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Research Progress of Tibial Transverse Transport in the Treatment of DFU

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Abstract

Diabetic foot ulcer (DFU) is a serious complication of diabetes, which is caused by hyperglycemia and decreased immunity, and the traditional treatment is not satisfactory. Transverse tibial bone transfer (TTT) therapy for DFU has attracted increasing attention, which promotes cell metabolism and tissue regeneration based on the "tension-stress" law. Domestic and foreign studies have shown that TTT has significant effects in the treatment of diabetic foot, which can improve symptoms, promote angiogenesis, change the polarization balance of macrophages, control inflammation and promote wound healing. However, the specific mechanism still needs to be further explored. At present, the prevalence of diabetes is on the rise, and the incidence and mortality of DFU are high, which brings a heavy burden to families and society. Stem cell therapy has a promising application in DFU therapy, and extracellular vesicles, especially exosomes, participate in related cellular activities. In addition, TGF-β/HIF-α plays an important role in wound healing, and M1/M2 polarization of macrophages affects wound inflammation and repair process. Studies in these aspects provide a new perspective for understanding the pathogenesis and treatment of DFU, and also provide a theoretical basis for searching for simple and effective treatment plans. It is expected to improve the prognosis and quality of life of DFU patients.

Keywords

TTT, DFU, M1/M2 Polarization Shift, Pathway

1. Introduction

Diabetic foot ulcer (DFU) is caused by hyperglycemia and decreased immunity in

diabetic patients, which is complicated with neuropathy and various degrees of peripheral vascular lesions, leading to lower limb infection, ulcer formation and deep tissue necrosis. The polarization of macrophages plays a regulatory role in the development of diabetes, the chronic inflammatory response of foot wounds, and the refractory healing of diabetic foot wounds [1] [2]. In the early stage of chronic ulcer wound infection and wound healing, macrophages are mainly polarized into M1 macrophages. M1 macrophages secrete inflammatory factors, present antigens, induce Th1 and Th17 responses, thereby activating innate and specific immunity, killing pathogenic microorganisms invading the body, and controlling infection [3]-[5]. The inflammatory response promoted by M1 macrophages plays a positive role in initially resisting pathogen invasion, but the reactive oxygen species, reactive nitrogen species, and activated Th1, Th17, IL-6, IL18 and TNF-α secreted by M1 macrophages can cause damage to the surrounding normal tissues. Therefore, if the inflammatory response is not controlled, it may lead to the occurrence of the disease or aggravate the original condition [6] [7]. In order to prevent M1 macrophages from promoting inflammatory response and killing their own tissues, it is necessary to transform them into M2 macrophages after infection is controlled to facilitate the repair of tissue damage. M2 macrophages can regulate inflammatory response and promote tissue repair, vascular regeneration and fibrosis [8].

In recent years, transverse tibial bone transport has gradually attracted attention to promote the healing of refractory wounds, and signaling pathway is a necessary means to explore the relationship between external factors and intrinsic factors in the study of chronic wound repair. In the process of wound healing, there are many cell growth and regulatory factors, among which TGF-β/Smad signaling pathway is closely related to it. TGF-β binds to its receptor, activates the TGF-β/Smad signal transduction pathway and mediates the inflammatory response. It participates in the proliferation of fibroblasts, extracellular matrix deposition and collagen secretion [9]-[12].

2. Research Status and Development Trend at Home and Abroad

2.1. Epidemiology of Diabetic Foot Ulcers

Diabetes is a global disease that seriously affects human health. According to statistics, the prevalence of diabetes in China over 18 years old was 10.4% [13] in 2013. The data released by the International Diabetes Federation in 2019 showed that there were 468 million diabetic patients in the world, and it is expected that there will be more than 500 million [14] diabetic people in the world by 2030. By 2040, there will be more than 500 million people with diabetes in the world, and most of them come from developing countries, accounting for 15.5% in China, accounting for the first [15] in the world. More than 15% of all diabetic patients will have foot complications, and 4% - 10% of patients will develop into DFU. DFU, as the most common cause of hospitalization in diabetic patients, is a serious

