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ROLE OF RIBONUCLEASES IN THE REGULATION OF IMMUNE RESPONSE

Ribonucleases (RNases) perform many different functions in living systems. They are responsible for the formation and processing of various ribonucleic acids (RNAs), including the messenger RNA and all types of microRNAs, and determine the duration of the existence of different RNAs in the cell and extracellular environment. RNases are ubiquitously expressed in many tissue types. This short review discusses the major types and main functions of RNases, their homeostatic functions, influence of transcription, immunomodulation, and the role of extracellular RNases in the immune defense mechanisms.

Keywords: ribonuclease, topography, immunomodulatory activity, homeostatic function, transcription influence, biological defense, immune defense.

Ribonucleases (RNases) perform a variety of functions in living systems. They are responsible for the formation and processing of various ribonucleic acids (RNAs), including the messenger RNA (mRNA) and all types of microRNAs (miRNAs), and determine the duration of the existence of different RNAs in the cell and extracellular environment [1]. RNases are ubiquitously expressed not only in the metabolic tissues, such as the adipose tissues and skeletal muscles but also in the immune system organs. Living organisms contain a huge number of enzymes that hydrolyze many types of RNAs. The physiological function of most of them remains unknown. Among many functions, some RNases are known to exert an antitumor effect [2]. Some RNases can also demonstrate antitumor activity apart from the participation in enzymatic hydrolysis of RNA molecules. Such activity is realized through immune mechanisms of antitumor protection [3]. Moreover, some RNases have ambiguous effects on tumor growth. For example, ribonuclease 5 (angiogenin) in the cell cytoplasm hydrolyzes ribosomal RNA, blocks protein synthesis, and induces apoptosis. However, when it translocates to the nucleus, this RNase is involved in the processing of ribosomal RNA and stimulates proliferation, angiogenesis, and tumor growth [4]. RNases can affect gene activity by influencing the formation and destruction of numerous non-coding RNAs, including miRNAs. Many effects of RNases are realized via signaling pathways of the immune response [3] and their influence on the polarization of macrophages

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[5]. The functions of RNases in maintaining the redox state of the extracellular microenvironment are important for the survival of tumor cells.

This short review analyzes the major types of RNases, a family of ancient extracellular RNases, and intracellular RNases topography. The main functions of RNases related to their activities, effects on transcription, and biological and immune defense are also discussed.

Types of RNases

RNases are the RNA-processing or degrading enzymes, which cleave the phosphodiester bonds in the RNA molecules. The hypotheses regarding different types of RNase activity and the presence of extracellular RNA communicators have been discussed [6].

Fig. 1 presents the major types of RNases that play an important role in host immune protection. The RNase A superfamily derives its name from bovine enzymes [3]. The RNase A is a family of vertebrate-specific genes demonstrating significant divergence in a short time, similarly to proteins associated with immunity. In humans, this family includes eight functional members (RNases 1—8).

RNase 1 has the highest catalytic activity and tissue abundance of all pancreatic RNases and has been detected in many body fluids [7]. In humans and mice, it circulates in the peripheral blood plasma at a concentration of ~0.5 μg/mL. The main source of plasma RNase is vascular epithelium, and the optimal value of enzyme activity (pH 7.3) is close to blood pH [8], indicating that the activity of this RNase may be manifested in the vascular bed.

Both RNase 2 and RNase 3 are among the main secretory proteins stored within the eosinophil granules, accounting together for about one-third of the total protein content [9]. Note that the components of eosinophilic granules were first isolated to induce neuronal degeneration. These RNases emerged from a gene duplication event about 50 million years ago and underwent a divergence at an extremely rapid evolution rate. Particularly, RNase 2 is an eosinophil-derived neurotoxin (EDN). EDN has a high affinity with cattle RNase A [10]. It exhibits high RNase activity and is expressed in blood cells such as monocytes and dendritic cells. RNase 3 is an eosinophilic cationic protein (ECP) accumulated in the secretory granules. During the drift of RNase 3 from a common RNase 2/3 ancestor, the protein acquired much higher cationicity (pI > 10) [11].

RNase 4 belongs to the pancreatic RNase family. RNase 4 is produced by epithelial cells of the urinary tract. There, the kidney's collecting duct is a source of RNase 4 production, where it is regulated by insulin receptor activation and downstream phosphatidylinositol 3-kinase/AKT (PI3K/AKT) signaling [12].

RNase 5 (angiogenin, Ang) is a representative of the RNase superfamily, members of which possess substrate specificity and divergent functional capacities, where angiogenesis is commonly attributed to angiogenin. The distinct structure of angiogenin contains an endothelial binding motif which in combination with endonuclease activity produces a potent stimulus for blood-vessel formation. Angiogenin is a 14.4 kD soluble protein, first isolated from the culture medium conditioned by colon carcinoma (HT-29) cells [13].

