Macrophage polarization in tissue fibrosis (#81507)

First submission

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- Clear, unambiguous, professional English language used throughout.
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- Does the Introduction adequately introduce the subject and make it clear who the audience is/what the motivation is?

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- Article content is within the Aims and Scope of the journal.
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- Methods described with sufficient detail & information to replicate.
- Is the Survey Methodology consistent with a comprehensive, unbiased coverage of the subject? If not, what is missing?
- Are sources adequately cited? Quoted or paraphrased as appropriate?
- Is the review organized logically into coherent paragraphs/subsections?

VALIDITY OF THE FINDINGS

- Impact and novelty not assessed. Meaningful replication encouraged where rationale & benefit to literature is clearly stated.
- Conclusions are well stated, linked to original research question & limited to
- Is there a well developed and supported argument that meets the goals set out in the Introduction?
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3

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Macrophage polarization in tissue fibrosis

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Macrophages are a class of pluripotent and highly plastic immune cells which polarize into different macrophage subpopulations involved in host defense, tissue repair and regeneration , as well as fibrosis. When the M1 / M2 imbalance, especially M2 macrophages persistent activation or sustained recruitment are likely to contribute to the development of pathological fibrosis by producing multiple pro-fibrotic cytokines to alter the tissue microenvironment required for the proliferation and transdifferentiation of myofibroblasts. Macrophages can also transform from one phenotype to another. Some studies have found that regulating macrophages polarization can inhibit the development of inflammation and cancer. However, the exact mechanism of macrophages polarization in different tissue fibrosis has not been fully elucidated. This review will discuss the major fibrosis-related pathways and the role of macrophages polarization in fibrosis of lung, kidney, liver, skin and heart, hoping to provide useful reference for the future treatment of fibrosis.

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Keywords:Macrophage polarization, type 2 macrophage, myofibroblasts, lung fibrosis, kidney fibrosis, liver fibrosis, skin fibrosis, cardiac fibrosis

Abstract

Macrophages are a class of pluripotent and highly plastic immune cells which polarize into different macrophage subpopulations involved in host defense, tissue repair and regeneration , as well as fibrosis. When the M1 / M2 imbalance, especially M2 macrophages persistent activation or sustained recruitment are likely to contribute to the development of pathological fibrosis by producing multiple pro-fibrotic cytokines to alter the tissue microenvironment required for the proliferation and transdifferentiation of myofibroblasts. Macrophages can also transform from one phenotype to another. Some studies have found that regulating macrophages polarization can inhibit the development of inflammation and cancer. However, the exact mechanism of macrophages polarization in different tissue fibrosis has not been fully elucidated. This review will discuss the major fibrosis-related pathways and the role of macrophages polarization in fibrosis of lung, kidney, liver, skin and heart, hoping to provide useful reference for the future treatment of fibrosis.

1. Introduction

Sentences in Abstract and Introduction are too similar. Please consider revising the beginning of the abstract.

Macrophages are a class of pluripotent and highly plastic immune cells that play a key role in host defense, tissue repair and regeneration , as well as fibrosis[1]. According to different

I am not sure how accurate this is, as monocyte differentiation can lead to various types of macrophages.

sources, macrophage is divided into Bone marrow-derived macrophage (BMDM) and tissue-resident macrophage (TRM). BMDM refers to monocyte-macrophage system, including monocytes in bone marrow and blood, and tissue-infiltrating macrophages, which are the main cells involved in the process of fibrosis. In different tissue environments, it can be polarized into two primary macrophage subpopulations: (1) The classically activated or CD11b+/Ly6C^{high} M1 macrophages highly express CD80/CD86 and nitric oxide synthase (iNOS), which are stimulated by interferon-γ (IFN-γ) and lipopolysaccharide (LPS), and secrete pro-inflammatory cytokines like TNF-α, IL-6 and IL-1β; (2) The alteratively activated or CD11b+/Ly6C^{low} M2 macrophages express CD206/CD163, which are stimulated by IL-4 and IL-13, and ~~play the roles of~~ promote tissue repair, regeneration, and fibrosis by secrete factors related to fibroblast activation and fibrosis progression, such as TGF-β, platelet-derived growth factor (PDGF), fibroblast growth factor 2, insulin-like growth factor binding protein 5 and galactin-3[2]. M2 macrophages can be further polarized into M2a, M2b and M2c ~~macrophages~~. M2a and M2c ~~macrophages~~ secrete TGF-β and other pro-fibrotic factors to induce tissue fibrosis [3]. M2b macrophages, also known as regulatory macrophages, maintain a balance between pro-inflammatory and anti-inflammatory functions. TRM, namely alveolar macrophages and hepatic Kupffer cells, can self-renew and proliferate.

Needs citations!

This section can be improved by breaking down into 3-4 sentences, and correcting for grammer

Fibrosis is a pathological process of parenchymal cell destruction, abnormal increase and excessive deposition of extracellular matrix (ECM) in tissues. Fibrosis can occur in multiple organs such as lung, kidney, liver, heart, skin and other organs. The mild ones only show fibrosis, and the severe ones show tissue structure damage and organ sclerosis, eventually leading to organ failure. At present, there are few effective treatments, which place a heavy burden on humans, and about 45-50% of deaths can be attributed to fibrosis in developed countries alone[4]. Myofibroblasts of excessive proliferation and activation produce ECM and collagen,which play an important role in the process of fibrosis. It is highly heterogeneous, such as mesenchymal progenitor cells/stem cells (MSC), adipocyte progenitor cells (AP), epithelial cells, endothelial cells and monocyte macrophages can transform into myofibroblasts. Most importantly, macrophages provide microenvironment required for the proliferation and activation of myofibroblasts.

Each sentence needs appropriate citation

What are the consequences of mild fibrosis?

Previous studies have mostly focused on the mechanism of macrophages involved in inflammation and tissue damage repair. In recent years, more studies have shown that macrophages polarization play a role in fibrosis of lung, kidney, liver, skin, heart and other organs. In different fibrosis models, M1 macrophages mainly secrete cytokines to promote inflammatory; M2 macrophages promote tissue regeneration and repair, while persistent activation or sustained recruitment not only produce fibrosis-related factors to change local immune microenvironment, but also directly transdifferentiate into myofibroblasts to regulate tissue fibrosis. However, different macrophage phenotypes convert and produce matrix metalloproteinases (MMP) involved in regression of fibrosis. Therefore, exploring the phenotype transformation and exact mechanism of macrophages in the process of fibrosis is helpful to provide a new therapeutic strategy for the future treatment of fibrosis.

