CHINESE MEDICAL SCIENCES JOURNAL

REVIEW

The Characteristics of Blood Supply and Tissue Hypoxia in Pathological Scars

Zifei Li¹, Qingliang Liu², Xiaojun Wang^{2*}, and Jie Luan^{1*}

¹Department of Aesthetic and Reconstructive Breast Surgery, Plastic Surgery Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100144, China

²Division of Plastic and Reconstructive Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, China

Key words: pathological scar; hypertrophic scar; keloid; blood flow; hypoxia

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.

Chin Med Sci J 2017; 32(2):113-118. DOI:10.24920/J1001-9294.2017.014

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.

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

---

Received for publication June 27, 2016.

*Corresponding author Tel: 86-17801014078, Fax: 86-10-69152711, E-mail: wxjpumch@163.com(Xiaojun Wang); 86-13341419733, Fax: 86-10-69152710, E-mail: JieLuands@163.com(Jie Luan).

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 microvessels 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 pathogenesises 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}

Metabolic manifestations of tissue hypoxia

Reduced oxygen partial pressure

The oxygen partial pressure within tissue is a direct index reflecting tissue hypoxia. Studies on the oxygen partial pressure within pathological scar tissues have mostly focused on investigating hypertrophic scar tissues. Studies found that, compared to normal skin, hypertrophic scars have lower oxygen partial pressure and higher carbon dioxide partial pressure, suggesting that hypertrophic scar tissues are in a hypoxic state.²¹ Sloan's measurement with a dual-port medical mass spectrometer found significant reduced oxygen partial pressures (13.1 ± 2.9 mmHg) in hypertrophic scars of burn patients compared to normal dermis.²¹ Zheng's study further demonstrated that transcutaneous pressure of oxygen within hypertrophic scars decreased gradually when scars transit from early stage to regressive stage, and then returned to near-normal levels upon scar maturation. These results suggest that during the process of regression and maturity, with apoptosis of most cells in hypertrophic scars, the collagen gradually hydrolyze, new blood vessels gradually open, and tissue oxygen level gradually return to near-normal levels.²²

Elevated lactate concentration

Lactate is a product of cellular anaerobic glycolysis that can be used as an indirect index of tissue hypoxia. Studies on the lactate level in pathological scars mainly focus on keloid tissues. Iwakiri reported that the lactate concentration in keloids was higher than that in the normal skin or normal scars. In normal scar tissues, lactate content decreases with the extension of posttraumatic time; whereas in keloids, the lactate content of posttraumatic tissue maintained at a high level continuously. Compared with hypertrophic scars, lactate content in keloids is higher and maintained at high level for a long time, suggesting persistent anaerobic glycolysis within keloids.²

Increased ATP level

ATP is produced mainly through the oxidative phosphorylation of glucose in the mitochondria under aerobic conditions, and partially through anaerobic glycolysis. There are studies that investigated in the hypoxia and metabolic status of pathological scar tissues through changes of ATP concentration within the tissues. Some researchers measured the tissue ATP levels and found that, with inhibiting glycolysis, there is more remarkable inhibition of ATP synthesis within keloid fibroblasts (KFs) than within normal fibroblasts (NFs), but there is more ATP production within KFs in the hypoxia and hypoxia-mimetic states.²³ These results indicate that ATP synthesis is dependent on

glycolysis in KFs, but on mitochondrial oxidative phosphorylation in NFs. Therefore, ATP can be considered as an index for active metabolism of pathologic scar tissues under hypoxia. Ueda *et al* studied the difference of ATP content in keloids, red hypertrophic scars, pink hypertrophic scars, and atrophic white scars, and found there was no significant difference in ATP concentration between red hypertrophic scars and keloids. Furthermore, compared with pink hypertrophic and atrophic white scars, the ATP concentration in keloids was higher and maintained at high levels for a long time.²⁴

Blood supply-related cytokines in tissues under hypoxic conditions

Hypoxia-inducible factor 1 (HIF-1)