complication caused by lower extremity nerve and peripheral vascular lesions, and [1] [2] is also the most serious complication of diabetes. The annual mortality rate of DFU is 14.4%. The mortality rate can reach more than 40% 5 years after amputation due to the occurrence of invasive cancer and heart failure, and the mortality rate can reach 70% [16] 10 years after amputation. Some recent studies have demonstrated that the mortality rate of patients with diabetic foot ulcers is more than two times higher than that of patients without diabetic foot ulcers, and the mortality rate of patients with a history of diabetic foot ulcers is nearly 40% [17] [18] higher than that of patients with diabetes without a history of diabetic foot ulcers. In the United States, the medical cost of diabetes in 2012 was $176 billion, of which, the cost of care for patients with DFU is $1.38 billion per year, while the cost of care for non-diabetic foot ulcers is only $130 million, only one-tenth of that for patients with DFU, and this figure has increased over time [19]. Diabetic ulcers are chronic wounds that are difficult to heal, with complex mechanisms, high treatment costs, poor efficacy, and high disability and mortality, which cause a huge burden to families and society. The traditional treatment of diabetic foot mainly includes symptomatic and supportive treatments such as blood glucose control, circulation improvement, and anti-infection, but the effect seems to be unsatisfactory. In recent years, with the rapid development of stem cell transplantation and tissue engineering, great breakthroughs have been made in the treatment of diabetic ulcer. However, due to the high cost of treatment, it is difficult to promote it in clinical practice, so it is always a difficult problem [20] to cure in clinical practice. Therefore, the search for a simple and affordable treatment scheme has become a global challenge.

2.2. The Significance of the "Tension Stress" Law in Tibial Transverse Bone Transfer Surgery (TTT)

TTT surgery, based on the "tension stress" law, slowly pulls the tibia after transverse osteotomy to generate tension between bone segments, activate the activity of bone related cells such as osteoblasts, stimulate the regeneration of new bone tissue, and provide stable mechanical support for the limb. At the same time, this tension can also stimulate the differentiation of bone marrow mesenchymal stem cells into osteoblasts, vascular endothelial cells, etc., promoting the regeneration of various tissues such as bone and blood vessels. Tension stimulation can promote the secretion of angiogenic cytokines such as vascular endothelial growth factor, inducing neovascularization. Continuous tension can cause adaptive changes in local blood vessels, leading to proliferation and migration of endothelial cells, formation of new vascular networks, improvement of local tissue blood supply, and provision of necessary nutrients and oxygen for tissue repair and metabolism. The "tension stress" effect can activate multiple cytokine pathways, such as the mitogen activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase/protein kinase B (PI3K/Akt) pathway. The activation of these pathways can promote cell proliferation, differentiation, and migration, enhance cellular me-

tabolism and functional activity, and contribute to tissue repair and regeneration. The "tension stress" stimulation during TTT can transform macrophages at the wound site from M1 type, which is mainly pro-inflammatory, to M2 type, which is mainly anti-inflammatory. M2 macrophages can secrete various growth factors and cytokines, promoting angiogenesis, cell proliferation, and tissue remodeling, which is beneficial for the resolution of inflammation and tissue repair [20] [21].

2.3. Research Progress of Ilizarov Transverse Tibial Transport

Tibial transverse transport (TTT), also known as Ilizarov tibial transverse transport, is based on the "tension-stress" law of distraction. It promotes cell metabolism and accelerates tissue regeneration through continuous, slow and stable stretch, which grows in a manner similar to cell division. It has a significant effect on the treatment of diabetic foot, so it has become a research hotspot [22] of microcirculation regeneration technology of diabetic foot. Ilizarov transverse tibial transport was proposed by Ilizarov in 1972. In 2000, on the basis of Ilizarov technique, Professor Qu Long developed a set of surgical instruments for tibial transverse bone transport and microvascular regeneration, and used it for the first time in China for the treatment [23] of lower extremity thromboangiitis obliterans. In 2019, Chen *et al*. published TTT technology for the first time in the world, and the limb salvage rate reached 97% [24]. Tang Fugang *et al*. [14] performed TTT on a patient with severe rest pain, intermittent claudication, numbness and other symptoms of lower limb vascular occlusion below the popliteal artery, and found that the symptoms of rest pain, intermittent claudication, numbness and other symptoms were significantly relieved. 25 days after the operation, they found that there was a rich capillary network formed around the removed bone, and through statistical analysis, they found that: The most obvious symptom of skin temperature improvement was not the most abundant blood vessel site, but the most terminal toe site. Does this mean that Ilizarov tibial transverse transport also plays a role in long-distance blood vessels? The latest studies have proved [24] that Ilizarov transverse tibial transport is widely used in the treatment of chronic osteomyelitis, which has the advantages of minimally invasive, improving microcirculation, and one-stage repair of bone and soft tissue defects. In addition, Ilizarov transverse tibial transport can promote the healing of diabetic foot ulcer by increasing the expression of vascular VEGF and reconstructing microcirculation.