It is not clear what the authors are trying to convey. This section needs more clarity and citations.

There is insufficient evidence to confirm how macrohages/monocytes to myofibroblasts transition or MMT occurs. MMT is still a theory.

Authors should explain briefly what MMT is in a few sentences, in the introduction.

At present, the incidence and mortality of fibrosis are high, ang there are few effective treatment methods. The purpose of this review is (1) to summarize the research progress of macrophage and tissue fibrosis; (2) to let people know that macrophages polarization play an important role in many kinds of tissue fibrosis and may be a potential target in fibrosis treatment. It may be helpful to researchers engaged in macrophage function, fibrosis pathogenesis and anti-fibrosis drug development.

It would be useful to include in the Introduction, towards the end of the final paragraph, what the review is going to discuss (signaling pathways relevant to macrophage driven fibrosis and tissue types most affected by fibrotic disease.

SURVEY METHODOLOGY

To summariza the role of macrophges polarization in tissue fibrosis from multiply perspectives, the Web of Science and PubMed search engines were used to search the literature, and search terms included “macrophges polarization,” “fibrosis,” and “M2 macrophage”. In the process of summarizing the literature on tissue fibrosis, we further refined the tissue classification. We searched the literature with two keywords for fibrosis and macrophages, adding the tissue type (‘‘lung,’’ ‘‘kidney,’’ ‘‘liver,’’ ‘‘skin,’’ or ‘‘cardiac,’’).

2. MAJOR FIBROSIS-RELATED SIGNALING PATHWAYS

Notch signaling pathway in involved in myofibroblast generation

2.1 TGF-β/Smad pathway

TGF-β is a multifunctional cytokine that regulates cell proliferation, differentiation, apoptosis and the production of ECM. TGF-β superfamily mainly includes TGF-β1, TGF-β2 and TGF-β3, which are produced by macrophages, fibroblasts, alveolar epithelial cells, activated T

cells or B cells. Macrophage-derived TGF-β1 is typically profibrotic, and numerous studies have identified various macrophage subsets as key producers of TGF-β1[5]. When the RAW 264.7 cells were treated with IL-4 for 48 h, the level of TGF-β1 in the supernatant of cell culture was significantly higher than the control group [6]. TGF-β binds to type I and type II TGF-β receptors on the cell membrane, phosphorylates Smad2 and Smad3, and forms a complex with Smad4, enters the nucleus to activate transcription factors, promotes collagen synthesis, ECM deposition and cell transdifferentiation involved in tissue fibrosis(Fig. 1). Smad7 negatively regulates TGF-β/Smad signaling pathway [7,8].TGF-β/Smad signaling pathway is one of the main pathways involved in fibrosis. TGF-β/Smad3 regulates the transformation of M2 macrophages into myofibroblasts (MMT) in renal fibrosis in a mouse model of unilateral ureteral obstruction [9]. In the lung tissue of bleomycin-induced pulmonary fibrosis mice, the expression of TGF-β and the phosphorylation level of Smad2 were significantly increased, and the endothelial cells were induced to transform into myofibroblasts (EMT). LY2109761, inhibited the phosphorylation level of Smad2, and inhibited the increase of α-SMA induced by M2 macrophages and the decrease of e-cadherin and CK-18 were[6]. Although over two decades of research on the TGF-β pathway, there is a lack of significant clinical progress of TGF-β signaling inhibitors in the treatment of fibrotic disease. Decreasing the number of TGF-β1-producing macrophages, rather than comprehensively attenuate TGF-β1 may provide a more rational approach to ameliorate fibrosis.

This sentence can be split in to two or more sentences to improve clarity. The authors should also appropriately cite this.

Can the author comment on Smad2 as a drug target? It is important to include data from in-vivo studies that have successfully decreased or halted tissue fibrosis through targeting of TGF-beta1

2.2 Wnt/β-Catenin pathway

Wnt, a cell signaling molecule, can stimulate cell proliferation, differentiation and migration. Wnt/β-Catenin pathway is the classic Wnt signaling pathway. Wnt binds to its receptor Frizzled (seven-time transmembrane protein) and co-receptor Low density Lipoprotein receptor-associated Protein 6 (LRP6) or LRP5, to activate Dishevelled (Dvl) leading to the phosphorylation of LRP5/6 and inhibiting the activity of β-catenin-degrading complexes formed by Serine/threonine protein kinase (GSK3) and other proteins, stabilizing free β-Catenin in the cytoplasm. β-Catenin accumulated in the cytoplasm enters the nucleus and binds to T cell factor (TCF)/lymphatic enhancer binding factor (LEF) to activate the transcription of target genes(Fig. 1) [10]. The expression products of these target genes can induce EMT to promote cardiac

fibrosis [11]. The Wnt/β-catenin signaling pathway also regulates the differentiation of alveolar macrophages and promotes the occurrence of pulmonary fibrosis [12].

2.3 JAK/STAT3 pathway

Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal pathways were first identified in mammals, which regulate cell growth, proliferation, differentiation, and apoptosis [13]. Many studies have confirmed that JAK/STAT3 signaling plays an important role in the pathogenesis of fibrosis, and the up-regulation of STAT3 expression has been detected in fibrotic tissues [14]. The phosphorylation of STAT3 can regulate the transcription of IL-4 and IL-10, and promote the polarization of M2 macrophages(Fig. 1) [15]. STAT3 promotes the fibrosis process through the following ways: 1) inducing the production of ECM; 2) regulating the transcription of MMP and tissue inhibitors of metalloproteinases (TIMPs); 3) inhibiting the apoptosis of fibroblasts; 4) participating in the EMT process as a non-standard TGF-β1 downstream factor; 5)promoting M2 macrophage polarization. Some JAK/STAT3 inhibitors, such as JSI-124, C188-9, S3I-201, and calinurin-B, have been shown to reduce fibrosis progression in preclinical animal models [16-19].

