УДК 577.112:616-006
https://doi.org/10.20538/1682-0363-2024-4-169-176

Angiogenin: biological role, mechanisms of action, and participation in oncogenesis

Mikhalev D.E., Korotenko S.N., Lomovskikh A.Yu., Baydik O.D.

Siberian State Medical University
2, Moscow Trakt, Tomsk, 634050, Russian Federation

ABSTRACT

Angiogenin is a small polypeptide consisting of 123 amino acids involved in the processes of angiogenesis and tumorigenesis. This protein plays an important role in various physiological and pathological processes through the regulation of cell proliferation, survival, migration, invasion, and differentiation.

The lecture presents data on angiogenin production and interaction with various proteins, describes mechanisms of its action, and shows its biological role in angiogenesis and oncogenesis. The literature search was carried out in the PubMed, Medline, Elibrary, Scopus, The Cochrane Library, and RSCI search engines.

Keywords: angiogenin, angiogenesis, carcinogenesis, biologically active substances

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

Source of financing. The authors state that they received no funding for the study.

For citation: Mikhalev D.E., Korotenko S.N., Lomovskikh A.Yu., Baydik O.D. Angiogenin: biological role, mechanisms of action, and participation in oncogenesis. *Bulletin of Siberian Medicine.* 2024;23(4):169–176. https://doi.org/10.20538/1682-0363-2024-4-169-176.

Ангиогенин: биологическая роль, механизмы действия и участие в онкогенезе

Михалев Д.Е., Коротенко С.Н., Ломовских А.Ю., Байдик О.Д.

Сибирский государственный медицинский университет (СибГМУ)
Россия, 634050, г. Томск, Московский тракт, 2

РЕЗЮМЕ

Ангиогенин – небольшой полипептид, состоящий из 123 аминокислот, вовлеченный в процессы ангиогенеза и онкогенеза. Данный белок играет важную роль в различных физиологических и патологических процессах посредством регуляции пролиферации, выживания, миграции, инвазии и дифференцировки клеток.

В лекции представлены данные о получении, взаимодействии ангиогенина с различными белками, приведены механизмы действия, показана биологическая роль в ангиогенезе и онкогенезе. Поиск литературы осуществлялся в поисковых системах PubMed, Medline, Elibrary, Scopus, The Cochrane Library, РИНЦ.

✉ *Mikhalev Dmitry E.,* dm199412@gmail.com

Ключевые слова: ангиогенин, ангиогенез, канцерогенез, биологически активные вещества

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Источник финансирования. Авторы заявляют об отсутствии финансирования при проведении исследования.

Для цитирования: Михалев Д.Е., Коротенко С.Н., Ломовских А.Ю., Байдик О.Д. Ангиогенин: биологическая роль, механизмы действия и участие в онкогенезе. *Бюллетень сибирской медицины.* 2024;23(4):169–176. https://doi.org/10.20538/1682-0363-2024-4-169-176.

INTRODUCTION

Bioactive substances are essential for our bodies. Since the beginning of the last century, scientists have been trying to experimentally determine which substances are responsible for tissue proliferation. The discovery of growth factors in the late 1970s and early 1980s prompted the scientific community to view tissue repair processes in a new light [1–4]. A separate direction in the study of growth factors has been their influence on carcinogenesis [5, 6]. Some of these factors were first isolated from malignant tumors [7, 8].

Currently, dozens of bioactive substances are known to be involved in the proliferation and migration of various cell types, including angiogenin (ANG) [9–12].

MAIN PART

General information. ANG is a member of the superfamily of ribonucleases (RNase 5) and is a primary protein consisting of 123 amino acids, with a molecular weight of 14.1 kDa. Ten types of ANG have been identified in various mammals and fish, each exhibiting specific biological activities. Evidence suggests that ANG (RNase5) and ribonuclease 4 (RNase4) represent the most ancient forms of ribonucleases, which appeared in the earliest vertebrates as part of a protective antimicrobial system. ANG shares 33% sequence identity and 65% sequence homology with pancreatic ribonuclease (RNase1). A common feature of all ribonucleases is their enzymatic activity toward ribonucleic acid (RNA) [13].

The protein contains three domains, which serve as distinct functional sites of biological activity [14, 15]: (a) cellular receptor binding site: it consists of amino acid residues in the Lys60, Asn68, and Asn109 loop segments, allowing for binding to motor neurons and endothelial cells [14]; (b) nuclear localization sequence (NLS), comprising residues Ile29–Leu35, which facilitate nuclear translocation of ANG [14]; (c) catalytic site: it includes residues His13, Lys40, and His114, which creates the catalytic center (P1), where the phosphodiester bond cleavage occurs [16]. ANG also has a pyrimidine base binding site (B1) and a purine base binding site (B2). Blockage of the B1 site partially explains why ANG reduces ribonucleolytic activity. These structures are responsible for the unique ribonucleolytic activity and diverse biological functions of this protein [15].

