healing. As previously shown, pro-fibrotic phenotype M2a macrophages, which secrete pro-fibrotic-related proteins, promote collagen deposition in wounds as well as promote fibroblast proliferation, migration, and tissue repair. It is believed that high concentrations of TGF-β1 are concentrated in the organism, which promotes the proliferation of fibroblasts and differentiation to myofibroblasts that secrete more collagen, enhancing the degree of wound healing. Tissue cell repair and differentiation and neovascular sprouting require a large supply of oxygen and nutrients, and the proliferation and differentiation of fibroblasts coincidentally provide the nutritional substrate for their growth.It was found that fibroblasts have different differentiated subpopulations at different anatomical locations in the tissue[21], but in general, fibroblasts are sporadically distributed on the wound surface rather than densely arranged in an orderly fashion[22]. The gap between them requires myofibroblasts with strong contractile force and ECM secreted by myofibroblasts to bridge the distance between the wound edges. However, pathological proliferation and differentiation of adult fibroblasts and neovascularization can lead to excessive tissue fibrosis, resulting in fibrous or scarred tissue[23]. Some studies suggest that overexpression of the Th2 cytokines IL-13 and IL-9, which overactivated M2 macrophages, can lead to pathological tissue fibrosis[24]. Interestingly, several experimental studies have found that the over-activation of the M2 anti-inflammatory phenotype is not the main cause of promoting organismal fibrosis. Functional studies on macrophages suggest that macrophages that are shifted toward the M2 phenotype play a role in reducing tissue fibrosis while ablating local inflammation[25]and are not pro-fibrosis. We have concluded that secretion of TGF-β1 by M2 macrophages is a potent factor in pro-fibrosis, and large concentrations of anti-inflammatory phenotypic macrophages have been detected in many scar and fibrotic tissues. However, Sarah et al. found that removal of pro-fibrotic factors did not affect late renal fibrosis in an experiment using transgenic mice deficient in TGF-β1 to observe renal fibrosis after renal ischemia-reperfusion[26]. It is well established that M2 macrophages promote traumatic fibrosis, but this result does not exclude the possibility that their pro-fibrogenic factors may also constantly adapt their function according to their different tissue repair environments.

3.3. Role of macrophages in wound angiogenesis

Anti-inflammatory phenotypic macrophages promote traumatic fibrosis while neovascular sprouting proceeds in an orderly manner. It is believed that microvessels help to stop bleeding and

reduce blood loss from the wound at the beginning of tissue damage, and simultaneously establish a temporary wound base station. This base station becomes the starting point for the growth of a neovascular network that ensures tissue nutrient perfusion and delivery of immune channels for matrix debris[27]. Okonkwo et al. concluded that the milestone step in wound repair is the generation of wound neovascularization and the stabilization of the neovascular basement membrane[28]. However, overgrowth of neovascularization can also lead to traumatic scarring and pathological fibrosis. As mentioned earlier, M2d macrophages are not only associated with pro-tumor growth infiltration but also inextricably linked to tissue neovascularization. Gurevich et al. used clodronate liposomes injected into mice to ablate macrophages in mice and metronidazole-nitroreductase to eliminate macrophages in injured fish and demonstrated that neovascularization was significantly poorer in traumatized surfaces after macrophage depletion[29], suggesting that macrophage guidance is required for neovascular sprouting and migration during wound healing.

Macrophages promote neovascularization by secreting TGF-β and VEGF, and both can be degraded by metalloproteinases (MMPs), serine endopeptidases, and endothelial cells' proteases to induce vascular endothelial cells to migrate to the wound surface and promote tissue repair. It is worth mentioning that, activated by M2 macrophages, especially VEGF, endothelial cells located at the tip of the vascular sprout - tip cells receive agonistic signals, start to develop and proliferate, and promote the migration of new blood vessels[30].However, it is believed that the tip cells cannot recognize the directionality and purpose of similar cells and the ability to fuse with similar cells. In a real-time imaging experiment of zebrafish blood vessels by Fantin et al., it was observed that macrophages could migrate to the site of vascular fusion and change direction depending on the state of wound healing and contact the corresponding tip cells to promote similar vascular fusion[31]. This experiment re-emphasizes the role of macrophages as guide dogs in this process. In normal wound repair, neovascularization does not proliferate indefinitely. It is believed that macrophages prune and engulf excess neovascularization, thereby inhibiting the angiogenic response to prevent excessive angiogenesis[32]. Gurevich et al. demonstrated in experiments using metronidazole to deplete macrophages during the vascular regression window in triple transgenic fish wounds that the absence of macrophages, leads to decreased levels of endothelial cell apoptosis[29]. Therefore, when the organism recovers to pre-injury or near pre-injury levels, the organism no longer needs excess neovascularization, which in turn prompts macrophages to control programmed endothelial cell death and phagocytosis of apoptotic cells through a mechanism that plays an undeniable role in vascular degeneration in the later stages of trauma recovery.