It is a small 123-amino acid protein that in humans is encoded by the *ANG* gene. The corresponding nucleotide sequences of angiogenin show 33% sequence identity and 65% homology with pancreatic RNase 1 (RNase A) and represent the most ancient form of the RNase superfamily. As the name implies, Ang is related to angiogenesis, in particular in tumors. Although there seems to be a contradiction with its proven antitumor activity, the answer lies in its special, compartment-dependent activity.

RNase 6 (family member k6) is a secreted antimicrobial peptide that was discovered as a human ortholog of bovine RNase K2 [14]. The RNase K6 catalytic activity is relatively weak compared to other canonical RNases being almost 40 times lower than that of RNase 2 (EDN) against yeast tRNA. This enzyme is unique in the RNase A family because of the second catalytic site that enhances the specificity of polynucleotide substrate cleavage. RNase 6 is a protein of myeloid origin and is expressed by monocytes, macrophages, and neutrophils. Similarly, RNase 6 in mice is detected in monocytes and macrophages of the genitourinary tract during *E. coli* invasion [15].

RNase 7 was first discovered in human skin and subsequently detected in other epithelial surfaces, including the respiratory and urogenital tracts [16]. The RNase 7 gene is constitutively expressed and

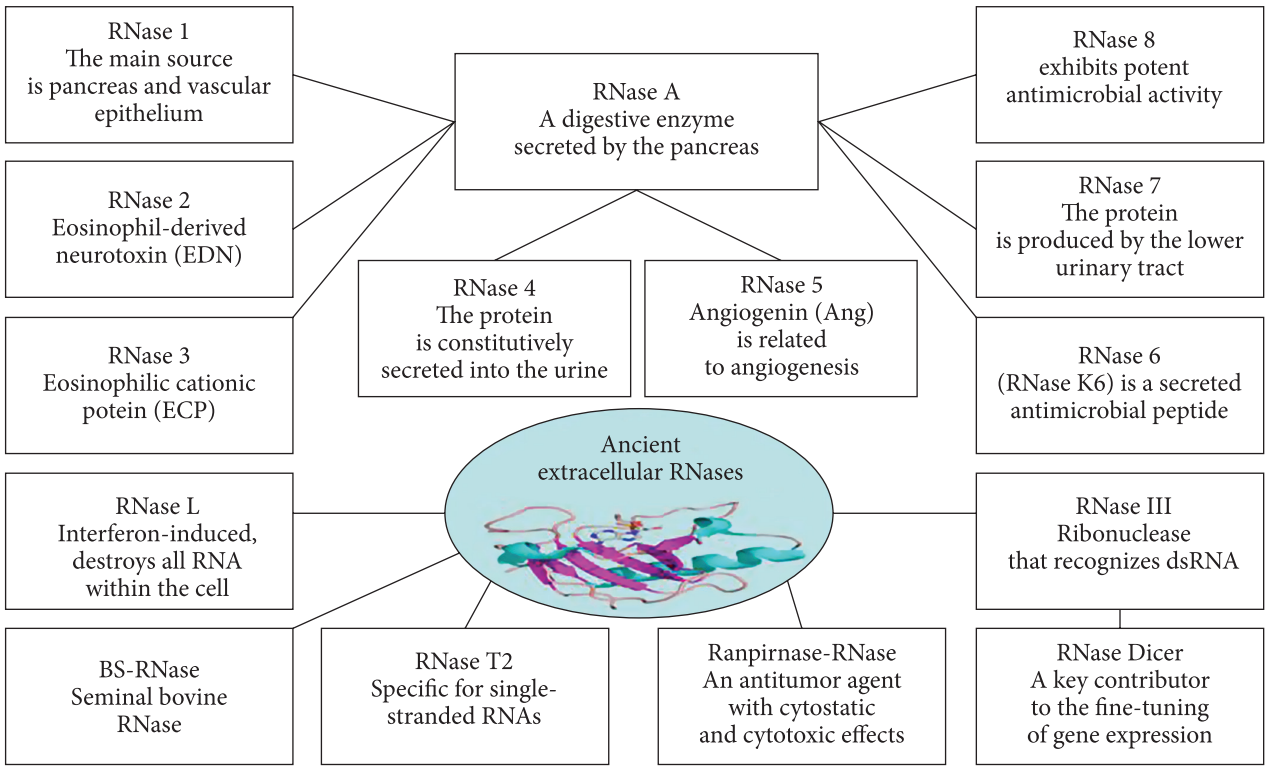

Fig. 1. Major types of RNases that play an important role in host immune defense.

the protein is abundantly secreted in mucosal tissues. Its expression is also induced by growth factors, UV rays, and bacterial products. The molecular mechanisms of this induction are poorly understood. The published data suggest that mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3 AKT (PI3K/AKT) signaling pathways regulate RNase 7 expression [17].

RNase 8 is a secretory ribonuclease; orthologs of its gene were found only in primate genomes. RNase 8 is a divergent paralog of RNase 7, lysine-enriched, highly conserved, and expressed in normal and diseased skin. RNase 8 gene expression was observed in adult human lung, spleen, and testicular tissue [18].