Gao Wei [25] *et al*. explored that macrophages promoted the healing of severe diabetic foot wounds after tibial transverse bone transport, and found that the M1 and M2 cell counts and M1/M2 ratio of patients after treatment were significantly lower than those before treatment. The inflammatory response of patients' wounds stimulated by pathogenic microorganisms persisted before treatment, and macrophages were mainly polarized into M1 macrophages. One month after treatment, inflammation has been controlled, and macrophages are more polarized into M2 macrophages, which can secrete anti-inflammatory factors and growth factors, thus regulating and inhibiting local inflammatory response and promoting tissue regeneration and wound healing. Yang [26] *et al*. also observed an im-

munoregulatory response after tibial transverse bone transport, which significantly promoted the recovery of M1 macrophages to M2 macrophages. The transition from M1 to M2 macrophages indicated the transition of wound healing from the inflammatory stage to the proliferative stage. In his [27] study on the expression changes of macrophages and the polarization of M1 to M2 in the process of diabetic wound healing by tibial transverse bone transport, Ma found that M1 and M2 were reduced, and M1 was reduced by a relatively greater amount, which was conducive to the polarization of wound toward M2. Therefore, it can be concluded that the inflammatory response of local wounds of patients after tibial transverse bone transport is controlled, and the surgery promotes the transformation of macrophages into M2 macrophages in patients with severe diabetic foot, thereby promoting the healing of ulcers at the wounds. In conclusion, the polarization of macrophages into M1 macrophages increased, while M2 macrophages decreased, and the imbalance of macrophage polarization was an important factor leading to prolonged healing of diabetic foot ulcers. TTT may be the reason for the healing of severe diabetic foot wounds by promoting the reconstruction of macrophage polarization balance. However, the mechanism by which TTT promotes the polarization balance of macrophages in patients needs to be further studied.

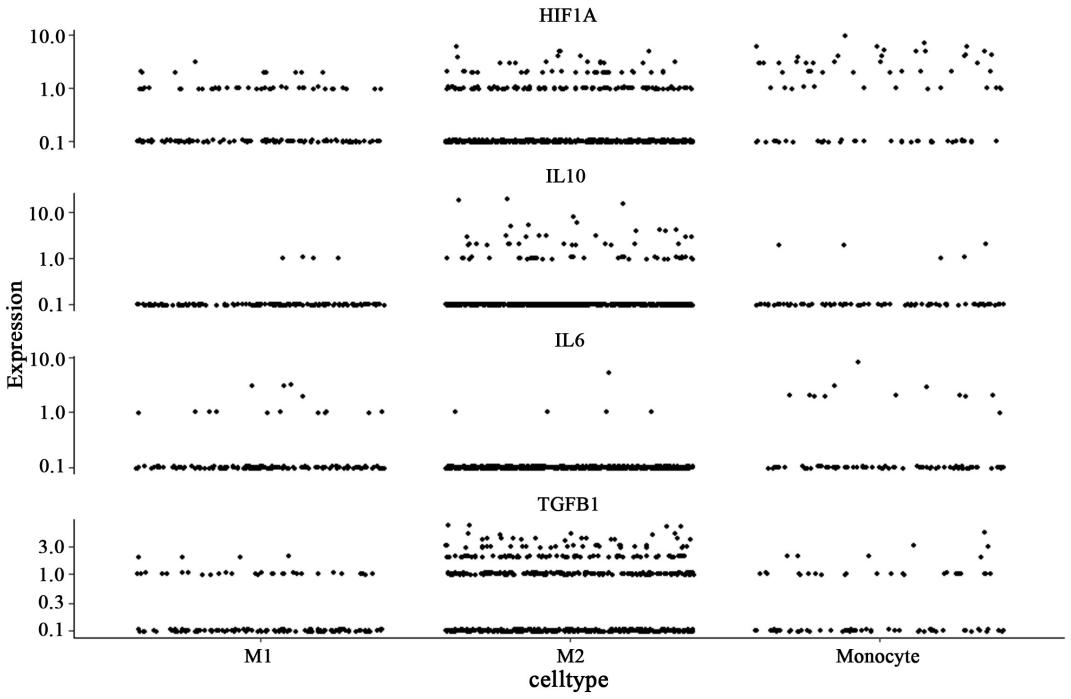
2.4. The Role of TGF-β/HIF-1α in Promoting Wound Healing with Macrophages