Angiogenin production. Since the late 1980s, scientists have been using various types of fungi as producers of heterologous proteins [17]. Recently, the methylotrophic yeast fungus of the *Pichia pastoris* genus has gained popularity as a producer of recombinant proteins. *P. pastoris* offers several advantages over *E. coli*, such as a lack of protein misfolding, a high level of recombinant protein secretion into the extracellular space (which simplifies the purification process), and the ability to perform post-translational modifications of the produced proteins [18].

Currently, a Russian patent has been granted for the synthesis of a recombinant chimeric human ANG protein using *P. pastoris* yeast culture [19].

The role of angiogenin in physiological processes. In healthy individuals, the concentration of ANG in blood plasma ranges from 274 to 496 ng / ml. Changes in ANG levels depend on numerous factors, including gender, age, and body weight. ANG concentrations can fluctuate under various physiological conditions, such as during different phases of the menstrual cycle and pregnancy. Additionally, ANG levels may change due to pathological processes of different etiology. This fact is of great scientific interest and opens new horizons for the early diagnosis of various diseases [20].

At the cellular level, ANG regulates proliferation, migration, invasion, adhesion, and differentiation of cells in various experimental cell models [21, 22].

It has been established that the ANG receptor is absent on the membrane of fused endothelial cells in blood vessels and does not induce ribosome biogenesis [23, 24]. However, high concentrations of ANG in blood vessels stimulate vascular growth and tissue repair in cases where endothelial cells fail to fuse, thereby promoting wound healing when vascular integrity is compromised [25]. Additionally, hemodynamic forces are linked to the cell cycle activity of endothelial cells, which tend to renew very slowly in adult tissues [26]. Thus, plasma ANG may control vascular homeostasis by maintaining the self-renewal of endothelial cells.

Besides stimulating angiogenesis through the activation of vascular endothelial and smooth muscle cells, ANG acts as a trigger in processes, such as tubular structure formation, cell proliferation, invasion, and migration [27].

According to L.M. Cucci et al. (2021), copper plays a significant role in ANG mechanism of action [28]. Copper ions enhance and promote vascular permeability as well as endothelial cell migration and proliferation by interacting with several factors involved in angiogenesis. Copper strengthens the binding of ANG to endothelial cells and affects the intracellular localization of the protein. L.M. Cucci et al. (2021) also suggest that copper can modulate ANG transcription [28].

Copper increases ANG expression in the HUVEC cell line, indicating that an increase in the extracellular copper level during angiogenesis may regulate ANG levels [29].

Mechanisms of action and biological role of angiogenin in angiogenesis. Several mechanisms of ANG action in angiogenesis are known:

1. It exhibits ribonuclease activity.
2. ANG binds to cell receptors.
3. It induces basement membrane degradation.
4. ANG binds to a 170 kDa protein (ANG-binding protein), subsequently transmitting a signal into the cell cytoplasm.
5. ANG translocates to the nucleus of the target cell, enhancing rRNA transcription [27].

Angiogenin-interacting proteins. The first identified ANG-binding protein is human placental ribonuclease inhibitor (RNH1), a leucine-rich protein with a mass of 50 kDa [29]. RNH1 and ANG have extensive binding interfaces, with key contacts involving the catalytic residue Lys-40 of ANG and the C-terminal segment (434–460) of RNH1 [30]. The angiogenic and enzymatic activities of ANG are inhibited by its binding to RNH1 [30]. The interaction between cellular ANG and RNH1 prevents accidental cleavage of cellular RNA. RNH1 has been found to control the subcellular localization of ANG to regulate cell growth and survival [30]. Several proteins interact with ANG, affecting various cellular functions, such as cell proliferation and survival, including follistatin [31], histone H3 [33], four and a half LIM domains 3 (FHL3) [32], and ANG receptor expressed in human endothelial cells [34], or syndecan-4 in astrocytes [35]. ANG also plays a role in apoptosis regulation, interacting with p53 [36], MDM2 [37], heat shock factor 1 (HSF1) [37], and RNH1 [30]. Comprehensive identification of ANG-interacting proteins may help create interaction maps and further clarify its roles and mechanisms.

Under stress conditions, secreted ANG accumulates in the cytoplasm and nucleoli via a receptor-mediated endocytosis mechanism, activating signaling pathways, such as PI3K/AKT, SAPK/JNK, and ERK1/2 in various cells. The interaction between ANG and cell surface complexes can lead to extracellular matrix (ECM) degradation and activation of matrix metalloproteinases (MMPs), supporting cell invasion and migration. Cytoplasmic ANG, under stress, cleaves tRNA to produce tiRNA, which inhibits translation initiation by recruiting eIF4G/A away from uncovered mRNA via interaction with the YB-1 translation silencer. ANG also promotes ubiquitination of p53 by inhibiting p53 phosphorylation at serine-15, allowing for subsequent binding to Mdm2. Furthermore, nuclear ANG enhances mRNA and rRNA transcription under growth conditions.

