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REVIEW

The Characteristics of Blood Supply and Tissue Hypoxia in Pathological Scars

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Abstract Blood supply is believed to be an important aspect in the development of pathological scars. However, there are controversies about vascular distribution, vascular structure and blood flow in pathological scars. Additionally, hypoxic microenvironment plays an important role in the vascularization of pathological scar tissues, and hypoxic conditions can be reflected by metabolic indexes and some cytokines. Furthermore, the correlation between blood supply and tissue hypoxia is controversial. The aim of this article is to review the literature on the characteristics of blood supply and tissue hypoxia in pathological scars, from which we can see pathological scars have unique characteristics of blood supply that are closely associated with tissue hypoxia. Moreover, development in the treatment of pathological scars is herein reviewed.

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PATHOLOGICAL scars include hypertrophic scar and keloid. They influence appearance and even cause functional disturbance, and place tremendous physiological and psychological burdens on patients. Therefore, pathological scars have been a challenge in plastic surgery and the focus of research. Blood supply is believed to be an important aspect in the development of pathological scars, and has thus attracted more attentions in recent years. However, there are controversies about blood supply in pathological scars. Hereby we summarized the advances of research on the blood supply in pathological scars, and explored future research directions.

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VASCULARITY OF PATHOLOGICAL SCARS

Vascular distribution of pathological scars

Vascular distribution of pathological scars is determined by vascular quantity and vascular type. In terms of quantity, papillary and reticular layers of hypertrophic scars and keloids have more blood vessels than normal skin.[1] Compared with normal scars, the number of blood vessels is markedly lower in hypertrophic scars, and even more lower in keloids.[2] Vascular distribution within pathological scar tissues has been controversial yet. Recently, Ryoma Touchi *et al* found that the central areas of keloids exhibited lower vascular density than the marginal areas. Besides, compared to the hypertrophic scars, keloids was noted to have lower vascular density in the central areas and higher vascular density in the marginal areas.[3] The characteristics of the vascular type within keloid tissues have received much attention. Some researchers divided keloids into different areas, including zone of hyalinizing collagen bundles (HCBs), fine fibrous area, area of inflammation, zone of dense regular connective tissue, nodular fibrous area, and area of angiogenesis.[4] HCB zone is the area where blood vessels, mainly venules, are distributed scarcely. Capillaries and postcapillary venules in the fine fibrous areas, which surround the HCB zone, are the main visible vascular structure. Compressed and degenerated small veins mainly distributed in the inflammation area, whereas severely compressed microvessels mainly scattered among bundles in the dense regular connective tissue zone. In the nodular fibrous area, degenerated microvessels are present in the wide extracellular spaces inside or outside the nodules. The angiogenesis at the junction area of keloids and normal skin, as well as junction area of keloids and papillary dermis, are characterized by progressively differentiated small blood vessels and small neurovascular bundles. In the nodules, there exists some islets of angiogenesis, where the vessels are of less severity in pathological changes and persist differentiating ability into arterioles.[4]

Vascular structure of pathological scars

The vascular structure of pathological scars has different manifestations between hypertrophic scars and keloids. In terms of spatial vascular structure, blood vessels within hypertrophic scar tissues have a structure perpendicular to the skin surface, whereas those within keloid tissues present a typical dispersed, extended vascular structure.[5,6] The diameter or patency of the blood vessels of pathological scar remains controversial. Thaís *et al* used stereological methods to obtain information on pathological scar tissues with a microscope, and proposed that the blood vessels within the pathological scars were dilated compared with those in normal skin and normal scars.[1] The reason for the dilatation of blood vessels may be associated with the keratinocyte mediation of vasodilation through nitric oxide-dependent mechanisms under hypoxia.[7] On the other hand, the bulk of studies investigating keloid blood supply found that the lumen of microvessles is occlusive.[8] One of the causes of vascular occlusion is the excessive proliferation of endothelial cells.[6] Under an electron microscope, marked bulging of the endothelial lining into vascular lumens was visible in keloids.[9] The second cause is the intense proliferation of fibroblasts. Before the development of pathological scars, fibroblasts have already begun to proliferate.[10] Fibroblasts increasing in number compresses the blood vessels, causing vascular distortion and narrowing. The third cause is the uncontrolled collagen production by fibroblasts in the extracellular matrix, which results in substantial collagen deposition in the microvasculature[11, 12] and further luminal stenosis. For a single vessel, vascular structures within the hypertrophic scars and keloids are also different. Compared with the blood vessels in hypertrophic scars, those in keloids are smaller in diameter and flatter in shape.[13] In keloid tissues, vascular structures also vary among different areas. Blood vessels in central area are relatively flatter than those in marginal area.[13]

Blood flow in pathological scars

In recent years, laser Doppler techniques have been widely used in studies on skin blood flow, such as laser Doppler flowmetry (LDF), laser Doppler perfusion imaging, and laser speckle contrast imaging (LSCI).[14-17] These techniques are increasingly used in the detection of blood flow in pathological scars. Blood flow measurements are related to the blood flow velocity and red blood cell concentration. Timar-Banu *et al* used LDF technique and found that, the blood flow in pathological scars was greater than that in normal skin.[18] Qingliang Liu *et al* used LSCI technique and found that the blood flow in the adjacent skin surrounding keloid tissues was greater than that in nonadjacent skin tissues.[15] Blood flow also changes with the progression of pathological scars. Ehrlich's study showed that, at 16–18 weeks after wound closure, the blood flow in hypertrophic scars was still three times higher than in normal skin and four times greater than in normal scars.[19]

TISSUE HYPOXIA IN PATHOLOGICAL SCARS

Although the pathogeneses of pathological scars remain unclear, studies have suggested that the hypoxic microenvironment may be one of the responsible factors. Recently, there have been a growing number of studies claiming that the hypoxic microenvironment plays an important role in the vascularization of pathological scar tissues.[8, 20]