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The selected functional activities of angiogenin

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ABSTRACT

Introduction: The ribonuclease A (RNase A) superfamily contains proteins homologous to the bovine pancreatic RNase A. In humans, the family contains eight RNases 1-8, including RNase 5, also known as angiogenin (ANG). ANG is probably the oldest member of the RNase A superfamily, and is distinguished by certain details in its structure and ribonucleolytic activity that confer it distinctive functional activities.

Aim: To present the characteristic structure of ANG and its relationship with protein functions, with particular emphasis on the selected functional activities both in physiological and pathological conditions.

Material and methods: This article is based on the available literature. A total of 57 articles were included in the study.

Results and discussion: Based on the literature review, the most detailed structural differences between ANG and its homologue RNase A have been explained. The structure of ANG contributes to the reduced ribonucleolytic activity and a variety of its biological functions, including the initiation of angiogenesis. The formation of blood vessel in reaction to ANG along with identified signal transduction pathways have been presented. The selected functional activities of ANG have been concisely described in the context of nucleic acid interaction processes, cellular stress response, tissue regeneration, and the antimicrobial properties of the protein. The article also discusses ANG's role in the development and spread of cancer, neurodegeneration and others.

Conclusions: ANG has shown a wide spectrum of functional activities in many biological processes. It seems to be a promising indicator in neoplastic, neurodegenerative and other diseases, but further research is needed.

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1. INTRODUCTION

The ribonuclease A (RNase A) superfamily contains proteins homologous to the bovine pancreatic RNase A. In humans, there are eight so-called 'canonical ribonucleases,' RNases 1-8, including RNase 5, also known as angiogenin (ANG).[1,2] These are secretory proteins with a molecular mass of approximately 14–16 kDa. Their structure is characterized by the 6–8 cysteines forming 3–4 disulfide bridges and a conserved catalytic triad consisting of two histidines (His12 and His119), and lysine (Lys41), responsible for the enzymatic hydrolysis of RNA.[1] Ribonucleases vary in their activity towards RNA. The mechanism of action of RNase A (EC 3.1.27.5) is a catalyzed reaction involving the cleavage of the 3',5'-phosphodiester bond at the 3'-position of the pyrimidine nucleotide to produce a 2',3'-cyclic nucleotide as an intermediate.[3] His12 and His119 act as a proton acceptor and proton donor, respectively, and Lys41 stabilizes the transition state.[3] The RNase A superfamily members play a key role in many biological processes, exhibiting i.e. antibacterial, antiviral, and angiogenic properties.[1,2] They are derived from a common ancestral gene, the RNase 5-like gene, which first emerged in vertebrates and encoded a protein important in innate immunity.[4] Therefore, the involvement of these ribonucleases in host defense is suggested to be their primary and physiological role.[1,2,4] In particular, ANG, which represents probably the oldest member of the RNase A superfamily,[4] is distinguished by certain details in its structure and ribonucleolytic activity that confer it distinctive functional activities.

2. AIM

The aim of this article is a concise presentation of the characteristic structure of ANG and its relationship with the protein functions, with particular emphasis on selected functional activities in both physiological and pathological conditions.

3. MATERIAL AND METHODS

A complete and reliable search of the current scientific literature was conducted using multi-disciplinary bibliographic and abstract databases, such as PubMed, Google Scholar and Scopus (accessed on January 20, 2025), as well as reference lists of some publications. The effective information search was possible thanks to the use of the following terms: 'angiogenin,' 'ANG,' 'angiogenesis,' and 'ANG gene.' The inclusion criteria for the study were only articles written in English and published in peer-reviewed journals between 1985 and 2022. The need to include older publications (before December 2000) resulted from their fundamental cognitive value in the process of discovering the structure, enzymatic activity and function of angiogenin. Ultimately, a total of 57 articles were taken into consideration. As a rule, foreign-language articles without an English abstract as well as conference materials were excluded from the analysis (with the exception of 1 recently published abstract of significant importance).