A family of ancient extracellular RNases

RNase T2 is built of 256 amino acid residues and has a molecular weight of 26 kDa. Human RNase T2 contains seven α- and eight β-chains, and two active sites (CAS motifs I and II), which are important for catalytic activity [19]. RNase T2 is widespread in living organisms, from viruses to mammals. It is discovered in different tissues, particularly in embryonic and immune cells. In humans, RNase T2 is the only identified enzyme in the T2 family [20].

RNase L is an 84 kDa protein with 741 amino acids. It is an interferon-induced enzyme that plays a key role in the antiviral activity of interferons [21].

Bovine seminal RNase (BS-RNase) is a member of the RNase superfamily produced by the bovine seminal vesicles, a 27 kDa homodimeric enzyme [22]. It is the only RNase with a quaternary structure, representing a mixture of two dimers. Owing to its natural dimeric form, BS-RNase can elude the blockage of the cytosolic RNase inhibitor (RI) in case of cellular internalization following endocytosis. In the most common form, the active site is formed by an exchange of the N-terminal segment.

RNase III enzymes were first described in 1968 by Zinder and colleagues [23]. All RNase III molecules exhibit specificity for dsRNA. RNase III enzymes are involved in RNA metabolism in many organisms, from phages to animals. Three structural classes of RIII molecules have been described. The first class is represented by *E. coli* RNase III, the second by Drosha, and the third by Dicer. RNase Dicer is a large protein (~200 kDa), first identified in drosophila. The structure of Dicer in mammals, despite the difficulties with protein crystallization, was established by biochemical and crystallographic studies.

Ranpirnase (Onconase (ONC)) is a cytotoxic amphibian RNase, a basic protein consisting of 104 amino acid residues, first isolated from the oocytes of the leopard frog *Rana pipiens* [24]. 30% of the amino acid sequence coincides with the RNase A sequence. The three catalytic residues of RNase A are homologous to ranpirnase. The enzyme has the ability to avoid the effects of RI and is resistant to proteolysis [25].

Intracellular RNase topography

A set of RNases is secreted or concentrated within cellular structures associated with the secretory pathway, vacuole, lysosomes, mitochondria, or other organelles [19]. Thus, these enzymes are usually located in spaces that are not associated with the presence of RNA. The localization of these enzymes shows that they are linked to the regulation of endogenous and exogenous RNAs in various subcellular structures [26]. After crossing the membrane, most RNases cleave RNA in the cytoplasm, although some enzymes, such as BS-RNase, are localized at least partially in the nucleus. Intracellular RNase T2 is mainly concentrated in lysosomes, mitochondria, vacuoles, and other organelles. RNase 2 is localized in the secondary granule matrix of eosinophils.

Functions of RNases

RNases are a large number of enzymes that catalyze the hydrolysis of many different RNA substrates. Initially, it was believed that the main function of RNases is the cleavage and removal of RNA molecules that have already performed their function. However, later it turned out that RNases perform a huge number of biological functions (Fig. 2), some of which remain undiscovered. RNases modify the function of genes, affecting the maturation of various types of coding and non-coding RNAs, and exert antitumor, antibacterial, and antiviral activities. An important role of RNases in the body's defense reactions, in particular, immune reactions, has been established, on some of which we will focus our attention.

Homeostasis support

The experimental and clinical data suggest that RNases play a role in host immunity and contribute to the maintenance of tissue homeostasis and sterility of body fluids. These enzymes are involved in different metabolic transformations of exogenous and endogenous RNAs. Secreted under the influence of cellular damage conditions, they trigger signaling processes and therefore can be attributed to alarmins. They can alter cellular RNA metabolism, specifically target noncoding RNAs, or induce signal transduction in a catalytically independent manner [27].

RNases are involved in the development of higher organisms through their enzymatic activity. Some RNases perform important physiological functions both at the cellular and whole-body levels [6, 28]. The use of a model of mouse embryo fibroblasts deficient in RNase L has revealed that RNase L controls adipocyte differentiation by regulating the expression of CHOP-10 (a negative regulator of adipogenesis) [29].

The important role of RNases in carcinogenesis and tumor growth has been demonstrated. Human RNase 1 (hRNase 1) plays a critical role in the removal of extracellular RNA, innate immune processes, homeostasis, and host protection [30]. However, its role in carcinogenesis remains unclear. It has been shown that hRNase 1, regardless of ribonucleolytic activity, enriches the population of stem cells and enhances the tumor-initiating ability of breast cancer cells. hRNase 1 plays a role in the digestive system by digesting food RNA and regulates homeostasis, inflammation, and innate immunity [6, 31].

The innate immune response serves not only as a first-line defense in protection from infection. It is also directly involved in the regeneration process, which is associated with maintaining homeostasis, modulating wound healing, and ensuring functional tissue integration [32]. In this context, a specific set of pattern recognition receptors (PRR) [33], such as Toll-like receptors, are known to play a key role not only in protecting the host (through regulation of the innate and adaptive immune systems) [34] but also in the regulation of different phases of wound healing and regeneration.

