Keywords: angiogenesis, teeth, periodontium, periodontal disease, dental pulp, pyogenic granuloma, gingiva, wound healing, orthodontics

Abstract: This chapter discusses the role of angiogenesis in non-neoplastic pathologies that affect the dentition and its supporting structures. Teeth and the tissues that support the teeth frequently respond to insults such as injury, infection, and orthodontic stress with the development of a robust proangiogenic environment. Yet aside from malignancies, the role of angiogenesis in pathologies of the oral cavity has not received widespread attention. Several recent studies suggest a role for angiogenesis in the development of diseases of the periodontium and the dental pulp. The evidence also supports the emerging concept that the severity of diseases such as chronic periodontitis depends upon individualized host responses.

Introduction

The tissues of the oral cavity represent some of the most highly vascularized areas of the body, and the robust vascularity of the oral mucosa has been suggested to support the greater proliferative capacity of the oral mucosa as compared to skin. The precise level of vascularity varies among the various anatomical locations within the oral cavity. Blood flow to oral tissues such as gingiva, tongue, lips, and dental pulp is known to be significantly greater than that of skin [1–4]. The highest level of blood flow appears to occur within the free gingiva (the portion of the gum tissue that surrounds the tooth but is not directly attached to the tooth) where flow has been recorded at levels more than ten-fold greater than that of skin. In contrast, the palatal mucosa is not particularly heavily vascularized, and blood flow to the hard and soft palate is quite similar to skin [1]. In addition to regionally high vascularity, the mucosa of the oral cavity is bathed in saliva. Saliva is rich in many growth factors, including those that can support epithelial proliferation and health, such as EGF and TGF-α [5,6]. Saliva also contains biological levels of several potent proangiogenic factors including FGF-2, VEGF, and TGF-β; these factors have been suggested to be involved in tissue repair or other pathologic processes in the mouth [7,8].

The role of angiogenesis in the development of oral cancer has been the subject of intensive investigation, and the link between oral cancer and angiogenesis is firmly established [9]. Beyond neoplasms, though, the role of angiogenesis in pathology that is specific to the tissues of the oral cavity has received only minimal experimental attention. The focus of this chapter is on the regulation and significance of angiogenesis in pathologies that affect the dentition and its supporting structures.

The Periodontium

An association between angiogenesis and pathologies that affect the periodontium, or the tissues that surround the teeth, has been demonstrated for several of the diseases that affect these supporting tissues. Links between angiogenesis and periodontal pathology are of particular interest, since diseases of the periodontium are an important cause of tooth loss in the United States [10]. Recently, interactions of periodontal disease with systemic diseases including cardiovascular disease and stroke have been described, providing new-found significance to understanding the pathogenesis of periodontal pathologies [11–15]. While an etiologic link between periodontal disease and systemic diseases remains to be proven, the associative data suggests either common susceptibility factors or causation [16]. Several theories exist to explain the described associations, including a possible influence of the oral bacteria that are released from sites of periodontal disease into the systemic circulation. Chronic inflammation within the periodontium has also been hypothesized to create a systemic pro-inflammatory effect that influences tissue responses at other locations [17,18]. This emerging data underscores the need for more information about the pathologic...
Chronic Periodontitis

One of the best studied associations of angiogenesis and oral disease is its relationship to chronic periodontal disease, or chronic periodontitis. Chronic periodontitis, a condition that may affect up to one-half of the US population, is an infectious process that involves the gingiva and bone that surround the teeth [10]. In the earliest phase of the disease, termed gingivitis, the gingiva becomes inflamed in response to bacterial plaque that forms on the teeth. Gingivitis can be reversed by professional treatment and maintenance of adequate oral hygiene. Untreated, though, gingivitis may progress to chronic periodontitis. In chronic periodontitis, a persistent inflammatory state within the gingiva ultimately results in destruction of the connective tissue attachment and the supporting bone around the teeth, and may result in tooth loss. Gingival recession may also occur. Chronic periodontitis generally progresses slowly over many years, although periods of rapid progression may take place.