Cellular angiogenin regulates nucleic acid metabolism

It has been established that secreted ANG accumulates in nucleoli via endocytosis mechanisms and promotes nucleic acid metabolism by facilitating the transcription of 47S pre-rRNA. This occurs through its binding to ABE (ANG-B-indicating element) and UCE (upstream control element) regions on the promoter of ribosomal DNA (rDNA). Secreted ANG increases the number of actively transcribing rDNA units and participates in the assembly of the initiation complex through epigenetic activation, involving promoter methylation and histone modification [38].

Excess ANG in the nucleus has also been linked to mRNA transcription regulation. ANG inhibits the expression of ERRγ by binding to the first exon region of the estrogen-related receptor gamma (ERRγ) [39]. For

genome-wide screening and identification of mRNA regulated by ANG, a chromatin immunoprecipitation analysis was conducted, identifying a total of 699 genes. This analysis revealed that these genes significantly enrich oncogenesis pathways. Given that ANG binds to histone proteins and remodels histone modifications, it likely acts as a chromatin remodeling activator by regulating mRNA transcription.

ANG also plays a crucial role in tRNA metabolism within the cytoplasm. Interestingly, tRNA was the first molecule used for the enzymatic quantification of ANG activity [39]. Recent studies have shown that ANG degrades single-stranded 3'-CCA ends of tRNA or the anticodon loop, producing tiRNA (stress-induced small RNA derived from tRNA) in response to stress (e.g., oxidative, hypoxic, or nutrient deprivation stress) [40–42]. Modification of specific tRNA anticodon loops (such as Val AAC, Gly GCC, and Asp GTC) protects tRNA from ANG-induced cleavage [42]. Additionally, RNH1 may regulate the stress-induced subcellular localization of ANG to control tiRNA production under stress conditions [42].

Angiogenin stimulates basement membrane degradation

In the tumor microenvironment, extracellular ANG can reach the surface of endothelial cells, where it binds to actin and dissociates as a complex known as AngBP [24, 43]. This complex initiates the synthesis of plasmin from plasminogen [44]. ANG-induced changes in the cytoskeleton include: alterations in the physical properties of F-actin and inhibition of G-actin polymerization; activation of the plasminogen / serine protease system and the matrix metalloproteinase (MMP) system, which are driven by the interaction between ANG and surface-bound actin [43, 44].

ANG serves as a bridging molecule, facilitating interactions with proteins, such as uPAR, A2, and the S100-A10 complex, which are essential for plasmin formation and cell migration at the interface of lipid and non-lipid rafts in cell membranes [45, 46]. A peptide has been identified (ANI-E) that inhibits the interaction between ANG and actin, as well as ANG-induced angiogenesis [43]. By activating the fibrinolytic system in cells, ANG at concentrations ≥ 100 ng / cm² enhances endothelial cell migration and invasion. Additionally, ANG promotes the adhesion of various target cells [44]. Thus, ANG contributes to the degradation of the basement membrane and ECM. Furthermore, cytoplasmic ANG optimizes the assembly of stress fibers and the formation of focal adhesions to facilitate cell migration by interacting with β-actin, α-actinin-4, and non-muscle myosin heavy chain 9 [43].

Angiogenin can maintain vascular homeostasis

As previously mentioned, ANG plays a crucial role in both normal angiogenesis and tumor growth by interacting with endothelial and smooth muscle cells. ANG mediates the migration, invasion, and proliferation of these cells, as well as the formation of tubular structures. In addition to these functions, ANG binds to actin in smooth muscle and endothelial cells, initiating proteolytic cascades that produce proteases, including plasmin, which facilitate the degradation of fibronectin and laminin layers in the basement membrane and ECM. This process supports the migration of endothelial cells into the perivascular tissue. Moreover, ANG activates extracellular signal-regulated kinases 1/2 (ERK1/2) and protein kinase B/Akt, which promote cell proliferation and invasion of the basement membrane, further contributing to angiogenesis. The nuclear translocation of ANG is a critical step in angiogenesis, as it enhances the transcription of ribosomal RNA (rRNA) by binding to the CT-rich ANG-binding element (ABE). This, in turn, activates other angiogenic factors that promote the formation of new blood vessels.

Angiogenin in oncogenesis

Tumorigenesis is a multi-step process characterized by genetic and epigenetic changes in tumor cells, as well as the creation of supportive conditions in the tumor microenvironment. It has been shown that ANG influences almost all stages of oncogenesis, including the stimulation of tumor cell proliferation, protection of tumor cells from adverse survival conditions, enhancement of tumor cell migration and invasion, and induction of angiogenesis.