Role in transcription

An important aspect of the action of RNases is their potential function as transcription-like factors and ligands for various cellular receptors that can trigger or limit their internalization [35]. Secreted extracellular Ang enters the cell through a 170 kD

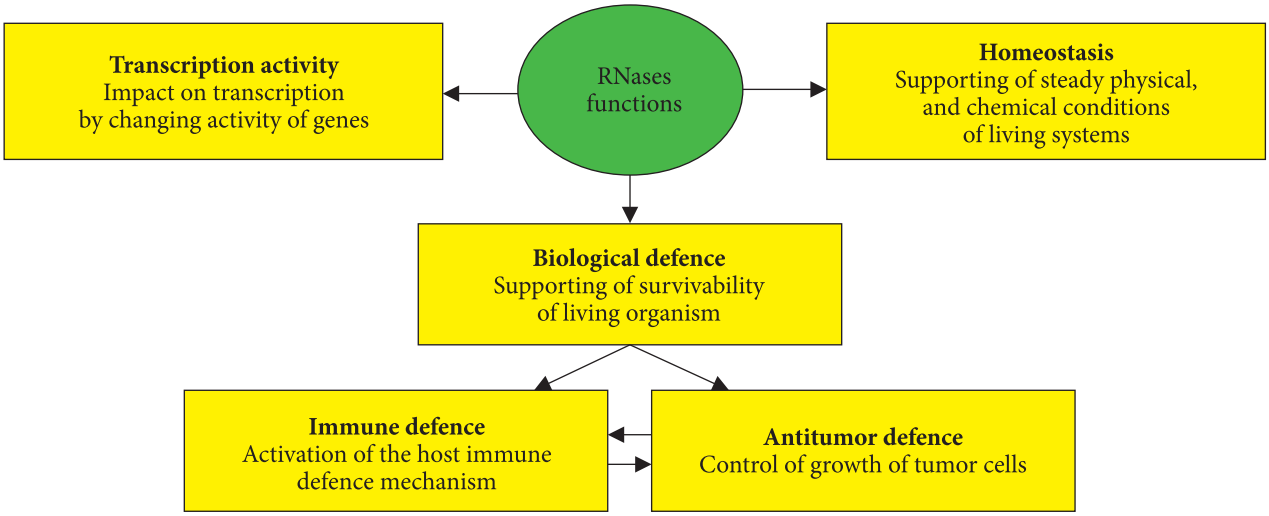

Fig. 2. Main functions of RNases

surface cell receptor, which facilitates its nuclear translocation. In the nucleus, Ang acts as a transcription factor in rRNA biosynthesis and processing.

The intracellular isoforms of RNase T2 can transcriptionally inhibit the expression of certain genes dependent on RNA cleavage [36]. AU-rich elements (ARE) and GU-rich elements (GRE) located in the 3'-untranslated region of mRNA can regulate mRNA stability at the posttranscriptional level [37]. Genome-encoded ARE and GRE products such as c-Myc, epidermal growth factor, prostaglandin-endoperoxide synthase 2, c-Jun proto-oncogene, and c-Fos proto-oncogene are closely associated with tumor growth, cell growth, resistance to apoptosis, angiogenesis, invasion, and metastasis [38]. Although RNase T2 has the function of specifically recognizing and cleaving AU or GU phosphodiester bonds in single-stranded RNAs, it can be assumed that intracellular RNases T2 can selectively recognize and cleave AU or GU bonds in ARE or GRE-mRNA [39].

The first evidence that blocking protein synthesis by RNA degradation is not the only cytotoxic mechanism of action of the RNase A superfamily was obtained for ONC [40]. The data on increasing or decreasing activity of genes encoding cell cycle proteins and transcription factors were also discussed. ONC has been shown to target rRNAs [41], tRNAs [42], mRNAs [43], and microRNAs as well as their precursors [44]. RNase 7 can selectively inhibit TH2 cytokine production by suppression of GATA3 transcription factor activation [45].

Dicer is an RNA-binding protein (RBP) that plays an important role in fine-tuning gene expression. Small noncoding RNA produced by Dicer targets mRNA and forms a complex that affects transcription at the post-transcriptional level [46]. RNase Dicer forms a complex with TAR-binding proteins to cleave pre-mRNA hairpins and generate mature miRNAs or small noncoding RNAs of approximately 22 nucleotides in length. Functional strands of mature miRNAs are loaded into the RNA-induced silencing complex (RISC) together with Argonaute proteins, and the RISC can induce post-transcriptional silencing through mRNA complementation. A decreased gene expression occurs through the translational repression with or without mRNA cleavage, depending on whether the miRNA is fully or partially complementary to the target mRNA. A deficiency or abnormal expression of the Dicer protein is associated with serious developmental abnormalities, cardiovascular diseases, and cancer [47].