4. RESULTS AND DISCUSSION

4.1. The structure and enzymatic activity of ANG

Human ANG, encoded by the angiogenin gene (ANG) located on chromosome 14q11.2,[1,2] is a 14,124 Da protein composed of a single 123 amino acid chain.[5,6] It shares 33% sequence identity and 65% homology with RNase A, the prototype of the ribonuclease family.[1,5,6] The key structural features of ANG include three α-helices, seven β-strands, and 'a short 3_{10} helix,' that is missing in RNase A,[7] as well as the functionally important regions.[8,9] The first one is the catalytic triad: His13-Lys40-His113, which determines the enzymatic activity of the protein.[6–8] It is worth mentioning here that the structure of ANG also contains binding sites for pyrimidines (B1) and purines (B2). But unlike RNase A, the B1 site is blocked by glutamine (Gln117).[6–8] This blockade is one of the reasons for the reduced ribonucleolytic activity of ANG by about 10^5–10^6 times compared to the activity of RNase A.[6,8] Furthermore, the presence of only 6 out of the 8 cysteines (found in RNase A) in the ANG structure results in the lack of a fourth disulfide bridge and the formation of a loop, from lysine (Lys60) to asparagine (Asn68), which is the second functional site responsible for binding to the cell surface receptors.[6] Finally, the third functional region is the nuclear localization sequence covering three subsequent arginine residues that play a supportive (Arg33) and regulatory (Arg31 and Arg32) role.[9,10] The differences in the structure of the functional regions of ANG affect not only its enzymatic activity, but also the diversity of its biological activities. In addition, the ribonucleolytic activity of ANG has been shown to be crucial to perform many functions in the body.[5,6,8]

4.2. The selected functional activities of ANG

ANG was first isolated from the culture medium of human colon cancer cells HT-29 as a protein with the ability to stimulate angiogenesis, the process of creating new blood vessels based on existing ones.[10–12] In general, it involves the stimulation of endothelial cells (ECs), degradation of the basement membrane and extracellular matrix, and migration and proliferation of ECs, leading to the formation of the tubular structures of new vessels.[10,12] The ANG-actin complex on the surface of ECs activates tissue plasminogen activator to release plasmin from plasminogen. Moreover, there are ANG-specific receptors on the surface of ECs. The 170-kDa receptor is expressed in a density-dependent manner, mediates angiogenesis and the activation of phospholipase A2.[10,12] The recently identified plexin-B2 receptor[13] also regulates neovascularization. ANG stimulates ECs, smooth muscle cells (SMCs) and fibroblasts (FCs) by activating the signal transduction pathways via extracellular signal-related

kinase 1/2 (ERK1/2), serine/threonine-protein kinases (B/Akt), and stress-associated protein kinase/c-Jun N-terminal kinase (SAPK/JNK).[12] It also has the ability to directly translocate into the nucleus where it triggers rRNA transcription, ribosome biogenesis, protein translation, and, as a result, cell growth and proliferation.[12,14] Finally, proliferating and migrating ECs lead to the creation of new blood vessels and their surrounding by SMCs and FCs.[10,12,14]

The expression of human ANG is not limited to vascular ECs, SMCs, FCs, and tumor cells,[15] but is widespread in tissues of the digestive system, reproductive system, heart, lung, skeletal muscle, kidney, leukocytes,[5,16] and motorneurons.[17] This suggests that angiogenesis is not the only physiological function of this protein.

The secreted ANG after the receptor-dependent endocytosis and nuclear translocation is localized, among others, in the nucleolus, where it may interact with nucleic acids.[8] In growth conditions, ANG has been shown to stimulate pre-rRNA synthesis by binding to the specific dinucleotide CT sequences within the ribosomal DNA (rDNA) promoter.[18] In addition, it promotes the transcription process by optimizing the interaction of the rDNA promoter with RNA polymerase I and increasing the number of transcribed templates, which is possible through epigenetic modifications.[19] On the other hand, ANG is able to degrade 28S and 18S rRNA as well as 5S RNA from *Saccharomyces cerevisiae* and *Escherichia coli*.[12] Additionally, Saxena et al.[20] reported that ANG injected into frog oocytes also hydrolyzed tRNA. Until recently, this property of angiogenin was referred to as 'cytotoxicity' because it inhibited protein biosynthesis.

The cytoprotective role of ANG has only been revealed relatively recently. Under stress conditions (oxidative stress, heat shock, UV radiation, hypothermia, hypoxia), ANG hydrolyzes mature tRNA by specifically cleaving the anticodon loop and generating non-coding small tiRNA (tRNA-derived, stress induced small RNA).[21] It has been shown that in the cytoplasm of cells, these tiRNAs can stimulate the formation of stress granules (SGs), in which untranslated messenger ribonucleoprotein particles (mRNPs) are temporarily stored.[22] In response to stress factors, they participate in reprogramming the protein translation in cells, which involves inhibiting the global protein synthesis and increasing the expression of antiapoptotic genes.[22] It turns out, however, that not 3'-tiRNA, but exclusively 5'-tiRNA$^{Ala/Cys}$ are managed to block the translation, due to their cooperation with the silencer YB-1 (Y-box binding protein).[23] The same tiRNAs are also implicated in the condensation of SGs under adverse conditions.[23] Additionally, in various stress-induced cell compartments, an important role in the regulation of ANG activity is played by RNH1 (ribonuclease/angiogenin inhibitor 1).[24] During cell growth, ANG accumulating in the nucleus is active and affects rRNA transcription, whereas the ANG in the cytoplasm, being in the ANG-RNH1 complex, remains inactive.[24] During stress, nuclear ANG is blocked by RNH1, while active ANG, localized in cytoplasmic SGs, generates small tiRNA fragments, reprogramming the protein translation.[24] In this way, ANG acts protectively, allowing cell survival.