3.4. Role of macrophages in wound re-epithelialization

Tissue skin regeneration can be divided into three parts, including proliferation, migration, and differentiation of epithelial cells. When tissue cells are in the late stage of repair, keratin-forming cells receive the body's repair instructions and start to proliferate by interacting with ECM proteins near the wound surface through integrin receptors. Keratin-forming cells are the key component of ECM synthesis and the key to the resynthesizing subcutaneous basement membrane[33]. Proliferating keratin-forming cells penetrate the granulation tissue and in the process, keratin-forming cells become flatter and more elongated than usual and extend their cellular synapses, migrating toward the wound surface and filling it[34]. When migrating keratin-forming cells meet each other at the trauma edge, some contact inhibition mechanism between cells causes cell migration to stall and a new lamellar epidermis with an underlying basement membrane is reconstructed from the trauma edge downward and inward. However, the new keratin-forming cells continue to divide and push toward the surface, gradually differentiating into a compound flat epithelium and completing the re-epithelialization of the trauma. Normally, keratin-forming cells do not proliferate or migrate indefinitely, which may be due to the autophagy of keratin-forming cells[35]. When the wound is repaired close to the pre-damaged skin, autophagy is initiated and excess organelles or proteins are degraded via lysosomes. Amitava et al. found in a wound repair experiment in diabetic mice that glycosylation decreased or even inactivated oncoprotein M function, thereby limiting the activation of keratin-forming cells and thus hindering the process of wound re-epithelialization[36]. And it is known that the main source of oncoprotein M is wounded macrophages.

It was found that TGF-β1 is an important factor for trauma re-epithelialization, and its main source is M2 macrophages. In addition, other growth factors include epidermal growth factor (EGF), keratinocyte growth factor (KGF) and heparin-binding epidermal growth factor (HB-EGF), and insulin growth factor (IGF) also have positive effects on epithelial cell proliferation and re-epithelialization. Interestingly, in a study by Gu et al. using macrophage therapy to treat diabetic rat wounds, the

researchers used TNF-α plus IFN-c to stimulate macrophages in rats and showed that after giving TNF-α plus IFN-c to stimulate macrophages in rats, the levels of VEGF and IFG-1 in rats were significantly increased, which advanced the process of vascular regeneration and re-epithelialization of rat wounds, and the speed of wound healing was significantly better than that of the control group[37]. However, it is known that the production of TNF-α and IFN-c is associated with pro-inflammatory phenotypic macrophages. It is worth considering whether the cytokines secreted by anti-inflammatory or pro-inflammatory phenotypic macrophages are dominant in wound re-epithelialization, or whether they act together in the wound repair process, which needs to be further investigated later.

3.5. Role of macrophages in the remodeling phase

The remodeling phase is a protracted battle for the final repair of the trauma. At this time, most cells such as macrophages, fibroblasts, and vascular endothelial cells begin to naturally apoptosis as fewer cells migrate to the trauma surface and cell proliferation decreases, and the demand for nutrient substrates for tissue growth and repair decreases[12]. Fibroblasts are influenced by signals such as TGF-β and VEGF from macrophages, platelets, etc. Fibroblasts receive signals and are directed to become fibroblasts and produce ECM proteins, or are differentiated into α-smooth muscle actin-rich myofibroblasts and increase ECM production to promote tissue remodeling[38]. Trauma remodeling is a constantly changing evolutionary process. Fibroblast growth factor plays a key role in wound repair, and this molecule stimulates angiogenesis and the proliferation of fibroblasts[39]. Fibroblasts produce various collagens, which form very intimate cross-links, thus increasing the tensile strength of the scar, which can be up to 80% of that of undamaged skin. In addition, collagen gradually becomes mature from infancy, in other words, type I collagen gradually replaces type III collagen in tissues, and the type III/type I ratio gradually decreases. However, the integrity and function of the scar tissue in the later stages of remodeling are much less than that of the pre-injury skin tissue. It is agreed that it is related to the different arrangement of collagen fibers in the scar versus the primary skin.

Macrophages are one of the major sources of stromal MMPs, and proteases bind to TIMPs to form complexes that regulate the function of MMPs.MMPs can degrade and remodel almost all ECM components and basement membrane macromolecules[40].MMP1 can promote the migration of keratin-forming cells to facilitate wound healing, but it is the late downregulation of MMP1 that allows wound remodeling to proceed smoothly. Moreover, MMP19, as an effective basement membrane degrading enzyme, can inhibit the excessive proliferation of human microvascular endothelial cells and play a negative feedback effect in the late regression of skin capillary proliferation[41].MMPs and TIMPs need to be in balance in the body to prevent delayed wound healing or excessive scarring of the wound. Stem cell diploid differentiation for wound healing has long been a hot topic of research. Jia et al. concluded that bone marrow mesenchymal stem cells can direct macrophages to polarize to anti-inflammatory M2 type and promote wound healing[42]. During the trauma remodeling phase, MSCs are activated to differentiate and increase the secretion of ECM, thus accelerating the production of damaged skin cells and the maturation of the trauma[43]. As the trauma matures, the body's demand for macrophages decreases in number and function. It is believed that during the later stages of normal repair of tissue injury, the decreased activity of macrophages that reside in the trauma surface or spontaneous programmed death promotes matrix remodeling and lysis of fibrosis, which leads to a decrease in ECM production. The natural contraction of the trauma substrate results in a smaller volume of healing scar tissue.

4. Conclusions

In conclusion, M1 macrophages play a defensive role in the body by killing pathogens, phagocytosing apoptotic cells, and limiting inflammation, while M2 macrophages also play a role in tissue repair by inhibiting inflammation, suppressing the immune response, tissue repair, and remodeling.M1 and M2 phenotypes can shift to each other under certain conditions, but the mechanism of M1 and M2 interconversion is not well understood. The variability and complexity of human individuals and the interspecies differences in experiments are among the reasons for the slow progress in the study of wound healing mechanisms. According to current trauma studies, impaired macrophage phenotypic polarization is the main cause of delayed wound healing. So, what is the best way to promote macrophage polarization? When is the best time point for M1 to M2 polarization? Or what is the optimal ratio of M1/M2 polarization? These urgent questions need to be further investigated.

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