Early studies of the tissue architecture of the chronic periodontitis demonstrated the highly vascular nature of these lesions in both animal models and humans, and increased vascularity has been described to be associated with disease progression [19–22]. Beyond changes in vascular density, the vascular structure appears altered within the periodontal lesion, with thickened vascular basement membranes. Chronic periodontitis is an inflammatory disease, and increased vascularity could participate in the pathogenesis in more than one way. Increased vascularity might assist in the delivery of leukocytes and serum derived pro-inflammatory mediators to the lesion. Moreover, the vessels within the chronic periodontal lesion have been described to be highly permeable, a situation that may increase tissue edema and promote tissue destruction. Interestingly, one mechanism for this increased permeability may be the degradation of platelet endothelial cell adhesion molecule 1 (PECAM-1), as virulence factors that are derived from specific periodontal pathogens, such as Porphyromonas gingivalis, have been shown to degrade this molecule [23].

Angiogenesis in chronic periodontitis is believed to be initiated by the over-production of proangiogenic mediators within the inflamed gingival tissue. The production of proangiogenic mediators, such as vascular endothelial growth factor (VEGF), interleukin-8 (IL-8), placenta growth factor (PIGF), and hepatocyte growth factor (HGF), have been described to be increased at sites of moderate to severe periodontitis [24–27]. The best studied of the proangiogenic factors that might play a role in periodontal disease is VEGF. VEGF levels have been measured in tissues from normal, mild, moderate, and severe periodontal disease in samples from human subjects by the enzyme-linked immunosorbent assay (ELISA) and using immunohistochemical techniques [24,28–30]. Little or no VEGF was reported to be present in normal, uninflamed gingiva [24,30]. In contrast, VEGF is prominently expressed at sites of periodontal disease. In a study by Johnson et al., the greatest level of VEGF was found in those lesions defined as moderate, while the greatest vessel density occurred in the most severe lesions [24]. This result may suggest that the specific pattern of VEGF induction occurs as the disease develops and matures. A link between VEGF levels and disease susceptibility has also been suggested. The examination of periodontally diseased tissue from diabetic patients, a population in whom periodontal disease is generally more severe, demonstrated increased VEGF expression in diabetic versus non-diabetic patients [30]. The profiling of cytokines and growth factors in gingival fluid derived from the site of disease is currently being explored as a diagnostic tool for disease severity and prognosis is an area of active investigation [27,31–35].

VEGF is produced by several cell types within the diseased periodontium, including inflammatory cells such as neutrophils, monocytes, macrophages and plasma cells, and the epithelium in the area of the lesion. Interestingly, the epithelium that lines the pocket adjacent to the tooth appears to produce less VEGF than the oral epithelium [29,30]. VEGF can also be detected in the fluid in the periodontal pocket surrounding the tooth, termed gingival crevicular fluid (GCF). GCF from healthy subjects contains detectable yet low levels of VEGF. In patients with periodontal disease, GCF from both healthy and diseased sites contains increased VEGF, with levels of up to 250 pg/ml of GCF [28]. These studies indicate that, in persons with chronic periodontitis, even apparently healthy sites may exhibit altered VEGF production. Whether this predicts disease progression remains speculative.

Vascular remodeling seems to be a prominent in the progression of chronic periodontal disease, as an accumulation of basement membrane remnants of probably vascular origin is seen within advanced lesions [29]. The numerical vascular density is known to increase in chronic periodontitis, with a selective increase in vessels that are ≥25 μm in diameter, suggesting that vascular enlargement is a feature of the angiogenic process in this disease [29].

The stimuli that induce VEGF production at sites of chronic periodontal disease are probably multiple. A wide variety of proinflammatory mediators are produced within periodontal lesions, including many that might stimulate the production of VEGF. Many of the proinflammatory cells that are prominent in the chronic periodontitis lesion, including macrophages and neutrophils, can produce VEGF [36,37]. Periodontal pathogens themselves may stimulate the production of proangiogenic factors. In in vitro studies, stimulation of gingival fibroblasts by vesicle or outer membrane protein components from either Actinobacillus actinomycetemcomitans or P. gingivalis resulted in enhanced expression of VEGF [38]. The expression of hepatocyte growth factor has been reported to increase in gingival fibroblasts exposed to P. gingivalis components [39]. Exposure to mechanical stress is also capable of inducing the production of VEGF by both gingival and periodontal ligament processes that define periodontal disease, including the role of angiogenesis. Such knowledge may be important in identifying the link between systemic and oral health.