3. MACROPHAGES POLARIZATION AND TISSUE FIBROSIS

3.1 Macrophages and lung fibrosis

Pulmonary fibrosis is a chronic, progressive lung disease in which abnormal proliferation of fibroblasts and myofibroblasts and excessive deposition of ECM destroy normal alveolar structure, decrease static lung compliance, interrupt gas exchange, and eventually lead to respiratory failure and death. The exact etiology has not been fully clarified and there are few effective treatments other than lung transplantation.

Pulmonary macrophages evolve from monocytes and widely present in the alveoli and lung interstitium. They are polarized into different subgroups to perform specific functions. When epithelial cells are damaged, monocyte precursors are largely activated in the action of monocyte chemoattractant protein-1 (monocyte chemotactic protein 1, MCP-1) and enter the lungs to differentiate into alveolar macrophages aggregated to the site of inflammation. Under the action of inflammatory factors, they are polarized into M1 macrophages and secrete TNF- α and IL-6, which play the role of promoting inflammatory and removing necrotic tissue [20]. Sakaguchi et

al [21] also confirmed in the rat acute lung injury model induced by LPS that M1 macrophages secrete IL-23 to promote the proliferation of lung memory Th17 cells and induce the production of IL-17, IL-22 and IFN-γ, thus accelerating the process of lung injury. Moreover, M1 alveolar macrophages can also produce MMP to promote ECM degradation and participate in the regression of fibrosis [22]. The sustained inflammatory response will promote the occurrence of tissue fibrosis in the later stage of injury. In the lung tissues of mice with bleomycin-induced pulmonary fibrosis, alveolar macrophages express CD11b (a marker of newly recruited macrophages) and CD206 [23], and about one-third of fibroblasts are transformed from lung epithelial cells [24]. M2 macrophages promote the generation of pulmonary fibrosis effector cells in the following ways: 1) Secreting TGF-β, IL-4 and IL-13 to transdifferentiate circulating fibroblasts into α-SAM+ myofibroblasts [25]; 2) TGF-β activates Smad2/3 to promote EMT involvement in pulmonary fibrosis [6]; 3) Secreting Wnt7a protein to activate the Wnt/ β-catenin channel and promote the differentiation of lung MSC to myofibroblasts [26]. In turn, more ECM is deposited in the lung interstitium to form pulmonary fibrosis(Fig. 2). At present, the FDA approved two new drugs, nintedanib and pirfenidone to treat pulmonary fibrosis. They can stabilize patients' conditions well, but do not reverse the progression of fibrosis[27]. Mannosylated albumin nanoparticles loaded with TGFβ1-siRNA specifically bind to the mannosylated receptor CD206 on the surface of M2 macrophages which silence the expression of TGFβ1 and significantly alleviate bleomycin-induced pulmonary fibrosis in mice [28]. Tacrolimus is able to suppress M2 macrophages polarization and M2-induced fibroblast to myofibroblast transition, thus resulting in a decline of collagen deposition and pro-fibrotic cytokines secretion, ultimately relieving the progression of lung fibrosis in vivo and vitro.[29]Thus, targeting M2 macrophage or inhibiting pro-fibrotic phenotype could be a novel strategy or target for the prevention and treatment of pulmonary fibrosis.

Include Tacrolimus in the figure with the original paper citation

3.2 Macrophages and kindey fibrosis

Kidney fibrosis is the ultimate common pathway of most progressive chronic kidney disease (CKD). Its pathological features are the replacement of normal tissue structure by ECM, the absence of functional cells, and the infiltration of numerous inflammatory cells. The number of macrophage infiltration in the fibrotic kidney tissue correlates with the severity and prognosis of

fibrosis. At the early stage of kidney injury, a large number of chemokines represented by CCL2 are released locally to recruit CCR2+/Ly6C^{high} monocyte/macrophages to the site of injury, and produce many inflammatory factors to trigger inflammatory response [30]. Studies have also shown that the accumulation of B cells in the early stage of kidney injury enhances the mobilization and recruitment of monocyte/macrophage cells, thus accelerating renal fibrosis [31]. Depletion of monocyte/macrophages through clodronate liposomes can lower blood pressure and reduce hypertensive kidney injury and fibrosis [32]. Hu et al also demonstrated that IL-10 and TGF-β expression in the clodronate liposomes treatment group was decreased, which may be attenuate renal fibrosis via M1/M2 polarization[33]. In the late repair stage of kidney injury, macrophages tranform into M2 type with anti-inflammatory and pro-fibrosis, and participate in kidney fibrosis through the following ways: Firstly, they release TGF- β , IL-1 β , PDGF and other pro-fibrosis factors to activate fibroblasts, produce ECM, and promote the occurrence of renal interstitium fibrosis. Secondly, M2 macrophages are directly involved in the process of kidney fibrosis by transforming into myofibroblasts through TGF- β / Smad3-mediated MMT. In the mouse model of unilateral ureteral obstruction (UUO) and kidney biopsy samples from patients with chronic active renal allograft rejection, CD68+/α-SMA + cells accounted for about 50% of the total number of α -SMA + myofibroblasts, of which 75% were M2 type co-expressing CD206, and a small number were M1 type co-expressing iNOS [34]. On the contrary, studies have shown that only a small part of monocyte/macrophages are transformed into myofibroblasts. These contradictory results are worthy of further study [35]. Thirdly, macrophage-derived cytokines activate EMT and transdifferentiate pericytes into myofibroblasts [36]. Fourthly, activated macrophages damage the glomeruli and peritubular capillaries, thereby promoting hypoxic-driven fibrosis. Furthermore, there is evidence that pro-fibrotic macrophages participate in the regression of fibrosis by producing MMP to degrade ECM [37].

