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REVIEW ARTICLE

Angiogenesis and Fibrogenesis in Oral Submucous Fibrosis: A Viewpoint

[1]Sheetal S Choudhari, [2]Deepak G Kulkarni, [3]Sangeeta Patankar, [4]Supriya M Kheur, [5]Sachin C Sarode
[6]Gargi S Sarode, [7]Shankargouda Patil

ABSTRACT

Oral submucous fibrosis (OSF) is characterized by excessive fibrosis of submucosa. The degree of vascularity in OSF has always been a matter of debate. Angiogenesis is the key mechanism involved in regeneration and repair. It also plays an important role in various pathologic conditions. Angiogenesis may contribute to the progression of fibrosis in fibrotic disorders. Inhibition of pathological angiogenesis is considered to be a new strategy for the treatment of various fibrotic disorders. In OSF, angiogenesis can be related to progression fibrosis. This article briefly describes the role of angiogenesis in pathogenesis of fibrosis in OSF and the importance of inhibition of pathologic angiogenesis in its prevention and treatment.

Clinical significance: Understanding the association between angiogenesis and fibrogenesis can help in developing new therapeutic strategies for treatment of OSF.

Keywords: Angiogenesis, Fibrogenesis, Fibrosis, Hypoxia, Inflammation, Oral submucous fibrosis.

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[1,4-6]Department of Oral Pathology and Microbiology, Dr. D. Y. Patil Dental College & Hospital, Dr. D. Y. Patil Vidyapeeth, Pune Maharashtra, India

[2]Department of Oral and Maxillofacial Surgery, Dr. D. Y. Patil Dental College & Hospital, Dr. D. Y. Patil Vidyapeeth, Pune Maharashtra, India

[3]Department of Oral Pathology and Microbiology, Yerala Medical Trust Dental College & Research Institute, Navi Mumbai Maharashtra, India

[7]Division of Oral Pathology, Department of Maxillofacial Surgery and Diagnostic Sciences, College of Dentistry, Jazan University Jazan, Kingdom of Saudi Arabia

Corresponding Author: Sheetal S Choudhari, B-504, Sarva Mangal Towers, Bld. No. 15, Tilak Nagar, Chembur (W), Mumbai 400089, Maharashtra, India, Phone: +919819331220, e-mail: kordesheetal@yahoo.co.in

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INTRODUCTION

Oral submucous fibrosis is characterized by juxtaepithelial inflammatory reaction followed by a generalized submucosal fibrosis.[1] In OSF, the degree of vascularity/angiogenesis has always been a matter of debate. Studies on the mucosal vasculature in OSF have reported controversial results. According to the conventional concept, there is decreased vascularity in OSF which leads to epithelial atrophy of diseased mucosa.[2] However, recent studies do not support the view of reduced vascularity in OSF.[3,4] Further, it is still unclear whether angiogenesis can induce and occur in parallel with the progression of fibrosis in OSF or is the consequence of it.

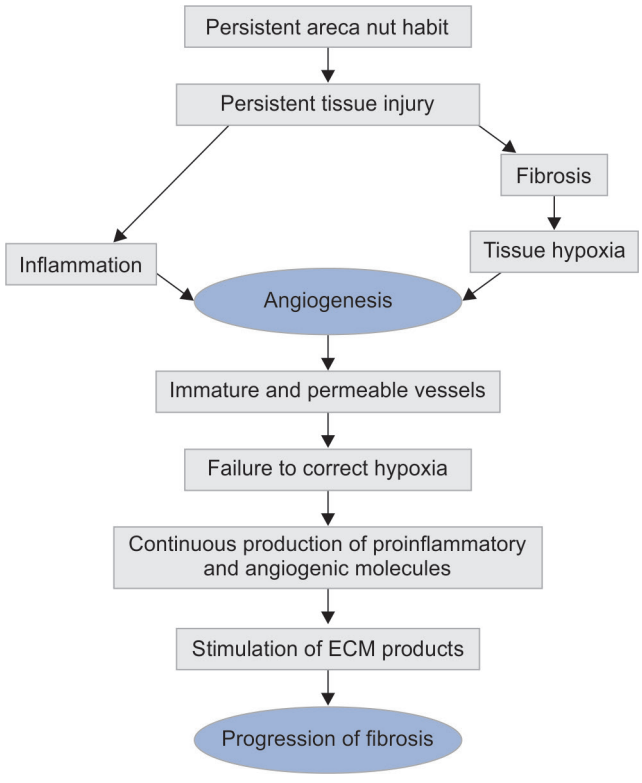
Angiogenesis is the process of new capillary blood vessel formation from preexisting vasculature. It is an important physiologic process during growth, tissue injury, repair, and wound healing. Large numbers of neovessels and marked inflammatory response are observed in early grade of OSF. Capillary density has been shown to be increased in early grades of OSF, whereas it decreases in the advanced grade.[5,6] This could be because inflammation and hypoxia trigger angiogenesis which results in increased vessel growth in the initial phase of the disease. Many inflammatory mediators, such as interleukins 6, 8, and 32, prostaglandin E1 and prostaglandin E2, tumor necrosis factor α, and nitric oxide can induce angiogenesis.[7-10] These inflammatory mediators can also induce expression of vascular endothelial growth factor (VEGF). Interleukin 1 and 6 and prostaglandin E2 have been shown to increase VEGF messenger ribonucleic acid (mRNA) levels.[11] Inflammatory cells, such as neutrophils and lymphocytes are involved in the early induction of angiogenesis by