Solid tumor cells, under unfavorable conditions, can reprogram gene expression to adapt to suboptimal conditions, survive, and continue to grow. ANG, as one of the stress-responsive proteins, significantly increases in cell lines of lymphoma, cervical cancer, and human malignant melanoma under hypoxic conditions [47–49]. It has been established that hypoxia-inducible factor-1 (HIF-1), which controls gene expression, is both necessary and sufficient to activate ANG expression in cells exposed to hypoxia [50].

ANG is secreted by tumor cells, promoting the formation of the microenvironment, tumor proliferation, and growth. This protein can constantly move into the nuclei of tumor cells regardless of

their density and contribute to proliferation [22]. Being one of the major angiogenic components of microvesicles (MV), ANG is released by glioblastoma and stimulates tube formation by endothelial cells [51]. Hepatocellular carcinoma cells also secrete ANG, inducing hepatic stellate cells and remodeling the ECM composition [52]. Consequently, ANG facilitates endothelial cell migration to the tumor by degrading the ECM and the basement membrane. Mast cells, accumulating in the tumor stroma, also promote the release of ANG [20]. Another source of ANG is MVs derived from mesenchymal stem cells under hypoxic conditions, whose primary function is the formation of new blood vessels [20]. It has been shown that ANG induces vascular mimicry in HT1080 fibrosarcoma cells, promoting tumor angiogenesis and metastasis through blood vessels [24].

Measuring ANG levels in blood serum is advisable for assessing risk and predicting the progression of various cancers. ANG serum levels vary depending on the cancer stage, type, and treatment. For example, elevated ANG levels in the serum of patients with solid tumors have been associated with poor prognosis [20]. It has been found that during the evolution of prostate epithelial cells from a benign to an invasive phenotype, ANG levels significantly increase [53]. There are ongoing discussions about the use of ANG as a clinical marker for detecting tumor recurrence and evaluating treatment efficacy.

The epithelial-mesenchymal transition (EMT) is a process in which epithelial cells lose their apical-basal polarity, change their phenotype to a mesenchymal state, and exhibit decreased cell – cell adhesion. This leads to increased adhesion to the ECM, acquiring invasive and mesenchymal-like properties. In tissues of squamous cell lung carcinoma, high ANG expression was positively correlated with mesenchymal marker expression and negatively correlated with epithelial markers. Vimentin and TGF-β1 play an important role in the EMT and are key regulators of mesenchymal cell migration. ANG overexpression leads to upregulation of vimentin, TGF-β1, and N-cadherin and downregulation of E-cadherin and β-catenin, indicating that ANG promotes lung cancer invasion and metastasis by inducing the EMT [54].

ANG may also contribute to tumor cell proliferation, invasion, migration, and EMT by cleaving mature tRNAs, forming tiRNAs, which influence cell proliferation, apoptosis, gene expression, post-transcriptional modification, kinase activity, and translation [55].

ANG binds to receptors associated with vascular endothelial cells, promoting tumor angiogenesis. Specific binding of ANG to the receptor tyrosine kinase (RTK) Tie-2 on the surface of endothelial cells leads to phosphorylation and dissociation of perivascular Sertoli cells. This facilitates the formation of vascular structural migration channels, as well as the activation and migration of endothelial cells, vascular remodeling, and the formation of new vascular branches, which in turn increase blood perfusion flow [56]. ANG induces angiogenesis in breast cancer tissue by activating protein kinase B/Akt through binding to its receptor (FHL3) on endothelial cells or by entering cells via endocytosis and undergoing nuclear translocation. Nuclear translocation of ANG is crucial for angiogenesis initiated by other angiogenic factors (e.g., vascular endothelial growth factor (VEGF)). Indeed, if ANG is blocked, these factors may lose their angiogenic function [57].

ANG is capable of regulating the sensitivity of malignant tumors to radiation and chemotherapy. Radiation can destroy blood vessels that supply the tumor with nutrients and oxygen, playing a vital role in cancer elimination [57]. Studies show that a combination of radiation therapy and anti-angiogenic drugs has a synergistic effect, and ANG inhibitors, combined with radiation therapy, hold promise in reducing recurrence rates after tumor radiotherapy and improving survival [58–60]. However, the specific molecular mechanisms behind this effect require further clarification. Research has also shown that ANG plays a role in resistance to radiation therapy (RT). Using a set of RayBio human cytokine antibodies, 297 protein levels were simultaneously investigated, and the conditioned media from HONE1 and HONE1-IR-resistant nasopharyngeal carcinoma cells were analyzed. ANG expression was significantly higher in HONE1-IR cells treated with 4 Gy radiation, which induced radioresistance in nasopharyngeal cancer cells and reduced both recurrence-free and overall survival in nasopharyngeal cancer patients [61].