Skin is the largest organ in the human body and an important barrier against external environmental aggression. When the skin barrier is breached by an injury, the wound healing process is activated. The process of wound healing can be divided into four stages: hemostasis, inflammation, proliferation, and remodeling. Vasoconstriction, platelet aggregation, and fibrin formation occur immediately after skin injury. As a result of platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and fibroblast growth factor (FGF) signaling, neutrophils, macrophages, and lymphocytes migrate sequentially into the wound, which initiates the inflammatory phase. Macrophages play an important role [3] in wound healing by secreting a variety of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-18 (IL-18). TGF-β superfamily signaling is essential for normal embryogenesis in animals and humans. TGF-β is a key mediator of fibrosis and a cytokine that plays an important role in the proliferative phase of wound healing. It protects the wound by stimulating the formation of granulation tissue (vascular tissue formed after inhibition of inflammation), epithelial re-formation, and angiogenesis, thereby providing blood for the newly formed skin. TGF-β activates downstream signal transduction to promote fibrosis, mainly through epithelial-mesenchymal transition (EMT) to promote fiber deposition in tissue wounds. Fibrosis is the result of wound scar healing after tissue injury, and it is defined as the dysregulated production and excessive accumulation of collagen-rich ECM and the replacement

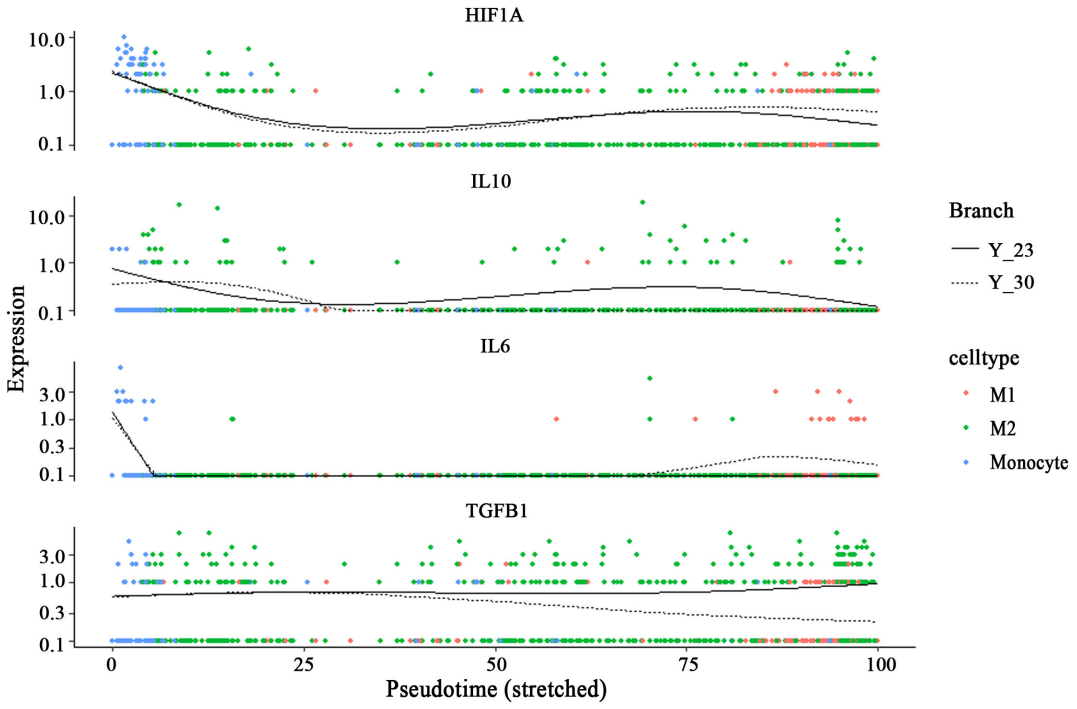
[28] of normal functional tissues by fibrotic tissues. In addition, TGF-β also recruits macrophages to tissue injury or inflammatory sites and is activated into pro-inflammatory M1 macrophages. Excessive inflammatory response activates TGF-β and converts macrophages into anti-inflammatory M2 macrophages, which promote proliferation and reduce local inflammation by secreting anti-inflammatory cytokines and collagen precursors, thereby stimulating fibroblast proliferation [6] [7] [29]. Macrophages also promote angiogenesis by producing matrix metalloproteinases (MMP), which degrade extracellular matrix (ECM) components and release chemokines, such as TNF-α and VEGF [30] (**Figure 1**).