Biological defense

RNase T2, or omega-1 secreted by *Schistosoma mansoni* eggs, can induce polarization of $CD4^+$ T cells to Th2 through dendritic cells [48]. Interestingly, omega-1 can alter the structure of the cytoskeleton and the function of dendritic cells after its absorption by these cells. The inhibition of RNase activity prevents the polarization of Th2 cells [48].

RNase L is an interferon-induced nuclease that, upon activation, destroys all RNA within the cell. RNase L is ubiquitously expressed not only in the

immune system organs but also in the metabolic tissues, such as the adipose tissues and skeletal muscles [29]. Using mouse embryo fibroblasts deficient in RNase L, it was reported that RNase L controls adipocyte differentiation via regulating the expression of CHOP-10, a negative regulator of adipogenesis.

The RNase T2 family has been shown to selectively cleave tRNA or rRNA under oxidative stress [49]. The expression of RNase T2 increases in response to tissue damage or oxidative stress [50, 51]. After tissue damage, RNase T2 is secreted and involved in host resistance against viral RNA or alarm signaling, tissue remodeling, and reparation [2]. The specific fragments (tRFs), derived from tRNA molecules, were found in the protein complex ARGONAUTE (AGO) in humans and plants [49]. RNase T2 participates in many physiological processes, such as proliferation, ribosome biogenesis, angiogenesis, apoptosis, and the regulation of immune response [52]. The secretion of RNase T2 is altered in many physiological and pathological states, for example, autoimmune diseases and cancer [53].

Immune defense

The components of the host's immunity

RNase T2 prefers GU or AU bases in single-stranded RNA, forming two nucleotide fragments with adenosine or guanosine terminal 2'3'-cyclic phosphate and uridine residue [19]. These cleavage products fill both TLR8 binding pockets, activating the innate immune cells to express PRR and pathogen-associated molecular structures (PAMP) derived from pathogens or damaged cells [54].

RNase 3 shares neurotoxic and antiviral activities with RNase 2 [55], but it has unique bactericidal properties [56]. RNase 3, along with its high cationicity, has an aggregation-prone region that promotes protein self-aggregation and mediates the agglutination of bacterial cells. RNase 3 activation and chemotaxis of fibroblasts may be involved in tissue repair. Eosinophil degranulation is activated by IL-5, leukotriene B4 (LTB4), platelet-activating factor (PAF) [57], or the P13K/MAPK pathway [58].

RNase 4 is constitutively secreted into the urine, and the neutralization of its antibacterial activity with RNase 4-specific antibodies facilitates the propagation of uropathogenic *E. coli*. Possibly, monocytes and macrophages are additional sources of RNase 4 in the urinary tract [12, 59].

RNase 6 contributes to the mechanism of host protection [60]. The RNase 6 in mice was detected in monocytes and macrophages of the genitourinary tract during *E. coli* invasion [15]. RNase 6 in humans and mice has bactericidal activity against gram-positive and gram-negative microorganisms. The mechanism of RNase 6 antibacterial action resembles RNase 3 in that it causes agglutination and depolarization of membranes in gram-negative bacteria.

RNase 7 activity of the skin is increased in chronic inflammatory skin diseases such as atopic dermatitis and psoriasis [61]. Both of these diseases are characterized by infiltration of activated T cells into the epidermis, where they release Th2 cytokines.

RNase 8 exhibited a broad spectrum of potent antibacterial activity against various bacteria [62]. The high activity of RNase 8 indicates that this antimicrobial protein can contribute to innate immunity and protect the body from infection. RNase 8 has prominent antibacterial activity and possibly plays a role in amniotic sterility.

Dicer is an essential enzyme for the maintenance of physiology [46]. It has an important role in the processes of regulation of gene expression, DNA damage response, cell growth and differentiation. Dicer serves as a multifaceted guardian entity to protect hosts by repressing viral replication and mitigating symptom induction [63].

Immune modulation

RNase 7 functions as an immunomodulatory molecule, enhancing inflammation and chemotaxis in acne and skin wound healing [64]. Finally, more and more evidence suggests that RNase 7 acts as an alarmin, turning its own DNA released from killed host cells into a danger signal that rapidly activates interferon genes and antimicrobial agents. RNase 7 acts as an immunomodulator, facilitates microbial cleansing, and stimulates autoimmunity in chronic inflammatory processes of the skin by facilitating the recognition of its own DNA by plasma dendritic cells [65].

The transfection of the exogenous circular RNA (circRNA), a product of the corresponding RNases, into mammalian cells can effectively induce innate resistance to a viral infection [66]. The endogenous

circRNA tends to form incomplete RNA duplexes and serves as an inhibitor of dnRNA-activated protein kinases (PKR) associated with innate immunity [67]. During tumorigenesis, chromosomal translocations can produce new aberrant circRNAs, so-called f-circRNAs. They can be transmitted to immunocytes and then induce an antitumor immune response [67]. Some exosomal circRNAs may function as tumor antigens, regulating antitumor immunity. Exosomes can be easily detected in serum and tissue fluids and used as potential tumor biomarkers [68]. Along with circRNA-enriched exosomes, exosomal circRNAs play a potential role in modulating intercellular contacts and the cellular microenvironment [69]. Exosomal circRNAs have been shown to play an important role in the homeostasis and functioning of T-regulatory (Treg) cells [70]. New data suggest that exogenous circRNA may also act as potent adjuvants by inducing T and B cell activity, antibody production, and antitumor immunity [66].