ANG is a ligand of the epidermal growth factor receptor (EGFR) and can act as a biomarker for predicting sensitivity to the EGFR tyrosine kinase inhibitor erlotinib in patients with pancreatic cancer. In this context, ANG is associated with decreased sensitivity to erlotinib treatment both *in vitro* and *in vivo*. In one patient cohort, high plasma levels of ANG in pancreatic cancer patients were positively correlated with the response to erlotinib treatment. Q93 ANG is necessary for effective EGFR binding

and activation. Activation of the ANG-EGFR axis makes tumors more sensitive to erlotinib treatment, while ANG knockdown reduces sensitivity to erlotinib treatment and sustains colony formation and cell viability [62].

CONCLUSION

ANG is a multifunctional protein with diverse mechanisms of action. On the one hand, it actively participates in cancer initiation and progression by promoting tumor neovascularization and regulating proliferation, invasion, migration, and therapy sensitivity in various cancer types. On the other hand, it acts as a reparative agent with anti-inflammatory properties. The conditions under which ANG wound-healing properties shift to oncogenic ones remain unclear, offering prospects for further research in fundamental oncology.

REFERENCES

1. Wee P., Wang Z. Epidermal growth factor receptor cell proliferation signaling pathways. *Cancers (Basel).* 2017;9(5):52–65. DOI: 10.3390/cancers9050052.
2. Schenck K., Schreurs O., Hayashi K., Helgeland K. The role of nerve growth factor (NGF) and its precursor forms in oral wound healing. *International Journal of Molecular Sciences.* 2017;18(2):386–398. DOI: 10.3390/ijms18020386.
3. Hume R.D., Deshmukh T., Doan T., Shim W.J., Kanagalingam S., Tallapragada V. et al. PDGF-AB reduces myofibroblast differentiation without increasing proliferation after myocardial infarction. *JACC. Basic to Translational Science.* 2023;(8)6:658–674. DOI: 10.1016/j.jacbts.2022.11.006
4. Yamakawa S., Hayashida K. Advances in surgical applications of growth factors for wound healing. *Burns & Trauma.* 2019;7:10–17. DOI: 10.1186/s41038-019-0148-1.
5. Mihaylova Z., Tsikandelova R., Sanimirov P., Gateva N., Mitev V., Ishkitiev N. Role of PDGF-BB in proliferation, differentiation and maintaining stem cell properties of PDL cells in *vitro. Archives of Oral Biology.* 2018;85:1–9. DOI: 10.1016/j.archoralbio.2017.09.019.
6. Heldin C.H., Lennartsson J., Westermark B. Involvement of platelet-derived growth factor ligands and receptors in tumorigenesis. *Journal of Internal Medicine*. 2018;283(1):16–44. DOI: 10.1111/joim.12690.
7. Lyons S.M., Fay M.M., Akiyama Y., Anderson P.J., Ivanov P. RNA biology of angiogenin: current state and perspectives. *RNA Biology.* 2017;14(2):171–178. DOI: 10.1080/15476286.2016.1272746.
8. Lugano R., Ramachandra M., Dimberg A. Tumor angiogenesis: causes, consequences, challenges and opportunities. *Cellular and Molecular Life Sciences.* 2020;77:1745–1770. DOI: 1007/s00018-019-03351-7.
10. Isali I., Al-Sadawi M.A.A., Qureshi A., Khalifa A.O., Agrawal M.K., Shukla S. Growth factors involve in cellular proliferation, differentiation and migration during prostate cancer metastasis. *International Journal of Cell Biology.* 2019;2(1-2):1–13.
11. Fernández-Guarino M., Hernández-Bule M.L., Bacci S. Cellular and molecular processes in wound healing. *Biomedicines.* 2023;11(9):2526–2532. DOI: 10.3390/biomedicines11092526.
12. Yurina N.V., Ageeva T.A., Goryachkin A.M., Varaksin N. Effects of recombinant angiogenin on collagen fiber formation and angiogenesis in the dermis of Wistar rats. *Clinical, Cosmetic and Investigational Dermatology.* 2021;14:187–196. DOI: 10.2147/CCID.S294825.
13. Sultana M.F., Abo H., Kawashima H. Human and mouse angiogenins: emerging insights and potential opportunities. *Frontiers in Microbiology*. 2022;13:1022945. DOI: 10.3389/fmicb.2022.1022945.
14. Marzo T., Ferraro G., Cucci L.M., Pratesi A., Hansson Ö., Satriano C. et al. Oxaliplatin inhibits angiogenin proliferative and cell migration effects in prostate cancer cells. *Journal of Inorganic Biochemistry*. 2021;226:111657. DOI: 10.1016/j.jinorgbio.2021.111657.
15. Naletova I., Cucci L., D'Angeli F., Anfuso C., Magrì A., Mendola D. et al. A tunable nanoplatform of nanogold functionalised with angiogenin peptides for anti-angiogenic therapy of brain tumours. *Cancers (Basel).* 2019;11(9):1322–1350. DOI: 10.3390/cancers11091322.
16. Hoang T.T., Raines R.T. Molecular basis for the autonomous promotion of cell proliferation by angiogenin. *Nucleic Acids Research*. 2017;45(2):818–831. DOI: 10.1093/nar/gkw1192.
17. Kastberg L.L., Barbera A.R., Jensen M.K., Workman C.T. Burden imposed by heterologous protein production in two major industrial yeast cell factories: identifying sources and mitigation strategies. *Frontiers in Fungal Biology.* 2022;3:827704. DOI: 10.3389/ffunb.2022.827704.
18. Mastropietro G., Aw R., Polizzi K.M. Expression of proteins in Pichia pastoris. *Methods in Enzymology*. 2021;660:53–80. DOI: 10.1016/bs.mie.2021.07.004.
19. Purtov A. A., Mamaev A.L. Recombinant plasmid for expression in *Pichia pastoris* yeast gene of chimeric protein of human angiogenin and *Pichia pastoris* yeast strain as a producer of recombinant chimeric protein of human angiogenin. Russian Federation RU 2658758, 2017.10.02 Angiopharm LLC. (In Russ.).
20. Yu D., Cai Y., Zhou W., Sheng J., Xu Z. The Potential of Angiogenin as a Serum Biomarker for Diseases: Systematic Review and Meta-Analysis. *Disease Markers.* 2018;15(2018):1984718. DOI: 10.1155/2018/1984718.
21. Garnett E.R., Raines R.T. Emerging biological functions of ribonuclease 1 and angiogenin. *Critical Reviews in Biochemistry and Molecular Biology.* 2022;57(3):244–260. DOI: 10.1080/10409238.2021.2004577.
22. Mao M., Chen W., Ye D. Research progress on the structure, function, and use of angiogenin in malignant tumours. *Heliyon.* 2024;10(9):e30654. DOI: 10.1016/j.heliyon.2024.e30654.
23. Stillinovic M., Sarangdhar M.A., Andina N., Tardivel A., Greub F., Bambaci G. et al. Ribonuclease inhibitor and angiogenin system regulates cell type-specific global translation. *Science Advances.* 2024;10(22):eadl0320. DOI: 10.1126/sciadv.adl0320.