During the rapid phase of wound healing, tissue hypoxia occurs due to accelerated oxygen utilization by cells within the wound. Hypoxia in the wound occurs through the activation of hypoxia-inducible factor-1α (HIF-1α), which acts in an oxygen-dependent manner. When tissue is hypoxic, HIF-α is activated rapidly and activates the PI3K-Akt-mtor signaling pathway. It recruits downstream VEGF and type III collagen deposition to promote angiogenesis [31]. This function of HIF-1α has obvious coordination with TGF-β.

During the final process of wound healing, TGF-β1 signaling stimulates the differentiation of fibroblasts into myofibroblasts, which recruit collagen types I and III for deposition. Collagen fibers are enhanced by the catalytic cross-linking of transglutaminase and lysyloxidase. In the late stage of wound healing, type III collagen is degraded and type I collagen rich scar tissue is formed. The tensile strength of the resulting healed wound is much lower than that of the uninjured skin, and the maximum tensile strength achieved by the injured skin is only 80% of that of the uninjured skin.



(A)



(B)

Figure 1. Time series analysis (A) shows the expression of related genes in macrophages at different stages; (B) is the dynamic expression profile of related genes during macrophage differentiation and development.

2.5. M1/M2 Cells Promote Anti-Inflammatory Repair

Wound healing needs to go through the inflammatory phase, proliferative phase, and remodeling phase, and one of the keys to the regulation of the inflammatory phase is macrophages. Macrophages are important immune cells in the body. They can phagocytize and kill bacteria and other pathogens and microorganisms, present antigens to activate specific immunity of the body, remove senescent and dead cells of the body, and secrete inflammatory or cytokine to regulate the body's immune response and tissue repair [32] [33]. Under the influence of different microenvironments, macrophages can be polarized into the classic M1 and M2 macrophages. M1 shows a pro-inflammatory effect, while M2 can inhibit the local inflammatory response, so it promotes tissue repair and regeneration [34] by changing the inflammatory balance. The activation of M1 macrophages can highly express TNF-α, IL-1α, IL-1β, IL-6, IL-12, IL-18 and other cytokines, and their surface markers include HLA-DR, CD197, etc. M1 macrophages can also directly differentiate into TH1 and TH7 anti-inflammatory cells to aggravate the inflammatory response [35]. M2 macrophages have no common surface markers such as CD163 and CD206, and highly express anti-inflammatory cytokines such as IL-10 and IL-1β. Macrophages play an important role in local anti-infection immunity and tissue regeneration of wounds. M1 and M2 macrophages are the most prominent cells in the inflammatory and proliferative stages of tissue repair. In the early stage, M1 macrophages play a role in wound debridement by killing pathogens and stimulating inflammatory responses. In the late stage, M2 macrophages pro-

duce and release anti-inflammatory factors and growth factors, promote the formation of new blood vessels and granulation tissue, and play a role in wound repair. The normal process of wound healing is usually accompanied by the transition [36] of macrophages from pro-inflammatory M1 macrophages to anti-inflammatory/pro-healing M2 macrophages. It has been reported that macrophages are polarized to the M2 phenotype by mechanical stretch stimulation and produce anti-inflammatory cytokines to regulate the local inflammatory microenvironment [25]. M2 macrophages can inhibit local inflammatory response and promote tissue regeneration and wound healing. The inflammatory response in diabetic foot wounds can promote the polarization of macrophages to M2 macrophages and secrete more growth factors, which may be considered as a treatment method to accelerate wound healing. Polarization of macrophages.

