Angiogenesis and oral diseases

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Abstract

Angiogenesis is the process of developing new blood vessels from pre-existing vessels. The basic prerequisite of angiogenesis is the presence of pro-angiogenic factor. As a result of this factor the activation of endothelial cells, capillary blood vessels and post-capillary veins takes place. Studies concerning the role of angiogenesis in oral diseases are scarce. Last years, an increased interest in this topic could be seen in all dental disciplines. These disciplines include endodontology, cariology, oral and maxillo-facial surgery, as well as implantology and periodontology. A special role in periodontal disease etiopathogenesis plays vascular endothelial growth factor (VEGF) – a cytokine stimulating angiogenesis. Vascular endothelial growth factor concentration in saliva and gingival fluid of patients affected with periodontitis is higher, as compared to the control group of clinically healthy periodontal tissue (P < 0.05). Anti-angiogenic therapy has been used with success in maxillo-facial surgery in case of mandibular giant cell granuloma in 4-year-old Australian boy.

Key words: angiogenesis, oral diseases.

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Angiogenesis is a critical process in diverse biological contexts, ranging from embryonic development to pathological conditions such as cancer and periodontal disease. It involves the formation of new blood vessels from pre-existing ones and is characterized by increased concentration of many other angiogenic factors, as compared to the clinically healthy periodontium. These factors include fibroblast growth factor, epithelial growth factor and endothelial growth factor, which are known to stimulate cell proliferation and differentiation of fibroblasts. These stimulators also lead to formation of three-dimensional tubular structures that will be turned into future blood vessels. A number of angiogenesis stimulators have been identified, among them: angiogenin, angiotropin, fibroblast growth factor, vascular endothelial growth factor (VEGF), epidermal growth factor, transforming growth factor (TGF-α), plasminogen activator, tumor necrosis factor, interleukin 1 (IL-1), IL-4, IL-6, IL-8, myeloid growth factors, hepatocyte growth factor, insulin-like growth factor, prostaglandin E, copper, hypoxaemia, macrophages derived P factor and many other endogenous substances. Angiogenesis inhibition takes place directly by total suppression of pro-angiogenic factors or in an indirect manner, by competitive blocking of receptors for these factors. Angiogenesis inhibitors comprise interferons, thrombospondin, angiotatin, endostatin, TGF-β, IL-10, IL-12, platelet-derived factor, vascular endothelial growth factor inhibitor (VEGI), tissue matrix metalloproteinase inhibitors (MMPI), plasminogen activator inhibitor, zinc and many other endogenous factors, as well as some of well known pharmaceuticals, such as cimetidine, furosemidum, spironolactone and thalidomide. They work first of all by inhibiting endothelial cells migration and proliferation, as well as by total inhibition of differentiation processes. Moreover interferons block onco genes expression. Well known angiogenesis inhibitors are tetracyclines (metacycline, minocycline, doxycycline) – antibiotics commonly used in periodontal treatment. Their properties (apart from antibacterial function) result from cellular matrix metalloproteinase (MMP) blocking, leading to the angiogenesis process inhibition.

Studies concerning the role of angiogenesis in oral diseases are scarce. Last years an increased interest in this topic could be seen in all dental disciplines. These disciplines include endodontology, cariology, oral and maxillo-facial surgery, as well as implantology and periodontology [8-11]. A special role in periodontal disease etiopathogenesis plays VEGF – a cytokine stimulating angiogenesis [12]. Vascular endothelial growth factor concentration in saliva and gingival fluid of patients affected with periodontitis is higher, as compared to the control group of clinically healthy periodontal tissue (P < 0.05). It is assumed that the clinical periodontal state correlates with VEGF concentration in saliva and gingival fluid [13]. Inflamed periodontal tissue is also characterized by increased concentration of many other angiogenic factors, as compared to the clinically healthy periodontium.

Yet another area of interest is the role of angiogenesis in drug-induced gingival hyperplasia. The first studies on drug-induced gingival overgrowth were performed before Second World War (in the 1930s) and concerned phenytoin. Currently the studies concentrate on potential correlations between gingival hyperplasia-inducing drugs (phenytoin, nifedipine, cyclosporin A, calcium channel blockers) and selected growth factors, especially the pro-angiogenic factors. A statistically significant difference (P < 0.05) was observed between connective tissue growth factor (CTGF) level in cells and extracellular matrix, as well as angiogenic process in phenytoin-induced gingival overgrowth, as compared to the control group and other drugs inducing gingival hyperplasia [17].

Very interesting studies concern etiology of so called pyogenic granuloma – gingival tissue pathology, affecting women in puberty, pregnant or using oral contraceptive agents. It is believed to reflect an increased inflammatory response to various stimulating and provoking factors. Women affected by pyogenic granuloma (exhibiting increased steroid hormone levels) were found to present dysfunction of angiogenesis control system. A significant increase in angiogenesis stimulators (angiopoietin, VEGF, fibroblast growth factor) as well as decrease in angiogenesis inhibitors (angiotatin and thrombospondin) level was observed, as compared to the control group with clinically healthy periodontium [18, 19].

Anti-angiogenic therapy has been used with success in maxillo-facial surgery in case of mandibular giant cell granuloma in 4-year-old Australian boy [20]. One million units of interferon-α-2a was administered once daily subcutaneously for 9 months (from March till December 1999). The paper reviews one year after interferon therapy completion: no relapse was observed, the boy feels well. “It is a great pleasure to see a healthy boy who is just about to go to school”, says the author of the paper and the attending physician.

References

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