24. Jinghao S., Zhengping X. Three decades of research on angiogenin: a review and perspective. *Acta Biochimica et Biophysica Sinica*. 2016;48(5):399–410. DOI: 10.1093/abbs/gmv131.
25. Gupta S., Chittoria R.K., Chavan V., Aggarwal A., Reddy L.C., Mohan P.B. et al. Role of burn blister fluid in wound healing. *Journal of Cutaneous and Aesthetic Surgery.* 2021;14(3):370–373. DOI: 10.4103/JCAS.JCAS_90_19.
26. Rajala R. How big is the endothelium? Comment on "Spatial and temporal dynamics of the endothelium". *Journal of Thrombosis and Haemostasis.* 2021;19(10):2634–2635. DOI: 10.1111/jth.15469.
27. Lyons S.M., Fay M.M., Akiyama Y., Anderson P.J., Ivanov P. RNA biology of angiogenin: Current state and perspectives. *RNA Biology.* 2017;14(2):171-178. DOI: 10.1080/15476286.2016.1272746.
28. Cucci L.M., Satriano C., Marzo T., La Mendola D. Angiogenin and copper crossing in wound healing. *International Journal of Molecular Sciences*. 2021;22(19):10704. DOI: 10.3390/ijms221910704.
29. Cong X., Cremer C., Nachreiner T., Barth S., Carloni P. Engineered human angiogenin mutations in the placental ribonuclease inhibitor complex for anticancer therapy: Insights from enhanced sampling simulations. *Protein Science.* 2016;25(8):1451–1460. DOI: 10.1002/pro.2941.
30. Sarangdhar M.A., Allam R. Angiogenin (ANG)-ribonuclease inhibitor (RNH1) system in protein synthesis and disease. *International Journal of Molecular Sciences.* 2021;22(3):1287–1293. DOI: 10.3390/ijms22031287.
31. Janik S., Bekos C., Hacker P., Raunegger T., Schiefer A.I., Müllauer L. et al. Follistatin impacts tumor angiogenesis and outcome in thymic epithelial tumors. *Scientific Reports.* 2019;9(1):17359. DOI: 10.1038/s41598-019-53671-8.
32. Huang Z., Yu C., Yu L., Shu H., Zhu X. The Roles of FHL3 in Cancer. *Frontiers in Oncology*. 2022;12:887828. DOI: 10.3389/fonc.2022.887828.
33. Shi P., Xu J., Cui H. The Recent Research Progress of NF-κB signaling on the proliferation, migration, invasion, immune escape and drug resistance of glioblastoma. *International Journal of Molecular.* 2023;24(12):10337. DOI: 10.3390/ijms241210337.
34. Wang Y.N., Lee H.H., Chou C.K., Yang W.H. Angiogenin/ribonuclease 5 Is an EGFR ligand and a serum biomarker for erlotinib sensitivity in pancreatic cancer. *Cancer Cell.* 2018;33(4):752–769.e8. DOI: 10.1016/j.ccell.2018.02.012.
35. Hoang T.T., Johnson D.A., Raines R.T., Johnson J.A. Angiogenin activates the astrocytic Nrf2/antioxidant-response element pathway and thereby protects murine neurons from oxidative stress. *The Journal of Biological Chemistry*. 2019;294(41):15095–15103. DOI: 10.1074/jbc.RA119.008491.
36. Yeo K.J., Jee J.G., Hwang E., Kim E.H., Jeon Y.H., Cheong H.K. Interaction between human angiogenin and the p53 TAD2 domain and its implication for inhibitor discovery. *FEBS Letters.* 2017;591(23):3916–3925. DOI: 10.1002/1873-3468.12899.
37. Bultman K., Uebersohn A., Dickson K. Angiogenin interacts with heat shock factor 1. *FASEB Journal*. 2015;29:sp880.30. DOI: 10.1096/fasebj.29.1_supplement.880.30.