HIF-1 is an important regulator for cell survival under hypoxic conditions, whereas it is rapidly hydroxylated and degraded under normoxic conditions.²⁵ Under hypoxic conditions, HIF-1 accumulates through dimer formation and enters the nuclei to promote the expression of a series of genes, thereby adapting cells and tissues to the hypoxic environment. Studies on mechanisms of pathological scars in relation to HIF-1 had focused on the expression of HIF-1 in keloid tissues. Zhang *et al* found that HIF-1 expression is upregulated in keloids compared with peripheral normal skin.²⁶ A study of hypertrophic scar tissues found the expression of HIF-1 increased firstly and then decreased with the progression of the scar, which indicated moderate to severe hypoxia.²² This is because, when the increase of hypoxia reaches a certain threshold level, HIF-1 no longer increases accordingly, but decreases instead. Such decrease is associated with inhibition of HIF-1 expression by the increased p53 under hypoxia.²⁷

Vascular endothelial growth factor (VEGF)

VEGF can promote proliferation of endothelial cells and induce angiogenesis, which plays important roles in wound healing. Hypoxia is an important mechanism for inducing VEGF expression.³ van der Veer found no significant difference in VEGF expression between hypertrophic scar tissues and normotrophic scar tissues.²⁸ However, VEGF was found to be highly expressed in keloid tissues.²⁹ Moreover, Steinbrech found that hypoxia could stimulate upregulating of VEGF expression in KFs.³⁰ Interestingly, Ryoma Touchi's study showed that there is no significant difference in VEGF expression between central and marginal areas.³ VEGF was not only highly expressed in local keloid tissues, but also elevated in serum in patients with keloids scars compared with normal population.³¹

Transforming growth factor β 1 (TGF- β 1)

TGF- β family members have important roles in embryonic development and regulation of tissue homeostasis.³² Hypoxia may facilitate high TGF- β 1 expression by mediating the TGF- β 1/Smad signaling pathway.³³ Moreover, the pathway is closely related to the formation of pathological scars. Many studies have demonstrated that TGF- β 1 can provide signal substances for normal healing during the early phase of scar healing, whereas the expression level of TGF- β 1 after epithelial healing is directly proportional to the degree of scar hyperplasia.³⁴ Some studies have shown that 90% of TGF- β 1 expression in pathological scar tissues is from the epidermis, whereas the proportion is 60% in normal postoperative scars and only 20% in normal skin. This suggests the active role of keratinocytes in keloid fibrosis. In addition, the shorter the interval time from wounding, the higher the expression of TGF- β 1 in the pathological scar dermis, which suggests that VEGF may play an important role in the early stages of pathological scar formation.³⁵

Relationship between cytokines

Pathological scar tissues produce a series of adaptive responses in a hypoxic environment, during which HIF-1 plays a pivotal role.²² In the hypoxic state, HIF-1 enters the nucleus, binds to the hypoxia responding elements, and regulates the transcription and expression of its downstream factors such as VEGF. There also exists a synergism between these cytokines. For example, TGF- β can regulate VEGF gene expression at the transcriptional level synergistically with HIF-1.³⁶ According to Masao's study, exogenous TGF- β 1 can directly stimulate VEGF expression in KFs, and anti-TGF- β 1 antibodies can inhibit the expression of VEGF.³⁷ These cytokines cooperate with one another and are jointly involved in the regulation of blood supply formation of pathological scars in hypoxic environments.

CORRELATION OF BLOOD SUPPLY AND TISSUE HYPOXIA IN PATHOLOGICAL SCARS

Abundant blood supply but insufficient oxygen supply

Whether the blood supply is sufficient or not is closely related to the metabolic status of tissues, which cannot be truly assessed simply by indices such as vascular density and blood flow. The hypoxic state within tissues is a comprehensive index of blood oxygen supply and tissue oxygen consumption; thus, the presence or absence of tissue hypoxia can indirectly reflect the adequacy of the tissue blood supply. A variety of evidences have indicated

that the hypoxic state in pathological scar tissues is caused by insufficient oxygen supply in spite of an abundant blood supply.

The relative lack of oxygen is partially due to insufficient supply of oxygen through the blood vessels. Despite the enhanced vascular density, increased blood flow, and rich blood supply within pathologic scar tissues, vascular occlusion in tissues prevents the effective exchange of oxygen from blood into tissues. As for the causes of vascular occlusion, aside from the aforementioned vascular structural change, endothelial cell malfunction caused by hypoxia may also exacerbate the occlusion and hypoxia.³⁸ A study indicated that, the vascular caliber was larger in pathological scars; even with the increased blood flow in the tissue, blood supply doesn't actually reach the periphery;¹³ and the ineffective oxygen exchange through vascular walls may still result in hypoxia.

