Review paper

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.*

(Centr Eur J Immunol 2012; 37 (2): 164-166)

Angiogenesis is the process of developing new blood vessels from pre-existing vessels. It is a complex, sophisticated process, subjected to many different conditions. Physiological angiogenesis takes place during embrional and fetal organogenesis, repair processes, healing, tissue regeneration, as well as female menstrual cycle. Angiogenesis generated interest in 1971, when Folkman for the first time formulated his hypothesis about the role angiogenesis plays in neoplastic process [1]. The next milestone in the studies on angiogenesis came in the last decade of XX century, with the discovery of angiostatin and endostatin – angiogenesis inhibitors. In view of these facts the scientists started seriously considering the anti-angiogenic cancer therapy, based on inhibiting the development of tumor blood vessels. Moreover the role of angiogenesis in natural history of psoriasis, diabetic retinopathy, rheumatoid arthritis and atherogenesis has been studied. Surprisingly it was discovered that the process of angiogenesis within tumor begins much earlier then it had been thought thus far. Cancer vasculature was believed to start forming once the tumor is as much as 2 mm big. In 1999 Holash *et al.* have proven that 60-80 cells are enough to initiate angiogenesis, while new functional blood vessels can be already observed when tumor counts 100-300 cells [2].

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. The vessels broaden and their walls' permeability increases. The extravasated fibrinogen cumulates in the extracellular matrix. The next step is degradation of basement membrane of vessel wall and migration of endothelial cells towards the pro-angiogenic factor. As a result of constant cell divisions the blood vessel continually lengthens. The process of cancerous angiogenesis as well as angiogenesis in course of other diseases depends on so called angiogenesis stimulators and inhibitors. First of all these are the natural, endogenous factors. Nowadays in many scientific centers all over the world the clinical trials are led to assess the efficacy of synthetic angiogenesis inhibitors in cancer treatment and other diseases [3-7]. They concern breast cancer, ovarian cancer, colorectal cancer, lung cancer, pancreas cancer, prostate cancer, renal cancer, solid tumors of various organs and malignant gliomas, among others.

Anti-angiogenic cancer therapy includes usually inhibition of angiogenesis stimulators activity or activation of endogenous angiogenesis suppressors. Under physiological conditions the protein angiogenesis factors, present in the extracellular matrix, are inhibited by angiostatic factors. This mechanism is to protect against excessive and uncontrolled angiogenesis. Most human cells synthesize angiogenesis inhibitors (glycoprotein 140, thrombo-

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spondin). When the inhibitors are blocked, angiogenesis can take place, leading to developing vasculature, e.g. within tumor. Intracellular dysregulation could also increase the expression of membrane receptors for angiogenic factors.

The angiogenesis process is induced by so called stimulators, that exhibit chemotactic and mitogenic activity against epithelial cells, stimulating them to synthesize proteolytic enzymes (collagenase and plasminogen activator), thus leading to the basal membrane degradation, as well as enabling the migration of new epithelial cells, proliferation and differentiation of fibroblasts. These stimulators do 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, proteases, 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, angiostatin, endostatin, TGF-β, IL-10, IL-12, platelet-derived factor, vascular endothelial growth 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 oncogenes 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. These are fibroblast growth factor, epithelial growth factor and endothelial growth factor, to name just a few. Chapple *et al.* suggest it is a response to the specific microorganisms residing in pathogenic periodontal pocket [14]. Many papers deal with angiogenic process related to healing phase after implant surgery. The comparative studies on clinically healthy periodontium and peri-implant tissue have revealed that VEGF is essential for physiological healing after implantation [15], as well as for periodontal tissue remodelling after regenerative surgery [16].

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 (angiostatin 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.

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