To sum up, different types of RNases are represented by protein molecules with different structures and functions. RNases are the key players in the human body's immunity, they participate in the control of cancer growth and contribute to the maintenance of tissue homeostasis. Immune response systems use similar strategies to fight both cancer and infection. In addition, RNases together with other antimicrobial peptides participate in bacterial clearance. A better understanding of the role of RNases is desirable for the development of new treatment methods. Therefore, further studies, in particular, regarding the mechanisms of antitumor immunological protection, may be the basis for the development of new approaches in the diagnosis and treatment of cancer.

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REFERENCES

1. Siraj YA. Promises of eukaryotic ribonucleases for cancer treatment: a systematic review. *Transl Med Commun*. 2022;7(1):5. https://doi.org/10.1186/s41231-022-00113-9
2. Baranzini N, Monti L, Vanotti M, et al. AIF-1 and RNASET2 play complementary roles in the innate immune response of medicinal leech. *J Innate Immun*. 2019;11(2):150-167. https://doi.org/10.1159/000493804
3. Boix E, Acquati F, Leonidas D, et al. Role of ribonucleases in immune response regulation during infection and cancer. *Front Immunol*. 2020;11:236. https://doi.org/10.3389/fimmu.2020.00236
4. Lyons SM, Fay MM, Akiyama Y, et al. RNA biology of angiogenin: Current state and perspectives. *RNA Biol*. 2017;14(2):171-178. https://doi.org/10.1080/15476286.2016.1272746
5. Murray PJ, Allen JE, Biswas SK, et al. Macrophage activation and polarization: nomenclature and experimental guidelines. *Immunity*. 2014;41(1):14-20. https://doi.org/10.1016/j.immuni.2014.06.008
6. Lu L, Li J, Moussaoui M, et al. Immune modulation by human secreted RNases at the extracellular space. *Front Immunol*. 2018;9:1012. https://doi.org/10.3389/fimmu.2018.01012
7. Su AI, Wiltshire T, Batalov S, et al. A gene atlas of the mouse and human protein-encoding transcriptomes. *Proc Natl Acad Sci U S A*. 2004;101(16):6062-6067. https://doi.org/10.1093/oxfordjournals.pcp.a029599
8. Eller CH, Lomax JE, Raines RT. Bovine brain ribonuclease is the functional homolog of human ribonuclease 1. *J Biol Chem*. 2014;289(38):25996-26006. https://doi.org/10.1074/jbc.M114.566166
9. Rosenberg HF. Eosinophil-derived neurotoxin (EDN/RNase 2) and the mouse eosinophil-associated RNases (mEars): expanding roles in promoting host defense. *Int J Mol Sci*. 2015;16(7):15442-15455. https://doi.org/10.3390/ijms160715442
10. Tota M, Łacwik J, Laska J, et al. The role of eosinophil-derived neurotoxin and vascular endothelial growth factor in the pathogenesis of eosinophilic asthma. *Cells*. 2023;12(9):1326. https://doi.org/10.3390/cells12091326
11. Torrent M, Sánchez D, Buzón V, et al. Comparison of the membrane interaction mechanism of two antimicrobial RNases: RNase 3/ECP and RNase 7. *Biochim Biophys Acta (BBA)-Biomembranes*. 2009;1788(5):1116-1125. https://doi.org/10.1016/j.bbamem.2009.01.013
12. Murtha MJ, Eichler T, Bender K, et al. Insulin receptor signaling regulates renal collecting duct and intercalated cell antibacterial defenses. *J Clin Invest*. 2018;128(12):5634-5646. https://doi.org/10.1172/JCI98595
13. Tello-Montoliu A, Patel JV, Lip GYH. Angiogenin: a review of the pathophysiology and potential clinical applications. *J Thromb Haemost*. 2006;4(9):1864-1874. https://doi.org/10.1111/j.1538-7836.2006.01995.x