2.6. Mechanisms of DFU Scar Healing

The injury caused by DFU will have a healing response to a certain extent. The first is to reduce the damage and restore the balance of damaged cells in the body, and then restore the damage of tissues and organs. Inflammation, tissue remodeling, and tissue remodeling are important processes in the healing response *in vivo*, and differences in any of these processes will affect scar healing [37]. Scar is composed of nuclear extracellular matrix (ECM), which is the result of cellular and tissue repair attempts. In most organs, scar formation is related [38] to the inflammatory state of the tissue, the function of fibroblasts, and the recovery of key functions.

It is well known that macrophages are an important class of cells that mediate the occurrence and outcome of inflammation. In the initial stage of inflammation, macrophages can release proteolytic enzymes and reactive oxygen species to remove neutrophils and cell debris from the body and reduce the inflammatory infiltration state. Subsequently, macrophages can promote fibrosis and inflammatory repair by producing cytokines, chemokines, and growth factors (such as TGF-β1, PDGF, and EDGF), which indirectly affect scar formation [39]. Previous studies have found [9] that this pro-inflammatory and anti-inflammatory mechanism of macrophages is actually the transformation between M1 and M2 phenotypes, and Exos can promote the transformation of macrophages to anti-inflammatory M2 phenotype, thereby reducing inflammatory response. As observed [10] [11] in adipose-derived Exos, Exos can activate the PI3K/Akt signaling pathway to promote the proliferation and migration of fibroblasts, optimize collagen deposition, and promote wound repair. In addition, the mechanism of adipose-derived Exos in alleviating scar formation is to promote the synthesis of type I collagen and type III collagen, and inhibit the formation of type I and III collagen in the late stage. In a model of cardiac ischemia, Ghadge *et al.* [12] found that overexpression of HIF-1α improved neovascularization and scar size, with the involvement of M2 macrophages. Another study showed [40] that during fetal wound healing, fibroblasts proliferated more rapidly, mainly synthesizing type III collagen, compared with adults. However, in adults, actin is involved in addition

to fibroblasts and characterized by the expression of α-smooth muscle actin (α-SMA), which is absent during fetal wound healing.

In recent years, with the rapid development of stem cell transplantation and tissue engineering, great breakthroughs have been made in the treatment of diabetic ulcer. However, due to the high cost of treatment, it is difficult to promote it in clinical practice, so it is always a difficult problem to cure in clinical practice. Therefore, the search for a simple and affordable treatment scheme has become a global challenge. Many studies have shown that transverse tibial bone transport has a clear effect on reducing inflammation and angiogenesis, and has a good therapeutic effect on lower limb ischemic diseases, but there is still a lack of basic experimental verification. In order to better understand the role of bone transport in the treatment of DFU, we have found that bone transport can activate TGF-β/HIF-1α pathway to a certain extent, showing a strong anti-inflammatory effect, which may be through down-regulating the expression of inflammatory factors such as IL-6, IL-18 and TNF-α. It can promote the transformation of M1 macrophages into M2 macrophages, so as to control the inflammation of DFU and promote wound healing. In view of the extremely important role of signaling pathways in promoting wound healing and regulating the production of cell growth factors, the expression of TGF-β in normal human foot tissue monocytes during the differentiation and development into M1 and M2 macrophages is significantly different. Compared with M1 macrophages, in the differentiation process into M2 macrophages, the expression of TGF-β in normal human foot tissue monocytes is significantly higher than that in M1 macrophages. Compared with M1 macrophages, the expression of TGF-β in the differentiation process of M2 macrophages was significantly increased, suggesting that TGF-β may be an important factor regulating the polarization of M1 and M2 macrophages. In addition, we also analyzed the dynamic expression of IL-6, IL-10, TGF-β and /HIF-1α related genes during the differentiation and development of macrophages. It was found that IL-6 was mainly expressed in M1 macrophages, while IL-10, TGF-β and /HIF-1α were mainly expressed in M2 macrophages.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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