38. Loveland A.B., Koh C.S., Ganesan R., Jacobson A., Korostelev A.A. Structural mechanism of angiogenin activation by the ribosome. *Nature*. 2024;630(8017):769–776. DOI: 10.1038/s41586-024-07508-8.
39. Su Z., Kuscu C., Malik A., Shibata E., Dutta A. Angiogenin generates specific stress-induced tRNA halves and is not involved in tRF-3-mediated gene silencing. *The Journal of Biological Chemistry*. 2019;294(45):16930-16941. DOI: 10.1074/jbc.RA119.009272.
40. Rashad S., Niizuma K., Tominaga T. tRNA cleavage: a new insight. *Neural Regeneration Research*. 2020;15(1):47–52. DOI: 10.4103/1673-5374.264447.
41. Fu M., Gu J., Wang M., Zhang J., Chen Y., Jiang P. et al. Emerging roles of tRNA-derived fragments in cancer. *Molecular Cancer.* 2023;22(1):30–36. DOI: 10.1186/s12943-023-01739-5.
42. Guzzi N., Bellodi C. Novel insights into the emerging roles of tRNA-derived fragments in mammalian development. *RNA Biology.* 2020;17(8):1214–1222. DOI: 10.1080/15476286.2020.1732694.
43. Weng C., Dong H., Mao J., Lang X., Chen J. characterization and function of the interaction of angiogenin with alpha-actinin 2. *Frontiers in Molecular Biosciences*. 2022;9:837971. DOI: 10.3389/fmolb.2022.837971.
44. Bharadwaj A.G., Holloway R.W., Miller V.A., Waisman D.M. Plasmin and plasminogen system in the tumor microenvironment: implications for cancer diagnosis, prognosis, and therapy. *Cancers (Basel).* 2021;13(8):1838–1845. DOI: 10.3390/cancers13081838.
45. Kushwaha A., Goswami L., Kim B.S. Nanomaterial-based therapy for wound healing. *Nanomaterials (Basel).* 2022;12(4):618–630. DOI: 10.3390/nano12040618.
46. Veith A.P., Henderson K., Spencer A., Sligar A.D., Baker A.B. Therapeutic strategies for enhancing angiogenesis in wound healing. *Advanced Drug Delivery Reviews.* 2019;146:97–125. DOI: 10.1016/j.addr.2018.09.010.
47. Weng C., Dong H., Bai R., Sheng J., Chen G., Ding K. et al. Angiogenin promotes angiogenesis via the endonucleolytic decay of miR-141 in colorectal cancer. *Molecular Therapy. Nucleic Acids.* 2022;27:1010–1022. DOI: 10.1016/j.omtn.2022.01.017.
48. Yang H., Yuan L., Ibaragi S., Li S., Shapiro R., Vanli N. et al. Angiogenin and plexin-B2 axis promotes glioblastoma progression by enhancing invasion, vascular association, proliferation and survival. *British Journal of Cancer*. 2022;127(3):422–435. DOI: 10.1038/s41416-022-01814-6.
49. Mao M., Chen W., Ye D. Research progress on the structure, function, and use of angiogenin in malignant tumours. *Heliyon.* 2024;10(9):e30654. DOI: 10.1016/j.heliyon.2024.e30654.
50. Manuelli V., Pecorari C., Filomeni G., Zito E. Regulation of redox signaling in HIF-1-dependent tumor angiogenesis. *The FEBS Journal*. 2022;289(18):5413–5425. DOI: 10.1111/febs.16110.
51. Marei H.E., Althani A., Afifi N., Hasan A., Caceci T., Cifola I. et al. Glioma extracellular vesicles for precision medicine: prognostic and theragnostic application. *Discover Oncology.* 2022;13(1):49. DOI: 10.1007/s12672-022-00514-0.
52. Bárcena C., Stefanovic M., Tutusaus A., Martinez-Nieto G.A., Martinez L., García-Ruiz C. et al. Angiogenin secretion from