14. Prats-Ejarque G, Blanco JA, Salazar VA, et al. Characterization of an RNase with two catalytic centers. Human RNase6 catalytic and phosphate-binding site arrangement favors the endonuclease cleavage of polymeric substrates. *Biochim Biophys Acta Gen Subj*. 2019;1863(1):105-117. https://doi.org/10.1016/j.bbagen.2018.09.021
15. Becknell B, Eichler TE, Beceiro S, et al. Ribonucleases 6 and 7 have antimicrobial function in the human and murine urinary tract. *Kidney Int*. 2015;87(1):151-161. https://doi.org/10.1038/ki.2014.268
16. Amatngalim GD, van Wijck Y, de Mooij-Eijk Y, et al. Basal cells contribute to innate immunity of the airway epithelium through production of the antimicrobial protein RNase 7. *J Immunol*. 2015;194(7):3340-3350. https://doi.org/10.4049/jimmunol.1402169
17. Eichler TE, Becknell B, Easterling RS, et al. Insulin and the phosphatidylinositol 3-kinase signaling pathway regulate Ribonuclease 7 expression in the human urinary tract. *Kidney Int*. 2016;90(3):568-579. https://doi.org/10.1016/j.kint.2016.04.025
18. Chan CC, Moser JM, Dyer KD, et al. Genetic diversity of human RNase 8. *BMC Genomics*. 2012;13(1):1-10. https://doi.org/10.1186/1471-2164-13-40
19. Wu L, Xu Y, Zhao H, et al. RNase T2 in inflammation and cancer: Immunological and biological views. *Front Immunol*. 2020;11:1554. https://doi.org/10.3389/fimmu.2020.01554
20. Thorn A, Steinfeld R, Ziegenbein M, et al. Structure and activity of the only human RNase T2. *Nucleic Acids Res*. 2012;40(17):8733-8742. https://doi.org/10.1093/nar/gks614
21. Liang SL, Quirk D, Zhou A. RNase L: its biological roles and regulation. *IUBMB Life*. 2006;58(9):508-514. https://doi.org/10.1080/15216540600838232
22. D'Alessio G, Di Donato A, Parente A, et al. Seminal RNase: a unique member of the ribonuclease superfamily. *Trends Biochem Sci*. 1991;16:104-106
23. Robertson HD, Webster RE, Zinder ND. Purification and properties of ribonuclease III from Escherichia coli. *J Biol Chem*. 1968;243(1):82-91. https://doi.org/10.1016/S0021-9258(18)99327-0
24. Ardelt W, Shogen K, Darzynkiewicz Z. Onconase and amphinase, the antitumor ribonucleases from Rana pipiens oocytes. *Curr Pharm Biotechnol*. 2008;9(3):215-225. https://doi.org/10.2174/138920108784567245
25. Benito A, Ribó M, Vilanova M. On the track of antitumour ribonucleases. *Mol Biosyst*. 2005;1(4):294-302. https://doi.org/10.1039/b502847g
26. Cheng Y, Liu P, Zheng Q, et al. Mitochondrial trafficking and processing of telomerase RNA TERC. *Cell Rep*. 2018;24(10):2589-2595. https://doi.org/10.1016/j.celrep.2018.08.003
27. Lee HH, Wang YN, Hung MC. Functional roles of the human ribonuclease A superfamily in RNA metabolism and membrane receptor biology. *Mol Aspects Med*. 2019;70:106-116. https://doi.org/10.1016/j.mam.2019.03.003
28. Vickers NJ. Animal communication: when I'm calling you, will you answer too? *Curr Biol*. 2017;27(14):R713-R715. https://doi.org/10.1016/j.cub.2017.05.064
29. Fabre O, Salehzada T, Lambert K, et al. RNase L controls terminal adipocyte differentiation, lipids storage and insulin sensitivity via CHOP10 mRNA regulation. *Cell Death Differ*. 2012;19(9):1470-1481. https://doi.org/10.1038/cdd.2012.23
30. Lee HH, Wang YN, Yang WH, et al. Human ribonuclease 1 serves as a secretory ligand of ephrin A4 receptor and induces breast tumor initiation. *Nat Commun*. 2021;12(1):1-18. https://doi.org/10.1038/s41467-021-23075-2
31. Zernecke A, Preissner KT. Extracellular ribonucleic acids (RNA) enter the stage in cardiovascular disease. *Circ Res*. 2016;118(3):469-479. https://doi.org/10.1161/CIRCRESAHA.115.307961
32. Muraille E. Redefining the immune system as a social interface for cooperative processes. *PloS Pathog*. 2013;9(3):e1003203. https://doi.org/10.1371/journal.ppat.1003203
33. Mahla RS, Reddy CM, Prasad D, et al. Sweeten PAMPs: role of sugar complexed PAMPs in innate immunity and vaccine biology. *Front Immunol*. 2013;4:248. https://doi.org/10.3389/fimmu.2013.00248
34. Girardello R, Baranzini N, Molteni M, et al. The medicinal leech as a valuable model for better understanding the role of a TLR4-like receptor in the inflammatory process. *Cell Tissue Res*. 2019;377(2):245-257. https://doi.org/10.1007/s00441-019-03010-0
35. Zylbersztejn F, Byelinska I, Jeanpierre S, et al. Human myeloid differentiation by BMP4 signaling through the VDR pathway in acute myeloid leukemia. *Cell Death Discov*. 2024;10:325. https://doi.org/10.1038/s41420-024-02090-4
36. Liu P, Huang J, Zheng Q, et al. Mammalian mitochondrial RNAs are degraded in the mitochondrial intermembrane space by RNASET2. *Protein Cell*. 2017;8(10):735-749. https://doi.org/10.1007/s13238-017-0448-9
37. Acquati F, Mortara L, De Vito A, et al. Innate immune response regulation by the human RNASET2 tumor suppressor gene. *Front Immunol*. 2019;10:2587. https://doi.org/10.3389/fimmu.2019.02587
38. Baranzini N, Pulze L, Acquati F, et al. Hirudo verbana as an alternative model to dissect the relationship between innate immunity and regeneration. *Invertebr Surviv J*. 2020;17(1):90-98. https://doi.org/10.25431/1824-307X/isj.v0i0.90-98
39. Greulich W, Wagner M, Gaidt MM, et al. TLR8 is a sensor of RNase T2 degradation products. *Cell*. 2019;179(6):1264-1275. https://doi.org/10.1016/j.cell.2019.11.001