Macrophages polarization is regulated by a variety of signaling pathways. Ren et al [38] found that Rictor/ mTORC2 signaling can promote macrophage activation and kidney fibrosis, while loss of Rictor or blocking of upstream Akt can eliminate M2 macrophage polarization stimulated by IL-4 or TGF-β1. Similarly, Notch signaling regulates cell differentiation, proliferation and apoptosis, can also affect the polarization of macrophages. Pagie et al [39]

Include clodronate in the figure

Authors should include a mention of pericyte transdifferentiation, briefly in a sentence or two in the introductory part, especially that CTGF secretion, can trigger pericytes to transdifferentiate PMID: 23302695

Given that podocytes are similar to pericytes, is it possibly that podocytes may trans-differentiate into myofibroblasts specific to the kidney? There is some evidence to suggest that diseased podocytes aquire pericyte like characteristics and may undergo transdifferentiation into myofibroblasts. PMID: 18337603; PMID: 21931791; PMID: 23325411 In any case podocytes and pericytes can secrete tgf-b1.

induced human blood monocytes in vitro and found that the selective DLL4 ligand of Notch receptor could not only promote the polarization of M1 macrophages, but also can prevent M2 macrophages differentiation by inhibiting M2-specific gene expression and inducing apoptosis. In addition, the Wnt/ β-catenin signaling pathway can also regulate macrophage polarization. Wnt5a[40] mediates macrophage polarization by stimulating the expression of YES-related proteins or transcriptional coactivators with PDZ-binding sequences. Wnt3a[41] intensifies IL-4 or TGF-β-induced M2 polarization by activating STAT3, and β-catenin deficiency inhibits macrophage polarization, thereby alleviating renal fibrosis. Recent studies have found that the abnormal expression of related genes in macrophages can also regulate the polarization and transdifferentiation of macrophages, such as the downregulation of mitochondrial fusion protein 2 (MFN2), which leads to its polarization into fibrosis type M2[42]; Upregulation of Twist1 increases downstream galactolectin 3, prompting M2 macrophages to secrete fibrotic growth factor or MMT(Fig. 3)[43]. In summary, immunomodulatory molecules related to macrophages recruitment and polarization may be potential therapeutic targets for the treatment of kidney fibrosis.

Are these mechanisms of fibrosis specific to kidney fibrosis?

Treatment with lisinopril as well as Ramipril therapy has also shown to decrease TGFb1 and delay renal fibrosis in mouse models PMID: 12631109. Can authors comment about that, especially because Angiotensin II stimulation also mediates macrophage recruitment and accumulated

3.3 Macrophages and liver fibrosis

Liver fibrosis is a pathological repair process for the formation of pseudolobules after hepatocyte destruction caused by chronic liver disease. If treated aggressively during this period, it can still be reversed; otherwise, progressive accumulation of fibrotic tissue leads to cirrhosis and further development to hepatocellular carcinoma and even liver failure.

Hepatic macrophages, including tissue macrophages, namely hepatic Kupffer cells and BMDM, play their respective roles in different stages of hepatic fibrosis. Kupffer cells exist in the hepatic sinusoids which recognize, phagocytic and eliminate foreign antigens, secrete inflammatory cytokines and chemokines to stimulate the body's inflammatory response and recruit monocytes/macrophages. Han et al [44] found that compared with the normal control group, the expression of CD68 in fibrotic fatty hepatitis tissue was significantly increased, and all were GFP+, F4/80+ and Ly6C+ macrophages. The consumption of macrophages with chlorphosphonate liposomes could alleviate liver fibrosis, indicating that the macrophages involved in liver fibrosis are BMDM rather than Kupffer cells. Interestingly, the number of

This sentence needs citation, how does chlorphosphonate liposomes alleviate liver fibrosis?

hepatic M2 macrophages is positively correlated with the severity of liver fibrosis, and the up-regulated expression of CCL promotes macrophages' conversion to the M2 type [45]. On the one hand, BMDM produces IL-1β and TNF-α to promote NF-κB-mediated myofibroblast proliferation [46]. On the other hand, profibrotic TGF- β is secreted to activate the resting hepatic stellate cells (HSC) in a smad2/ Smad3-dependent manner, and transforming them into myofibroblasts, producing excessive ECM components and promoting the occurrence of liver fibrosis [47]. It has recently been found that increased expression of Mer tyrosine kinase regulates downstream STAT3, ERK1/2, and p38 phosphorylation, and promotes HSC migration and proliferation [48]. HSCs can secret a large amount of lactate to increase the levels of acetylation modification at the promoter regions of genes (Arg-1, CD163, IL-10, and TGF-β1), thereby promote the transformation of macrophages from M1 type to M2 type and the progression of liver fibrosis [49]. Furthermore, macrophages are involved in the regression of fibrosis after injury by secreting MMP9 to degrade ECM or by polarizing into M2b-like macrophages (Fug. 4)[50]. Transcriptome sequencing analysis of over 100,000 human single cells revealed TREM2 and CD9 positive macrophage subsets are associated with fibrosis [51].

3.4 Macrophages and skin fibrosis

Keloid (KD) is a common fibroproliferative disease with unknown etiology. It is characterized by the excessive proliferation of fibroblasts and collagen fiber deposition in the healing process of skin injury, which is often accompanied by itching and pain. It is difficult to treat and has a high recurrence rate, which brings heavy psychological and financial burden to patients.

Skin macrophages include Langerhans cells in the epidermis and BMDM in the dermis. Fibrosis is mainly found in the dermis, M2 macrophages play a key role in skin fibrosis. Knipper and colleagues have showed that collagen fibril assembly following mammalian dermis injury and repair is highly dependent on M2 macrophages[52]. Compared with normal skin and scar tissue, M2 macrophages in keloid significantly increased [53,54], and promoted the proliferation and migration of skin fibroblasts by generating connective tissue growth factor and activating ERK1/2/STAT3 and AKT/STAT3 signaling pathways [55]. tsRNA-14783 participates in KD formation via promoting M2 macrophages polarization[56]. $IL_{13}RA2$ downregulation, a ‘decoy’ receptor of IL13, in fibroblasts promotes M2 macrophages polarization and KD fibrosis via

STAT6 activation[57]. Bhandari et al [58] recently showed that macrophages and skin fibroblasts were mutually activated to secrete IL-6 and TGF-β and promote the fibrosis process through STAT3 phosphorylation. HPH-15, a histidine pyridine-histidine ligand derivative, alleviates bleomycin-induced mouse skin fibrosis by inhibiting the phosphorylation of Smad3 in skin fibroblasts and macrophages [59]. In addition, Shook et al [60] found that CD301b+ macrophages produce PDGF and insulin-like growth factors, which selectively promote AP proliferation and adipocyte-myofibroblast transformation at the trauma site, and then secrete ECM and collagen fibers to promote the fibrosis process(Fig. 5). In skin fibrosis, macrophages tend to polarize into M2 type, which secrets pro-fibrotic factors to change in local microenvironment and further promote M2 macrophages polarization.