On the other hand, hypoxia is also associated with increased oxygen consumption in pathological scar tissues. Studies have shown that oxygen consumption of keloid tissue is higher than that of mature scars,³⁹ so that even if blood flow is good and the blood supply is rich within the keloid tissues, the oxygen supply is relatively insufficient owing to increased tissue oxygen consumption, thus the internal environment is still in a relatively hypoxic state.²²

Formation of mutual cause-effect relationship between tissue hypoxia and blood supply in pathological scars

It is unclear whether tissue hypoxia is the initial mechanism for blood supply formation in pathological scars. Some researchers believe that vascular deformation in pathological scars is a causative factor, and that microvascular occlusion leads to tissue hypoxia.⁴⁰ Moreover, the gradual accumulation of vascular endothelial cells, fibroblasts and collagens aggravates the vascular deformation and occlusion, forming a cycle with hypoxia, and thereby leading to gradually exacerbated early hypoxic state. In addition, cytokines produced during tissue adapting to hypoxia are important promoters of angiogenesis. For example, upregulation of the expression of VEGF, Ang-1, and periostin can promote angiogenesis.⁴⁰ Tissues produce a variety of proangiogenic factors in the hypoxic state to induce a hypoxia-vascular hyperproliferation-hypoxia cycle. The vascular hyperproliferative state may be an important factor for the neoplastic infiltrative growth of keloids.

Nevertheless, hypoxia is not increasingly intensified, and there may be dynamic changes in the oxygen consumption of tissues. According to a study, severe hypoxia inhibits VEGF expression in scar tissues. Severe hypoxia

and malnutrition in scar tissues play key roles in inducing the regression of hypertrophic scar through fibroblast inhibition and cell apoptosis.⁴¹

PERSPECTIVES OF FURTHER RESEARCH

Many controversies still exist in the study of blood supply in pathological scars. For example, the quantity and openness of blood vessels in different areas of keloid and hypertrophic scar are still inconclusive. Moreover, the mechanisms for blood supply formation in pathological scars, such as expression of the initial factor, cytokines and relevant pathways, are still unclear and need further study. At present, invasive treatments for pathological scars, especially keloids, are primarily surgery and postoperative radiotherapy. A study has shown that HIF-1 enhances the tissue's resistance to radiotherapy by promoting angiogenesis and strengthening glycolysis.⁴² The radiotherapy-resistant mechanism of pathological scars needs further investigation. Targeted therapy based on the blood supply for pathological scars still has room for further development.

Conflict of Interest Statement

The authors have no conflict of interest to disclose.