hepatoma cells activates hepatic stellate cells to amplify a self-sustained cycle promoting liver cancer. *Scientific Reports.* 2015;5:7916. DOI: 10.1038/srep07916.
53. González L.O., Eiro N., Fraile M., Beridze N., Escaf A.R., Escaf S. et al. Prostate cancer tumor stroma: responsibility in tumor biology, diagnosis and treatment. *Cancers (Basel).* 2022;14(18):4412. DOI: 10.3390/cancers14184412.
54. Xu L., Yan Y., Xue X., Li C.G., Xu Z.Y., Chen H.Z. Angiogenin elevates the invasive potential of squamous cell lung carcinoma cells through epithelial-mesenchymal transition. *Oncology Reports.* 2016;36(5):2836–2842. DOI: 10.3892/or.2016.5107.
55. Li S., Shi X., Chen M., Xu N. Angiogenin promotes colorectal cancer metastasis via tiRNA production. *International Journal of Cancer*. 2019;145(5):1395–1407. DOI: 10.1002/ijc.32245.
56. Duran C.L., Borriello L., Karagiannis G.S., Entenberg D., Oktay M.H., Condeelis J.S. Targeting Tie2 in the tumor microenvironment: from angiogenesis to dissemination. *Cancers (Basel).* 2021;13(22):5730. DOI: 10.3390/cancers13225730.
57. Li Y., Qu X., Cao B., Yang T., Bao Q., Yue H. et al. Selectively suppressing tumor angiogenesis for targeted breast cancer therapy by genetically engineered phage. *Advanced Materials (Deerfield Beach, Fla.)*. 2020;32(29):e2001260. DOI: 10.1002/adma.202001260.
58. Rani V., Prabhu A. Combining angiogenesis inhibitors with radiation: advances and challenges in cancer treatment. *Current Pharmaceutical Design*. 2021;27(7):919–931. DOI: 10.2174/1381612826666201002145454.
59. Li D., Weng S., Zhong C., Xu D., Yuan Y. Risk of second primary cancers among long-term survivors of breast cancer. *Frontiers in Oncology*. 2019;9:1426–1435. DOI: 10.3389/fonc.2019.01426.
60. Procaccio L., Damuzzo V., Di Sarra F., Russi A., Todino F., Dadduzio, V. et al. Safety and tolerability of anti-angiogenic protein kinase inhibitors and vascular-disrupting agents in cancer: focus on gastrointestinal malignancies. *Drug Safety.* 2019;42(2):159–179. DOI: 10.1007/s40264-018-0776-6.
61. Guo S., Liang Y., Liu L., Chen Q., Wen Y., Liu S. et al. Increased angiogenin expression correlates with radiation resistance and predicts poor survival for patients with nasopharyngeal carcinoma. *Frontiers in Pharmacology*. 2021;12:627935. DOI: 10.3389/fphar.2021.627935.
62. Wang Y.N., Lee H.H., Chou C.K., Yang W.H., Wei Y., Chen C.T. et al. Angiogenin/ribonuclease 5 is an EGFR ligand and a serum biomarker for erlotinib sensitivity in pancreatic cancer. *Cancer Cell*. 2018;33(4):752–769. DOI: 10.1016/j.ccell.2018.02.012.

Authors' information

Mikhalev Dmitry E. – Teaching Assistant, Dentistry Division, Siberian State Medical University, Tomsk, dm199412@gmail.com, https://orcid.org/0000-0002-0647-3576

Korotenko Sergey N. – Teaching Assistant, Dentistry Division, Siberian State Medical University, Tomsk, dr.korotenko@mail.ru. https://orcid.org/0009-0008-7371-318X

Lomovskikh AnastasiaYu. – Student, General Medicine Department, Siberian State Medical University, Tomsk, anastasia17070316@mail.ru, https://orcid.org/0009-0001-7162-1475

Baydik Olga D. – Dr. Sci. (Med.), Professor, Head of the Dentistry Division, Siberian State Medical University, Tomsk, olgabajdik@yandex.ru, https://orcid.org/0000-0002-4748-4175

(✉) **Mikhalev Dmitry E.,** dm199412@gmail.com

Received 01.07.2024;
approved after peer review 09.17.2024;
accepted 12.09.2024