include the proposed therapeutic in the figure

3.5 Macrophages and cardiac fibrosis

Cardiac fibrosis is the differentiation and proliferation of cardiac fibroblasts and excessive deposition of ECM, leading to cardiac hypertrophy and reduced diastolic function, eventually leading to heart failure. It is a key prognostic factor of heart disease. In the early stage of injury, M1 macrophages are used to induce inflammation and transition from pro-inflammatory M1 to reparative M2 mitigate cardiac dysfunction after myocardial infarction (MI). In the later stage of injury, M2 macrophages primarly induce cardiac fibrosis. In the fibrotic area of MI, BMDMs differentiate into a-SMA+ fibroblasts and coronary artery endothelial cells undergo an endothelium-to-mesenchymal transition induced by TGF-β , which further increase the number of fibroblasts [61]. M2 macrophages aggregate and activate to promote cardiac fibrosis in an angiotensin II-induced hypertensive cardiac model [62]. Similarly, in elderly mice, aldosterone-exposed mice as well as cardiac biopsy specimens of patients with left ventricular ejection fraction retained, M2 macrophages increased and secreted IL-10 to activate fibroblasts and promote collagen deposition and myocardial fibrosis(Fig. 6) [63]. In addition, Shiraish et al [64] demonstrated that Nrg1 produced by BMDM and Nrg1 co-receptor ErbB expression on the surface of cardiac fibroblasts increased after MI, which combined to activate the downstream PI3K/Akt pathway, inhibit the aging and apoptosis of cardiac fibroblasts, promote their proliferation and lead to fibrosis. On the contrary, some studies have found that the transformation of macrophages from the pro-inflammatory M1 to the anti-inflammatory M2 can

into myofibroblasts?

alleviate cardiac fibrosis, and M2b macrophages can improve cardiac fibrosis in rat models of myocardial ischemia/reperfusion injury [65,66].

4. DISCUSSION

Recently, the role of macrophages in tissue fibrosis has attracted people's attention. Under the influence of different microenvironments, macrophages switch to specific phenotypes to participate in the process of inflammation and fibrosis. Macrophages are a driver of fibrosis. It can regulate myofibroblast function and ECM degradation. This review summarizes recent studies on the role played by macrophages during the fibrosis of different tissues. It found that the number of M2 macrophages is positively correlated with the severity of fibrosis and supressing M2 macrophages polarization be likely to relieve the progression of fibrosis. But it is not absolute whether any form of macrophage is beneficial or disadvantageous for tissue fibrosis, as macrophages have multiple phenotypes and play distinct roles in specific processes in different tissues. We need to study the correlation between different phenotypes of macrophages and fibrosis as well as the transformation and evolution process of macrophages in different stages of fibrosis in depth. In addition to clarifying mechanism of different macrophage subpopulations promote, inhibit, or reverse fibrosis, future research should also elucidate the timing and target of regulating macrophage polarization and phenotypic conversion. It will help us understand the unique contribution of macrophages in tissue fibrosis and bring greater breakthrough for fibrosis treatment.

due to?

Sentences could be restructured to remove redundancies and improve readability.

may

This sentence is confusing. Perhaps it can be broken into two sentences with more specifics such as naming the specific subpopulations.

It is not evident what the authors refer to by timing

Discussion comes across as vague. Perhaps it can be improved by providing specific examples.

ACKNOWLEDGEMENTS

The authors thanks their laboratory colleagues for their help in this review.

ADDITIONAL INFORMATION AND DECLARATIONS

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Competing interests

The authors declare that they have no competing interests.

Author Contributions

Huidan Yang conceived and designed the experiments, performed the experiments, analyzed the data, prepared figures and/or tables, authored or reviewed drafts of the article, and approved the final draft.
Hao Cheng conceived and designed the experiments, performed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
Rongrong Dai performed the experiments, analyzed the data, prepared figures and/or tables, and approved the final draft.
Lili Shang performed the experiments, analyzed the data, authored or reviewed drafts of the article, and approved the final draft.
Xiaoying Zhang conceived and designed the experiments,authored or reviewed drafts of the article, and approved the final draft.
Hongyan Wen conceived and designed the experiments,authored or reviewed drafts of the article, and approved the final draft.

Data Availability

The following information was supplied regarding data availability:

This is a literature review and does not have raw data.

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Figure 1

Fig1. The major fibrosis-related signaling patnways.

Some signaling pathways are associated with tissue fibrosis, such as TGF-β/Smad, Wnt/β-Catenin, and JAK/STAT3, which regulate target gene transcription, ECM production and transformation of different cells into myofibroblasts to lead to tissue fibrosis.