REFERENCES

1. Amadeu T, Braune A, Mandarim-de-Lacerda C, et al. Vascularization pattern in hypertrophic scars and keloids: a stereological analysis. *Pathol Res Pract* 2003; 199: 469-73. doi:10.1078/0344-0338-00447.
2. Ueda K, Yasuda Y, Furuya E, et al. Inadequate blood supply persists in keloids. *Scand J Plast Reconstr Surg Hand Surg* 2004; 38: 267-71. doi:10.1080/02844310410029552.
3. Touchi R, Ueda K, Kurokawa N, et al. Central regions of keloids are severely ischaemic. *J Plast Reconstr Aesthet Surg* 2016; 69: e35-41. doi:10.1016/j.bjps.2015.11.006.
4. Bux S, Madaree A. Keloids show regional distribution of proliferative and degenerate connective tissue elements. *Cells Tissues Organs* 2010; 191: 213-34. doi:10.1159/000231899.
5. Gauglitz GG, Korting HC, Pavicic T, et al. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. *Mol Med* 2011; 17: 113-25. doi:10.2119/molmed.2009.00153.
6. Yoo MG and Kim IH. Keloids and hypertrophic scars: characteristic vascular structures visualized by using dermoscopy. *Ann Dermatol* 2014; 26: 603-9. doi:10.5021/ad.2014.26.5.603.
7. Boutin AT, Weidemann A, Fu ZX, et al. Epidermal sensing of oxygen is essential for systemic hypoxic response. *Cell* 2008; 133: 223-34. doi:10.1016/j.cell.2008.02.038.
8. Jumper N, Paus R, Bayat A. Functional histopathology of keloid disease. *Histol Histopathol* 2015; 30: 1033-57. doi:10.14670/HH-11-624.
9. Lametschwandtner A, Staindl O. Angioarchitecture of keloids. A scanning electron microscopy study of a corrosion specimen. *HNO* 1990; 38: 202-7. German.
10. Wolfram D, Tzankov A, Pulzl P, et al. Hypertrophic scars and keloids-a review of their pathophysiology, risk factors, and therapeutic management. *Dermatol Surg* 2009; 35: 171-81. doi:10.1111/j.1524-4725.2008.34406.x.
11. Ghajar CM, Chen X, Harris JW, et al. The effect of matrix density on the regulation of 3-D capillary morphogenesis. *Biophys J* 2008; 94: 1930-41. doi:10.1529/biophysj.107.120774.
12. Ring HC, Mogensen M, Hussain AA, et al. Imaging of collagen deposition disorders using optical coherence tomography. *J Eur Acad Dermatol Venereol* 2015; 29: 890-8. doi: 10.1111/jdv.12708.
13. Kurokawa N, Ueda K, Tsuji M. Study of microvascular structure in keloid and hypertrophic scars: density of microvessels and the efficacy of three-dimensional vascular imaging. *J Plast Surg Hand Surg* 2010; 44: 272-7. doi: 10.3109/2000656X.2010.532923.
14. Liu J, Xu L, Hu D, et al. Advances in the research of laser Doppler perfusion imaging in burn wounds. *Zhonghua Shao Shang Za Zhi*, 2014, 30: 175-8. Chinese.
15. Liu Q, Wang X, Jia Y, et al. Increased blood flow in keloids and adjacent skin revealed by laser speckle contrast imaging. *Lasers Surg Med* 2016; 48: 360-4. doi: 10.1002/lsm.22470.
16. Hop MJ, Hiddingh J, Stekelenburg C, et al. Cost-effectiveness of laser Doppler imaging in burn care in the Netherlands. *BMC Surg* 2013; 13: 2. doi:10.1186/1471-2482-13-2.
17. Lenasi H. Skin microvascular reactivity in patients with hypothyroidism. *Clin Hemorheol Microcirc* 2016. doi:10.3233/CH-162062.
18. Timar-Banu O, Beauregard H, Tousignant J, et al. Development of noninvasive and quantitative methodologies for the assessment of chronic ulcers and scars in humans. *Wound Repair Regen* 2001; 9: 123-32.
19. Ehrlich HP and Kelley SF. Hypertrophic scar: an interruption in the remodeling of repair-a laser Doppler blood flow study. *Plast Reconstr Surg* 1992; 90: 993-8.
20. Zhang Z, Kang C, Chen B, et al. The effects of conditioned medium from keloid fibroblasts under hypoxia on angiogenesis. *Zhonghua Zheng Xing Wai Ke Za Zhi* 2014; 30:

