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DOI: 10.15225/PNN.2024.13.4.6 JNNN 2024;13(4):168–172 **Review**

Angiogenesis, Angiogenin and Postoperative Wounds in Neurosurgery

Angiogeneza, angiogenina i rany pooperacyjne w neurochirurgii

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Abstract

Angiogenesis is one of the processes leading to the formation of new blood vessels, in which blood vessels are formed from existing blood vessels by branching and elongation. Angiogenesis is relevant to many physiological as well as pathological processes. One of the factors involved in the early stages of angiogenesis is angiogenin (ANG). Its concentration in tissues or blood changes in physiological and pathological processes. This paper presents issues related to the wound healing process in neurosurgery with a focus on angiogenesis and angiogenin. **(JNNN 2024;13(4):168–172)**

Key Words: angiogenesis, angiogenin, neurosurgery, wound

Streszczenie

Angiogeneza to jeden z procesów prowadzących do powstania nowych naczyń krwionośnych, w którym naczynia krwionośne powstają na bazie już istniejących, poprzez ich rozgałęzianie i wydłużanie. Angiogeneza ma znaczenie dla wielu procesów fizjologicznych jak i patologicznych. Jednym z czynników biorących udział we wczesnym etapie angiogenezy jest angiogenina (ANG). Jej stężenie w tkankach czy krwi zmienia się w fizjologicznych i patologicznych procesach. W pracy przedstawiono zagadnienia związane z procesem gojenia się rany w neurochirurgii z uwzględnieniem angiogenezy oraz angiogeniny. **(PNN 2024;13(4):168–172)**

Słowa kluczowe: angiogeneza, angiogenina, neurochirurgia, rana

Introduction

A wound (vulnus) can be defined as an interruption of tissue continuity as a result of mechanical, physical or chemical trauma. In general, a distinction is made between superficial, deep and complicated wounds (penetrating into body cavities, damaging vessels, nerves). Taking into account the type of trauma and the shape of the wound, one can distinguish between: incised, stab, lacerated, contused, crush, bite and gunshot wounds [1]. Wounds can heal by first intention (primary closure), by granulation or by second intention. Two basic phenomena occur during wound healing, these are regrowth of the parent tissue and a repair process involving the replacement of the focus of "post-traumatic" destruction by connective tissue [1,2]. The phases of wound healing can overlap, often happening partly simultaneously. The wound healing process consists of various phases, for example: homeostasis (primary, secondary), inflammation, the proliferation phase (epidermal regeneration, synthesis of intercellular substance, regrowth of blood vessels, production of connective tissue) and the remodelling phase (wound contraction, remodelling of the extracellular matrix, scar formation) [1,2]. Locally secreted messengers are involved in the wound healing process. These include arachidonic acid derivatives formed from cell membrane lipids, cytokines and growth factors, as well as nitric oxide,

peptides, amines and platelet activating factor (PAF). Among the best-known growth factors involved in the wound healing process are [1,3–7]:

— platelet-derived growth factor — PDGF,
— vascular endothelial growth factor — VEGF,
— epidermal growth factor — EGF,
— fibroblast growth factor — FGF,
— keratinocyte growth factor — KGF,
— transforming growth factor α and β — TGF,
— insulin-like growth factor (IGF).

When we speak of a post-operative neurosurgical wound, we are referring to a wound caused by a mechanical incision during surgery. After surgery, we are therefore dealing with a wound that heals by first intention (primary closure). A sutured wound generally results in a scar of negligible size. The healing time for such a wound is approximately 7–14 days.

Among the most commonly performed procedures in neurosurgery are those of the head and spine, however — according to Cote et al. — in recent years, the number of spinal surgeries has been increasing and the number of cranial procedures has been decreasing [8]. Attention is also drawn to the increase in the frequency of spine procedures performed by orthopaedic surgeons [8–10]. According to the literature, the place of residence and the reimbursement scheme of spine surgery procedures may influence the trend described [11,12]. As with any surgical speciality, wound healing problems are inevitable in neurosurgery as well, and can be particularly cumbersome due to various specific risk factors [13]. According to various authors, the incidence of these complications in neurosurgery may be underestimated; reported overall infection rates after neurosurgical procedures range from 1.1% to 8.1% and increase with the complexity of the procedure performed [8,13–15]. Although they are rare complications (due to the dense network of vessels of the circulatory system, supplied from different vascular systems), in patients repeatedly operated on due to nervous system pathology, they are a very alarming problem in neurosurgical practice, leading to significant morbidity and mortality [13,16,17]. They can progress from simple wound dehiscence to complex pathological processes, including cerebrospinal fluid leak and infection, which requires an individualised treatment plan [13]. Factors that will predispose to the occurrence of this type of complication include, but are not limited to: prolonged surgery time, vascular procedures, emergency surgery, paranasal sinus injury, reoperation, neoplastic disease, implantation of foreign material [13,15–19].

Angiogenesis and Angiogenin

Angiogenesis is one of the processes leading to the formation of new blood vessels, in which blood vessels are formed from existing (endothelium-lined) blood vessels by branching and elongation. It occurs in the embryonic as well as in the post-embryonic period. Angiogenesis is important for many physiological processes (embryonic development, wound healing, menstrual cycle) as well as pathological processes (tumour growth and expansion, metastasis formation, pathology in ischaemia, inflammatory processes, nervous system diseases) [20–23].