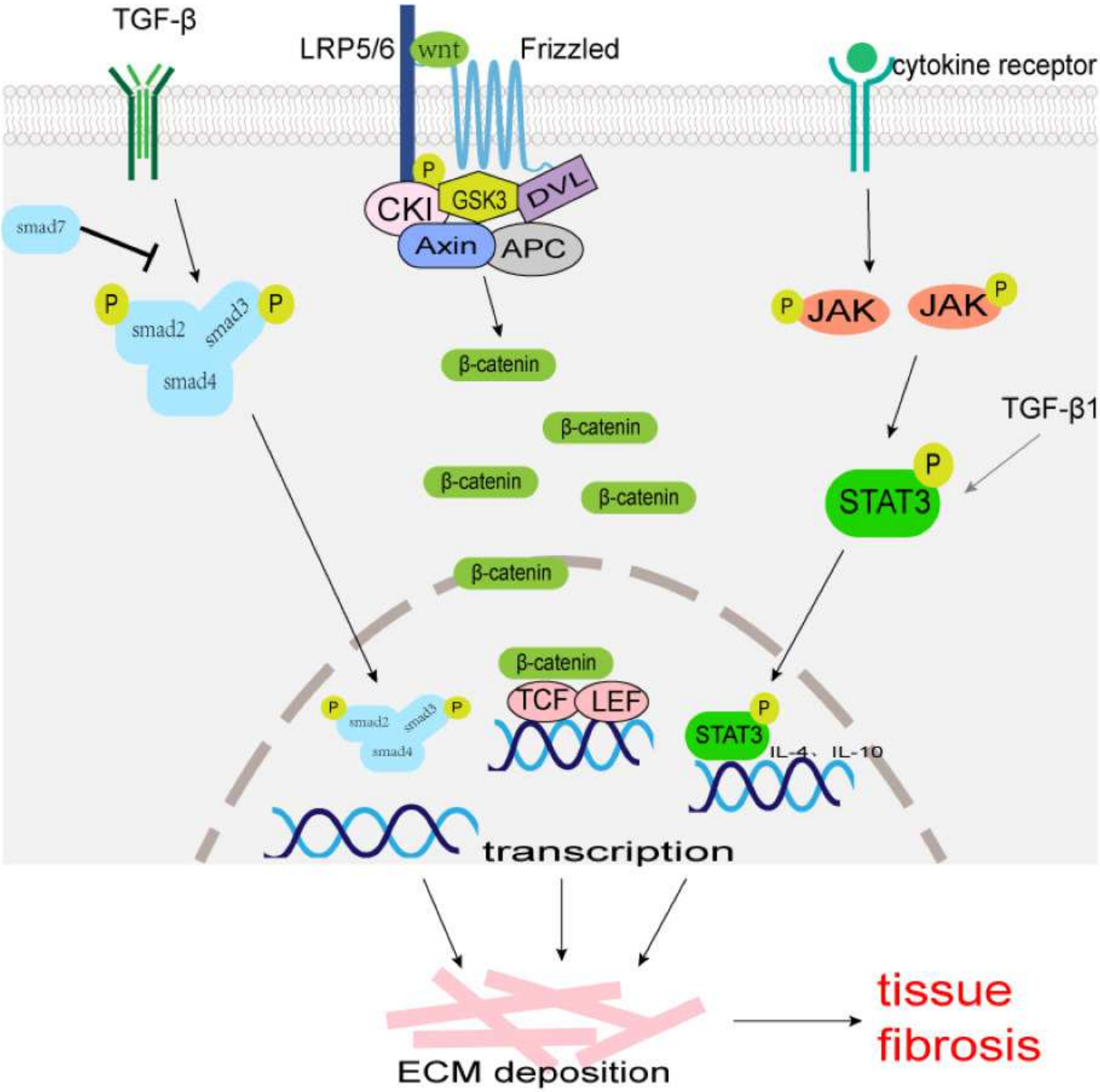
TGF-β
LRP5/6
wnt
Frizzled
cytokine receptor
smad7
P
CKI
GSK3
DVL
Axin
APC
smad2
smad3
smad4
β-catenin
JAK
TGF-β1
STAT3
TCF
LEF
IL-4、IL-10
transcription
ECM deposition
tissue
fibrosis

Figure 2

Fig2. Macrophages in lung fibrosis.

After damage of alveolar epithelial cells, monocytes are activated by MCP-1 chemotaxis and further differentiated into M1 and M2 macrophages under the action of inflammatory factors. M1 macrophages secrete TNF-α, IL-6 and IL-23 to promote inflammation, and also produce MMP to degrade ECM. The secretion of TGF-β, IL-4, IL-13 and Wnt7 by M2 macrophages makes fibroblasts, endothelial cells and MSC transdifferentiate into myofibroblasts, producing ECM and leading to pulmonary fibrosis.

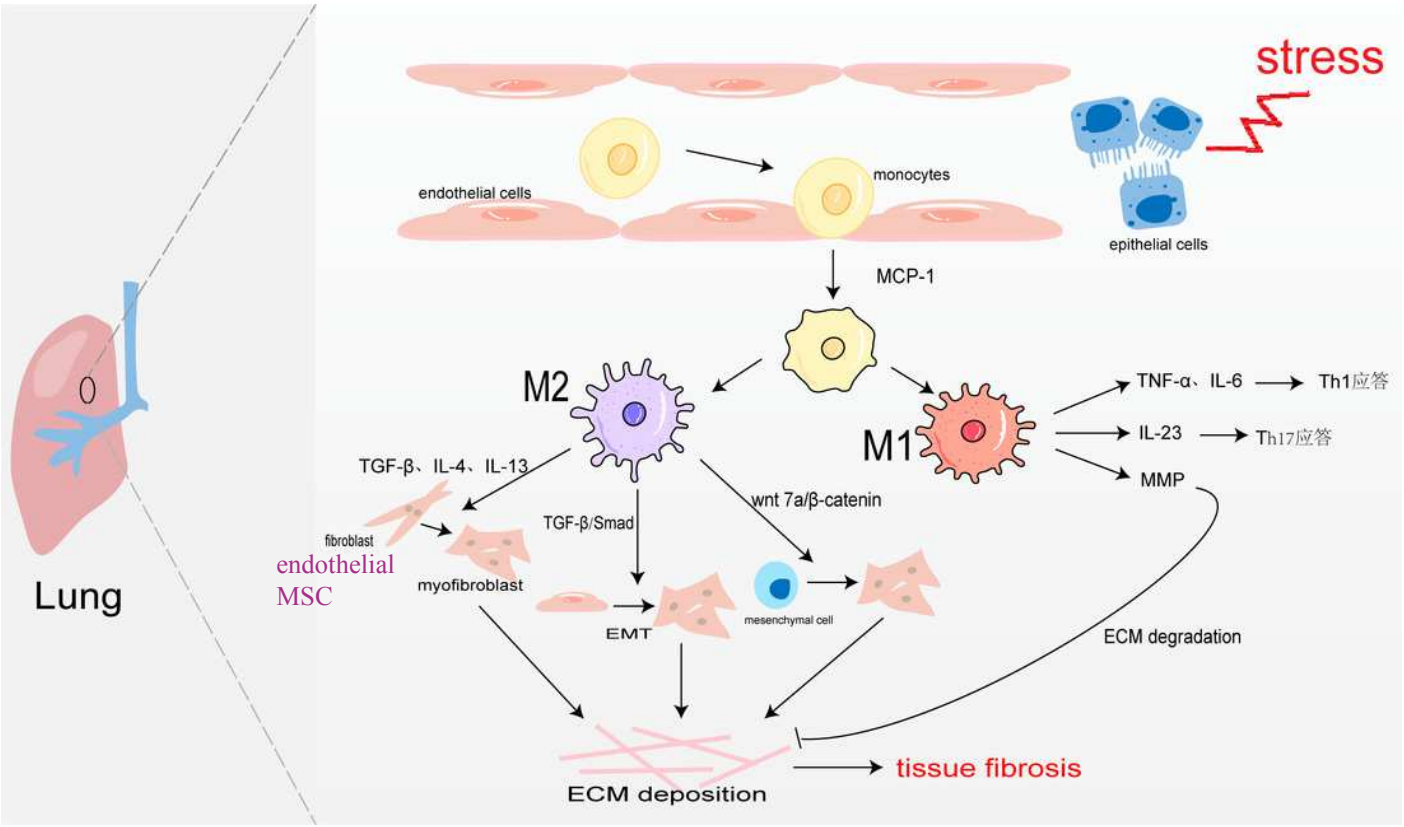

Figure 3

Fig3. Macrophages in kindey fibrosis.