The serum concentration of ANG in healthy individuals ranges from 274 to 496 ng/mL.[25] However, in many diseases accompanied by chronic inflammation, its level exceeds the physiological norm.[25] In mice, inflammation causes increased hepatic ANG expression and serum protein content.[25] ANG secretion is therefore regulated as a positive acute phase protein, as confirmed by the stimulation of its synthesis and secretion in cultured liver cells by interleukin (IL)-6.[26] The role of ANG in this regard is manifested in its ability to regenerate damaged tissues. Through neovascularization in injured tissue, ANG accelerates its repair process.[14] It mainly activates fibroblasts and extracellular matrix glycoproteins, vital for proper wound healing.[6] In chronic diabetic wounds, ANG promotes the synthesis of nitric oxide, alleviating the inflammatory processes.[27] This is reflected in the negative correlation between ANG and IL-8 concentrations in the blood.[27] Furthermore, Lee et al.[28] explain the previously unknown mechanism of the anti-inflammatory effect of ANG. It inhibits TANK binding kinase 1, which mediates the activation and translocation of nuclear factor kappa B (NF-κB). In this way, ANG reduces the mRNA expression of the pro-inflammatory cytokines: IL-1β, IL-6 and IL-8, while increasing the mRNA expression of the anti-inflammatory cytokines: IL-4 and IL-10.[28] It can also suppress the expression of tumour necrosis factor receptors 1 and 2 (TNFR1 and TNFR2), thus inhibiting the translocation of NF-κβ, which in turn reduces the synthesis of monocyte chemoattractant protein-1 (MCP-1), IL-6 and IL-8 by monocytes/macrophages.[28]

In turn, Kulka et al.[29] report that human mast cells synthesize, store, and release angiogenin after exposure to *Escherichia coli*, lipopolysaccharide (LPS), peptidoglycan, flagellin, and nerve growth factor. This presumed role of angiogenin in host defense is also indicated by Hooper et al.[30] The colonization of the mouse gastrointestinal tract with *Bacteroides thetaiotaomicron* induces Ang4 (the ortholog of human ANG) expression in the Paneth cell secretory granules at the bottom of intestinal crypts.[30] The LPS stimulation causes the secretion of angiogenin into the intestinal lumen as well.[30] Hence, it is speculated that angiogenin may act as a regulator of the intestinal microflora. Especially since, during colitis in mucin gene-deleted mice, morphological changes were observed only in the distal part of the intestine, where Ang4 expression was low, but not in the proximal part, where it was the highest.[31] Furthermore, ANG has been shown to inhibit the growth of colitogenic bacteria leading to the predominance of beneficial *Lachnospiraceae* strains, which may contribute to the restoration of intestinal homeostasis and attenuates symptoms.[32] Murine Ang4 has also exhibited antibacterial activity against *Enterococcus faecalis* and *Listeria monocytogene*s, human ANG – against *Candida albicans*, *Streptococcus pneumoniae*[30] and *Mycobacterium tuberculosis*, and its chemically modified form – against *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* as well.[33] ANG, in addition to its bacteriostatic and fungistatic properties, has the ability to suppress HIV-1 replication in proliferating T lymphocytes.[34] Increased ANG

secretion was also found in the primary T-cells obtained from asymptomatic HIV-infected individuals, as opposed to uninfected donors or AIDS patients.[35]

In human medicine, ANG has long been the subject of intensive research. In oncogenesis, ANG enhances the rRNA transcription in cancer cells, stimulates the biogenesis of ribosomes and increases the cell proliferation. By conditioning the angiogenesis, it affects the invasiveness and metastasis of cancer cells.[14,12] The expression of ANG is upregulated in serum and/or clinical tissues in many types of cancer including, but not limited to, pancreatic cancer, prostate cancer, colorectal cancer or malignant melanoma.[36,37] There is also a known link between enhanced levels of ANG and the development and aggressiveness of cancer.[38] Recent studies in the model of pancreatic ductal adenocarcinoma have shown that ANG can directly bind to the epidermal growth factor receptor (EGFR) and thereby activate, in a non-enzymatic manner, a signal transduction cascade leading to neoplastic transformation.[39] Importantly, the same research has demonstrated that there is a relationship between the high levels of ANG in plasma and the increased response of pancreatic cancer cells to EGFR inhibitor – the so-called 'erlotinib.'[39] According to the authors, this is the basis for the assumption that serum ANG levels may be considered as a prognostic factor in the treatment of patients with this type of cancer.[39] Similarly, in the case of prostate cancer, in addition to its influence on tumor growth and metastasis, angiogenin may assume the role of an indicator, as well as a 'molecular target' in the development of treatment.[40] ANG may even support the survival of cancer cells, because as a result of various interactions it leads to the inactivation of the p53 suppressor protein through its ubiquitination, and thereby exerting an anti-apoptotic effect.[41]