producing angiogenic factors, such as basic fibroblast growth factor and VEGF.[12] Activated monocytes and macrophages can also induce angiogenesis.[13] During the course of the disease, accumulation of inflammatory cells along with fibrosis can lead to hypoxia.[14-16] In hypoxia, hypoxia-inducible factor 1 (HIF-1) induces angiogenesis and also stimulates inflammation through nuclear factor κB pathway.[17,18] Newly formed vessels express various chemokines and adhesion molecules which stimulate recruitment of more and more inflammatory cells. This results in prolongation of inflammatory response.[19] As newly formed vessels are immature and vulnerable, correction of the ischemic state of fibrosis could become difficult.[20] This sets in persistent hypoxia resulting in the continuous production of proinflammatory and angiogenic molecules. These can eventually stimulate extracellular matrix (ECM) deposition and progression of fibrosis. Persistent hypoxic condition leads to elevation of HIF-1α protein levels which drives various factors related to fibrosis, such as transforming growth factor β1, thrombospondin-1, plasminogen activator inhibitor 1, and VEGF.[21,22] Chronic hypoxia and consistent HIF-1 accumulation can potentiate the action of fibroblasts resulting in excessive matrix production through increased myofibroblastic differentiation.[23] Thus, pathologic angiogenesis and hypoxia may act synergistically in disrupting normal tissue repair, resulting in development and progression of fibrosis.

Reduced vascular density along with diminished total vascular area and increased vessel obstruction is observed in advanced OSF. Reduced vascularity in advanced grade can be related to increasing matrix concentration, as increased matrix density can act as a physical barrier that restricts cell migration. Extracellular matrix stiffness has emerged as a critical extracellular parameter that can modulate capillary network formation and barrier integrity. Moreover, matrix stiffness can alter how endothelial cells respond to soluble, angiogenic factors released by stromal cells, such as VEGF.[24] As more and more collagen is deposited in submucosa, fibrosis can impede material exchange, signal communication, and cell migration causing impaired angiogenesis with vessel loss resulting in reduced vascular surface area. This can explain reduced vascularity in advanced grade of OSF.

Angiogenesis can be related to fibrosis (Flow Chart 1). Pathologic angiogenesis should be intimately associated with fibrogenic progression in OSF as angiogenesis is a major feature of any wound-healing response, and chronic activation of wound healing is a general mechanism believed to be involved in the progression of fibrosis in OSF. Experimental evidence has suggested that the inhibition of angiogenesis can be used to prevent and treat liver and lung fibrosis.[20,25,26] Mechanistic links between

Flow Chart 1: Interrelationship between angiogenesis and fibrogenesis



angiogenesis and fibrogenesis can provide novel clues for the development of antifibrotic therapeutic strategies in OSF. Clarity is required if impaired angiogenesis in OSF is a consequence of fibrosis due to angiostatic signals derived from the continuous deposition of ECM or if it is a cause for abnormal tissue repair and fibrosis due to impaired angiogenic signals. For this, angiostatic molecules should also be studied in OSF apart from studying angiogenic factors.

Based on aforementioned scientific background, one can hypothesize the presence of a vicious cycle between fibrosis and pathological angiogenesis in OSF. Hypoxia, which starts at an early stage in OSF, may contribute to the progression of this vicious cycle. It stimulates activation of HIF-1, which facilitates repair and revascularization by producing various growth factors and mediators. Although required for successful repair, angiogenesis may fail to correct tissue hypoxia as these newly formed vessels are inefficient being more permeable and immature. Chronic hypoxic condition causes continuous production of the mediators that stimulate more ECM production leading to progression of fibrosis. Thus, vascular remodeling and hypoxia can be critically connected to the mechanisms of fibrosis in OSF (Flow Chart 1). Initially, angiogenesis could be a consequence of inflammation, rather than a cause for disease initiation. However, at later stages, the contribution of pathological angiogenesis may become more and more causal

resulting in progression of fibrosis, transition from OSF to dysplasia, and then to squamous cell carcinoma. Thus, pathologic angiogenesis along with inflammation and hypoxia can exacerbate the severity of fibrosis in OSF. Future studies are needed to further unravel the molecular, cell, and tissue mechanisms linking angiogenesis and fibrogenesis in OSF. Assessing the evidence supporting a clear relationship between angiogenesis and fibrogenesis in OSF would help in identifying new treatment targets for OSF.

Clinical Significance

The conventional therapeutic options for treatment of OSF yield limited results. Molecular-targeted therapies for the treatment of OSF are the demanding challenge today with the increasing understanding of its molecular pathogenesis. Vascular remodeling seems to be closely related to fibrosis in OSF and its malignant transformation as well. Experimental evidence has shown that inhibition of the angiogenesis signaling system can treat liver and lung fibrosis. Understanding the molecular mechanisms that regulate angiogenesis in various grades/stages of OSF and the mechanistic link between angiogenesis and fibrosis in OSF can help in designing molecular therapies against OSF. Blocking pathological angiogenesis could be a promising antifibrotic therapeutic option in OSF patients. However, with the use of drugs that inhibit pathological angiogenesis, the degree of inhibition should be controlled as it can lead to suppression of physiological angiogenesis which plays a critical role in normal wound-healing response. These issues need further research so as to identify and develop effective antifibrotic therapies in OSF.

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