After kidney injury, locally released CCL2 recruits CCR2+/Ly6C monocyte/macrophages to the injured site, leading to local inflammatory response. Under the mediation of different signaling pathways macrophages are polarized to M1 and M2, which produce a variety of cytokines to maintain inflammation, activate fibroblasts, MMT, EMT and hypoxia-induced fibrosis. [high]

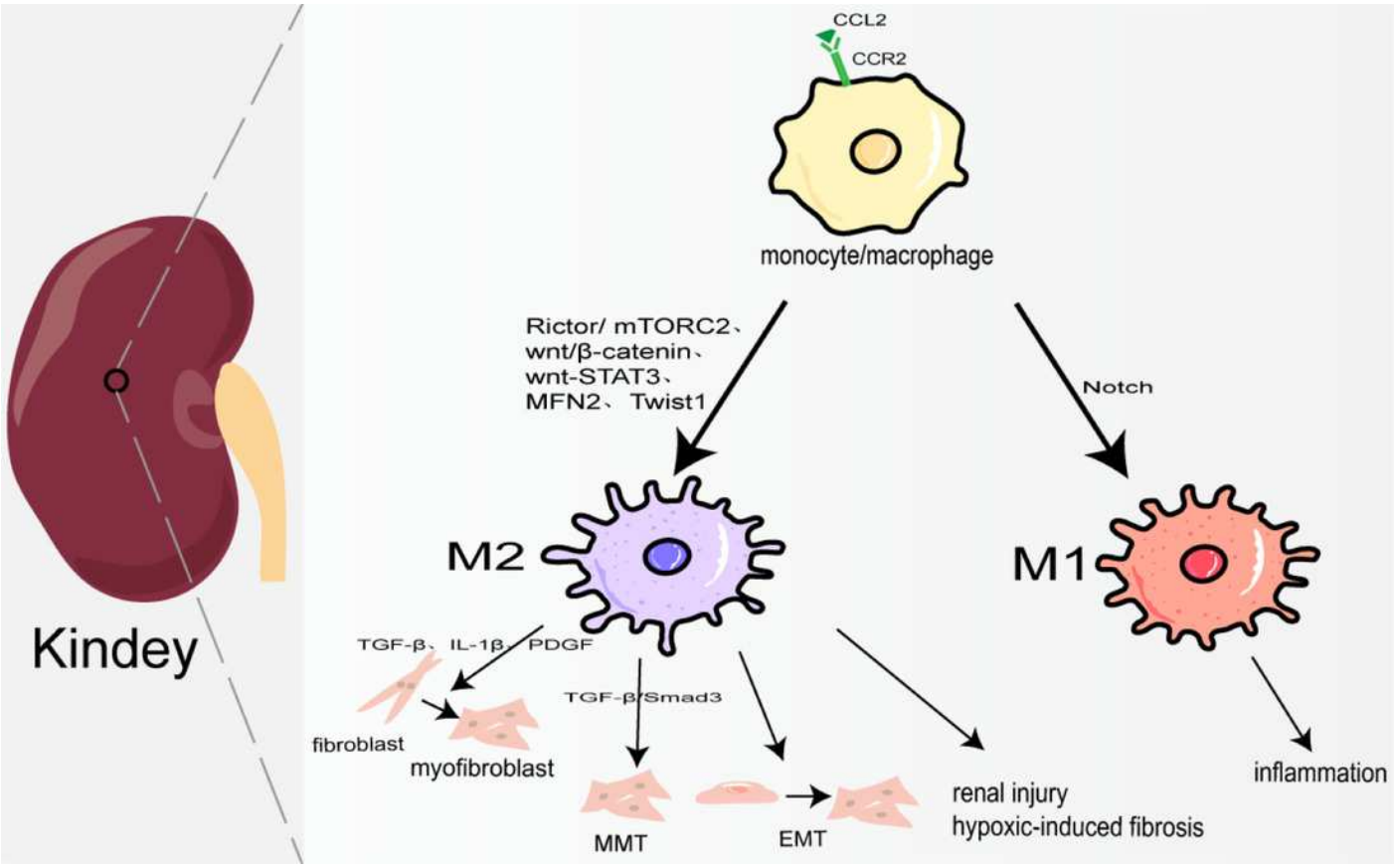

Figure 4

Fig4. Macrophages in liver fibrosis.

Kupffer cell is an inherent macrophage in hepatic sinusoids. When hepatocytes are damaged, inflammatory mediators such as chemokines are produced, and monocytes/macrophages are recruited into the tissues. The proliferation of myofibroblasts and the activation of resting HSC resulted in excessive deposition of ECM leading to liver fibrosis. Moreover, monocytes/macrophages are also involved in fibrosis regression by secreting MMP9 or polarizing into M2b macrophages.