- 283-8. Chinese. doi: 10.3760/cma.j.issn.1009-4598.2014.04.012.
21. Sloan DF, Brown RD, Wells CH, et al. Tissue gases in human hypertrophic burn scars. *Plast Reconstr Surg* 1978; 61: 431-6.
22. Zheng J, Song F, Lu SL, et al. Dynamic hypoxia in scar tissue during human hypertrophic scar progression. *Dermatol Surg* 2014; 40: 511-8. doi:10.1111/dsu.12474.
23. Vincent AS, Phan TT, Mukhopadhyay A, et al. Human skin keloid fibroblasts display bioenergetics of cancer cells. *J Invest Dermatol* 2008; 128: 702-9. doi:10.1038 / sj.jid.5701107.
24. Ueda K, Furuya E, Yasuda Y, et al. Keloids have continuous high metabolic activity. *Plast Reconstr Surg* 1999; 104: 694-8.
25. Deschene K, Celeste C, Boerboom D, et al. Hypoxia regulates the expression of extracellular matrix associated proteins in equine dermal fibroblasts via HIF1. *J Dermatol Sci* 2012; 65: 12-8. doi:10.1016/j.jdermsci.2011.09.006.
26. Zhang Q, Wu Y, Ann DK, et al. Mechanisms of hypoxic regulation of plasminogen activator inhibitor-1 gene expression in keloid fibroblasts. *J Invest Dermatol* 2003; 121: 1005-12. doi:10.1046/j.1523-1747.2003.12564.x.
27. Nalwoga H, Ahmed L, Arnes JB, et al. Strong Expression of Hypoxia-Inducible Factor-1alpha (HIF-1alpha) Is Associated with Axl Expression and Features of Aggressive Tumors in African Breast Cancer. *PLoS One* 2016; 11: e0146823. doi:10.1371/journal.pone.0146823.
28. van der Veer WM, Niessen FB, et al. Time course of the angiogenic response during normotrophic and hypertrophic scar formation in humans. *Wound Repair Regen* 2011; 19: 292-301. doi:10.1111/j.1524-475X.2011.00692.x.
29. Gira AK, Brown LF, Washington CV, et al. Keloids demonstrate high-level epidermal expression of vascular endothelial growth factor. *J Am Acad Dermatol* 2004; 50: 850-3. doi:10.1016/j.jaad.2003.11.061.
30. Steinbrech DS, Mehrara BJ, Chau D, et al. Hypoxia up-regulates VEGF production in keloid fibroblasts. *Ann Plast Surg* 1999; 42: 514-9; discussion 519-20.
31. Mogili NS, Krishnaswamy VR, Jayaraman M, et al. Altered angiogenic balance in keloids: a key to therapeutic intervention. *Transl Res* 2012; 159: 182-9. doi:10.1016/j.trsl.2011.10.002.
32. Heldin CH, Moustakas A. Signaling Receptors for TGF-beta Family Members. *Cold Spring Harb Perspect Biol* 2016; 8. doi:10.1101/cshperspect.a022053.
33. Wang XB, Wang W, Zhu XC, et al. The potential of asiaticoside for TGF-beta1/Smad signaling inhibition in prevention and progression of hypoxia-induced pulmonary hypertension. *Life Sci* 2015; 137: 56-64. doi:10.1016/j.lfs.2015.07.016.
34. Wu D, Kuang RX, Wang Z, et al. Effects of 6-O-carboxymethyl-chitosan on the expression of TGF- β 1 in human hypertrophic scar fibroblasts. *Zhong Guo Mei Rong Yi Xue* 2011; (02): 240-3. Chinese. doi:10.15909/j.cnki. cn61-1347/r.2011.02.029.
35. Abdou AG, Maraee AH, Al-Bara AM, et al. Immunohistochemical expression of TGF- beta1 in keloids and hypertrophic scars. *Am J Dermatopathol*, 2011; 33: 84-91. doi: 10.1097/DAD.0b013e3181d0c3ad.
36. Sanchez-Elsner T, Botella LM, Velasco B, et al. Synergistic cooperation between hypoxia and transforming growth factor-beta pathways on human vascular endothelial growth factor gene expression. *J Biol Chem* 2001; 276: 38527-35. doi:10.1074/jbc.M104536200.
37. Fujiwara M, Muragaki Y, Ooshima A. Upregulation of transforming growth factor-beta1 and vascular endothelial growth factor in cultured keloid fibroblasts: relevance to angiogenic activity. *Arch Dermatol Res* 2005; 297: 161-9. doi:10.1007/s00403-005-0596-2.
38. Wang XQ, Liu YK, Qing C, et al. Hyperactivity of fibroblasts and functional regression of endothelial cells contribute to microvessel occlusion in hypertrophic scarring. *Microvasc Res* 2009; 77: 204-11. doi:10.1016/j.mvr.2008.08.007.
39. Ichioka S, Ando T, Shibata M, et al. Oxygen consumption of keloids and hypertrophic scars. *Ann Plast Surg* 2008; 60: 194-7. doi:10.1097/SAP.0b013e318053ec1d.
40. Kischer CW. The microvessels in hypertrophic scars, keloids and related lesions: a review. *J Submicrosc Cytol Pathol* 1992; 24: 281-96.
41. Lynam EC, Xie Y, Dawson R, et al. Severe hypoxia and malnutrition collectively contribute to scar fibroblast inhibition and cell apoptosis. *Wound Repair Regen* 2015; 23: 664-71. doi:10.1111/wrr.12343.