The process of angiogenesis is regulated by a system of stimulating and inhibiting factors. Stimulating factors (stimulators) of angiogenesis include, for example: those that affect the endothelium through specific receptors (VEGF and angiopoietins) and pleiotropic factors (FGF — *fibroblast growth factor*, PDGF — *platelet derived growth factor*, TGF — *transforming growth factor*). Inhibitory factors (inhibitors) of new vessel development include, for example: angiostatin, endostatin, interferon α [20,22,24].

Among the above-mentioned proangiogenic factors, VEGF appears to be crucial [21,23]. VEGF is a cytokine with proven importance in various biological processes. However, it is most active as an endothelial growth factor and as a vascular permeability enhancer. It has been found that almost all known signalling pathways in endothelial cell cultures are activated when exposed to VEGF. VEGF is one of the primary regulators of angiogenesis. The main point of action for VEGF are the cells of vascular endothelium, which contains receptors for VEGFR-1 (*vascular endothelial growth factor receptor type 1*) and VEGFR-2 (*vascular endothelial growth factor receptor type 2*). Stimulation of the VEGFR-2 receptor ultimately induces endothelial cell division [21,25].

Among the numerous proteins described as promoting angiogenesis is angiogenin (ANG). Angiogenin is a 14-kDa soluble protein first isolated in 1985 from colorectal adenocarcinoma cells [26]. It is mainly synthesised by liver cells, but also fibroblasts, monocytes and epithelium of the large intestine [27]. ANG is detectable at relatively high concentrations in the serum of healthy individuals, with concentrations ranging from 250 to 360 ng/ml [28]. Elevated ANG levels have been observed in numerous neoplastic processes such as pancreatic, gastric, colorectal and prostate cancer [29–31]. Numerous studies report the involvement of ANG in diseases such as inflammatory bowel disease, nasal polyps, heart failure or chronic lower limb ischaemia [28,32–34].

It is assumed that the main physiological function of the protein is neovascularisation during wound healing. Angiogenin is also likely to participate in the process of

wound healing and tissue regeneration associated with the host response to injury. Angiogenin binds to actin and this complex is more effective than actin alone in stimulating t-PA to produce plasmin, which plays an essential role in processes such as wound healing, inflammation, and even tumour cell metastasis [28,35].

As reported above, ANG is directly involved in the wound healing process as its primary biological function is blood vessel homeostasis regulation, through both the stimulation of new vessel growth and the maintenance of endothelial cell self-renewal. Furthermore, ANG activates fibroblasts and the factors that they produce, thus also indirectly influencing the course of wound healing [36].

Studies have shown [36,37] that intracutaneous injections of recombinant ANG in rats induce a dose effect causing morphological changes in the dermis, playing an important role in regenerative processes. The thickness of the stratum corneum is increased, as well as the density of collagen fibres and the proliferation rate of epidermal cells in animals injected with ANG compared to animals used as a control group. In the same study, the addition of recombinant ANG was shown to stimulate blood cells to produce and release both pro- and anti-inflammatory cytokines, suggesting that ANG may act as a protective homeostatic factor through angiogenic process activation or through the activation in the dermal blood vessels of other circulating cells, such as lymphocytes, neutrophils and endothelial cells. Therefore, ANG may exert its effects on wound healing by triggering different and combined biochemical pathways in the basal layer of the dermis.

Positive influence of ANG on wound healing is observed in different endothelial cells [36,38]. Studies have shown that corneal endothelial cells (CECs) form the innermost monolayer of the cornea and must be physiologically protected against injuries. A scratch wound assay performed on CECs shows that ANG promotes cell migration and wound closure through the activation of the phosphatidylinositol 3-kinase (PI3-k) signalling pathway [36,39].

The properties of ANG have prompted the development of modified CECs capable of overexpressing the protein, with the aim of mimicking the corneal endothelium in vivo and increasing graft cellularity for transplant approaches [36,40].

An important aspect of ANG's action is its involvement in the immune system. The protein is also a component of tears and has an immunomodulatory function in corneal fibroblasts [36,41]. Experiments conducted on a rat model of corneal alkali burns showed that the addition of ANG in vivo restored normal corneal transparency and caused a significant reduction in corneal opacity compared to the control group [36,42].

The studies conducted found high levels of ANG measured in wound fluid collected post-injury [36,43,44]. It has been shown that high levels of ANG in wound fluids are able to induce endothelial cell proliferation andcircular angiogenic cells (CAC) differentiation. The results obtained from the research confirm the positive correlation between ANG and the wound healing process [36,45].

According to studies, the use of ANG for the topical treatment of ulcerative wounds in humans has been tested and patented in Russia. The authors of the study claim that this reduces wound healing and tissue generation time — unfortunately, there are currently no pharmaceutical forms containing ANG for application in wound healing [36].

Conclusions

In conclusion, learning about angiogenesis and its regulatory mechanisms is of great importance for understanding the mechanisms of the wound healing process. Despite numerous studies on ANG, there are still many uncertainties regarding the physiological role of this protein in angiogenesis. Due to the discrepancies in the results obtained, further studies will be required to answer the questions that still arise. The fact that most pro-angiogenic factors are soluble proteins whose concentrations can be determined in a non-invasive manner makes such studies more accessible to researchers and less burdensome for the patient.

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