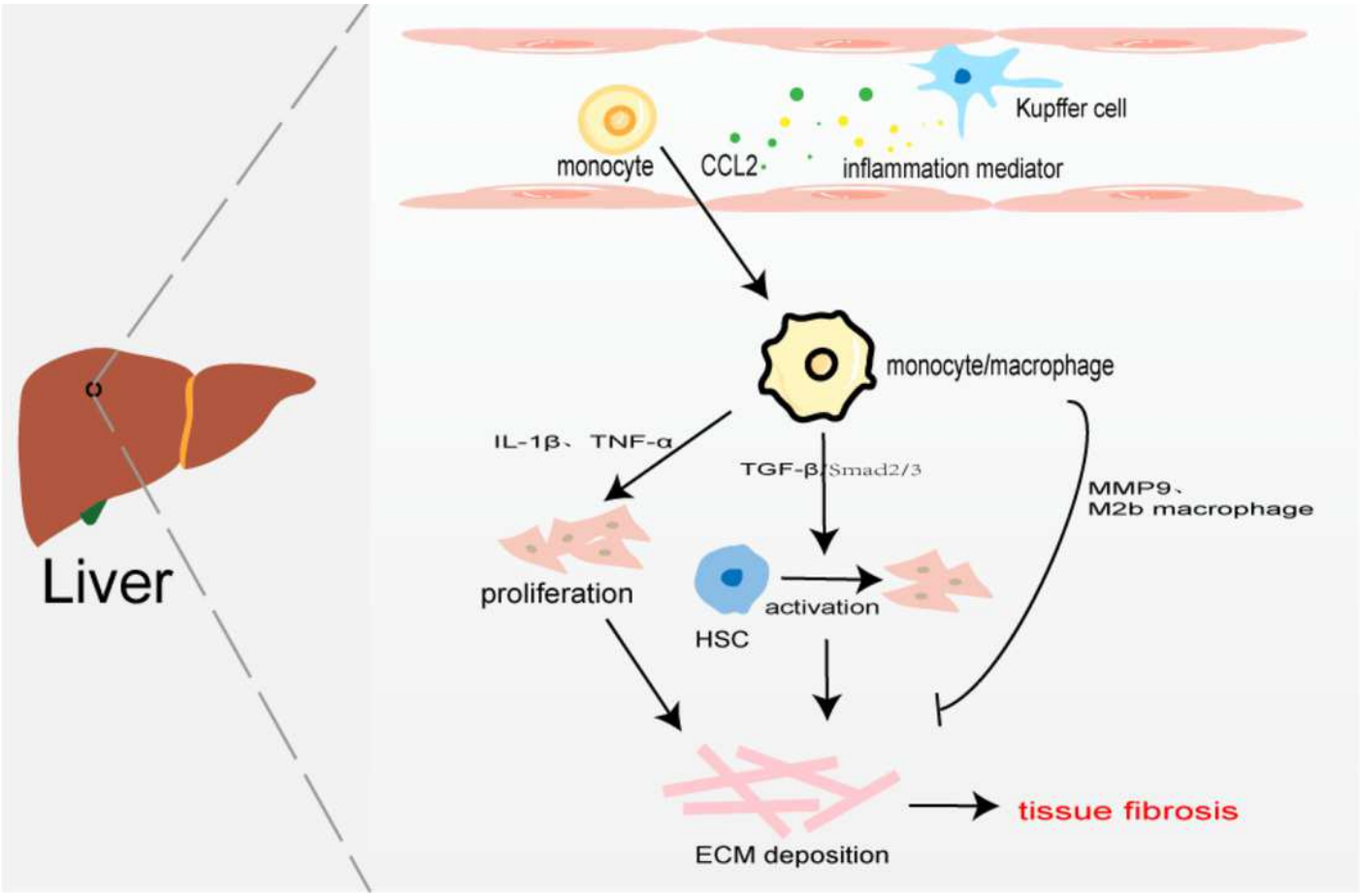

Figure 5

Fig5. Macrophages in skin fibrosis.

M2 macrophages not only secrete cytokines such as IL-6 and TGF-β to promote the proliferation and migration of skin fibroblasts, but also produce PDGF and IGF to transform adipose cells into myofibroblasts, resulting in excessive deposition of collagen, and eventually leading to skin fibrosis.

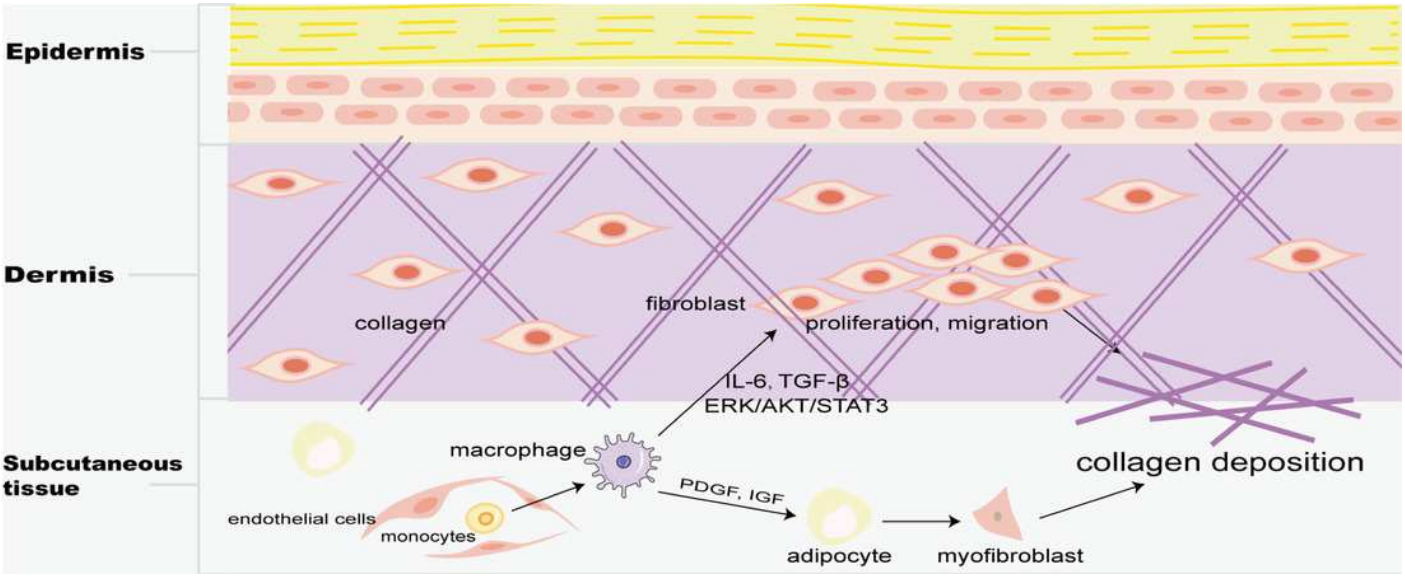

Figure 6

Fig6. Macrophages in cardiac fibrosis.

M1 macrophages produce inflammatory cytokines to promote inflammatory response, which can also be converted into M2 macrophages to participate in the process of fibrosis. M2 macrophages differentiate into myofibroblasts, activate cardiac fibroblasts and promote coronary endothelial cells to transform into myofibroblasts.