ANG has also attracted interest in various nonmalignant pathological conditions such as diabetes, peripheral arterial disease, endometriosis, rheumatoid arthritis, and others.[8] Most of these studies have focused on the analysis of protein levels and its involvement in local pathological angiogenesis.[8,12] In particular, its participation in the pathogenesis of neurodegenerative disorders has been considered. The amyotrophic lateral sclerosis (ALS) model studies using cell cultures and transgenic mice have reported that ANG, as a stress-induced protein, protects motoneurons from death via the previously described mechanism resulting in translational reprogramming by activating the phosphatidylinositol 3'-kinase PI3K/Akt pathway.[17,42] In turn, in the in vitro model of Parkinson's disease (PD), ANG also turned out to be a factor effectively extending the lifespan of dopaminergic neurons.[43] The similar neuroprotective effects of ANG have been described on astrocytes via the syndecan receptor.[8,44] Moreover, a number of mutations in the ANG gene occurring in humans are associated with both familial and sporadic forms of ALS, leading to neuronal damage.[17,42,45–49] Afterwards, some genetic variants have also been confirmed in PD and Alzheimer's disease.[42,45–49] In the vast majority of cases, the consequence of these mutations is related to the loss of ribonucleolytic activity of the protein, disruption of its nuclear translocation and impairment of functions necessary during angiogenesis.[42,46–48] This confirms the role of ANG as a key factor controlling the survival of motoneurons.[42,45–48]

Additional examples of studies on the above-mentioned functional activities of ANG, as well as some others, are briefly presented in Table 1.

Table 1. Additional examples of studies regarding the selected functional activities of ANG.

Author	Functional activity of ANG
Kishimoto et al., 2005[50]	In endothelial cells, the presence of ANG is necessary for the induction of angiogenesis by vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and fibroblast growth factor (FGF). Inhibition of ANG expression or blockade of its translocation to the nucleus stops vasculogenesis even at high concentrations of these factors. ANG therefore plays a fundamental role in the activation of the angiogenesis process.
Sheng et al., 2016[51]	ANG, interacting with mRNA, can regulate the expression of several hundred genes (~700), most of which are related with carcinogenesis. In this regard, it demonstrates activity in the regulation of epigenetic processes.
Yurina et al., 2021[52]	In the rat model, injections of ANG into the dermis caused an increase in the intensity of angiogenesis, collagen production, and the number of fibroblasts and blood vessels. In response to ANG, blood cells released a range of cytokines, resulting in pro-homeostatic effects.
Liu et al., 2021[53]	ANG released by osteoclasts promotes endothelial cell proliferation and angiogenesis and thus indirectly influences the regulation of bone tissue cell growth.
Miyake et al., 2015[54]	To elucidate the molecular pathway of angiogenin's influence on tumorigenesis, the authors demonstrated that it activates matrix metallopeptidase-2 (MMP2) via ERK1/2 kinase in human cancer cells.
Burgmann et al., 1996[55]	The patients with advanced peripheral arterial disease were characterized by the significantly higher levels of ANG in blood serum than those with less severe symptoms or control subjects. The authors report that ANG levels may have informative value regarding the degree of vascular damage.
Oikonomou et al., 2011[56]	Notably higher ANG levels were also observed in the blood serum of patients suffering from inflammatory bowel disease in comparison to the control group.
Kolben et al., 1997[57]	It turns out that during pregnancy, as a result of physiological angiogenesis and intensive endometrial neovascularization, the ANG level in the blood of pregnant women increases from 150 (10th week) to 250 ng/ml (40th week). On the other hand, significantly lower levels of this protein were noted in women with placental blood flow disorders.

5. CONCLUSIONS

(1) ANG, is probably the oldest member of the RNase A superfamily, and displays some distinctive structural, enzymatic and functional features.
(2) ANG, although originally discovered as a proangiogenic factor, due to its widespread distribution in body tissues, has revealed a wide spectrum of functional activities in many biological processes, both under physiological and pathological conditions.
(3) Due to its ability to respond by changing in serum protein concentrations, ANG appears to be a promising indicator in neoplastic, neurodegenerative and other diseases. However, further intensive research into its medical use is necessary.

Conflict of interest
None declared.

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