40. Iordanov MS, Ryabinina OP, Wong J, et al. Molecular determinants of apoptosis induced by the cytotoxic ribonuclease onconase: evidence for cytotoxic mechanisms different from inhibition of protein synthesis. *Cancer Res*. 2000;60(7):1983-1994.
41. Tsai SY, Ardelt B, Hsieh TC, et al. Treatment of Jurkat acute T-lymphocytic leukemia cells by onconase (Ranpirnase) is accompanied by an altered nucleocytoplasmic distribution and reduced expression of transcription factor NF-κB. *Int J Oncol*. 2004;25(6):1745-1752. https://doi.org/10.3892/ijo.25.6.1745
42. Saxena SK, Sirdeshmukh R, Ardelt W, et al. Entry into cells and selective degradation of tRNAs by a cytotoxic member of the RNase A family. *J Biol Chem*. 2002;277(17):15142-15146. https://doi.org/10.1074/jbc.M108115200
43. Altomare DA, Rybak SM, Pei J, et al. Onconase responsive genes in human mesothelioma cells: implications for an RNA damaging therapeutic agent. *BMC Cancer*. 2010;10(1):1-12. https://doi.org/10.1186/1471-2407-10-34
44. Qiao M, Zu LD, He XH, et al. Onconase downregulates microRNA expression through targeting microRNA precursors. *Cell Res*. 2012;22(7):1199-1202. https://doi.org/10.1038/cr.2012.67
45. Kopfnagel V, Wagenknecht S, Brand L, et al. RNase 7 downregulates TH 2 cytokine production by activated human T cells. *Allergy*. 2017;72(11):1694-1703. https://doi.org/10.1111/all.13173
46. Theotoki EI, Pantazopoulou VI, Georgiou S, et al. Dicing the disease with Dicer: the implications of Dicer ribonuclease in human pathologies. *Int J Mol Sci*. 2020;21(19):7223. https://doi.org/10.3390/ijms21197223
47. Song MS, Rossi JJ. Molecular mechanisms of Dicer: endonuclease and enzymatic activity. *Biochem J*. 2017;474(10):1603-1618. https://doi.org/10.1042/BCJ20160759
48. Steinfelder S, Andersen JF, Cannons JL, et al. The major component in schistosome eggs responsible for conditioning dendritic cells for Th2 polarization is a T2 ribonuclease (omega-1). *J Exp Med*. 2009;206(8):1681-1690. https://doi.org/10.1084/jem.20082462
49. Megel C, Hummel G, Lalande S, et al. Plant RNases T2, but not Dicer-like proteins, are major players of tRNA-derived fragments biogenesis. *Nucleic Acids Res*. 2019;47(2):941-952. https://doi.org/10.1093/nar/gky1156
50. Diaz-Baena M, Galvez-Valdivieso G, Delgado-Garcia E, et al. Nuclease and ribonuclease activities in response to salt stress: identification of PvRNS3, a T2/S-like ribonuclease induced in common bean radicles by salt stress. *Plant Physiol Biochem*. 2020;147:235-241. https://doi.org/10.1016/j.plaphy.2019.12.016
51. Bielins'ka I V, Lynchak OV, Rybal'chenko TV, Hurniak OM. Hematological effects of the protein kinase inhibitor maleimide derivative in dimethylhydrazine E-induced colorectal carcinogenesis of rats. *Fiziol Zh*. 2014;60:40-49. https://doi.org/10.15407/fz60.04.040 (in Ukrainian).
52. Khabar KSA. Hallmarks of cancer and AU-rich elements. *Wiley Interdiscip Rev RNA*. 2017;8(1):e1368. https://doi.org/10.1002/wrna.1368
53. Gonsky R, Fleshner P, Deem RL, et al. Association of ribonuclease T2 gene polymorphisms with decreased expression and clinical characteristics of severity in Crohn's disease. *Gastroenterology*. 2017;153(1):219-232. https://doi.org/10.1053/j.gastro.201 7.04.002
54. Zhu G, Xu Y, Cen X, et al. Targeting pattern-recognition receptors to discover new small molecule immune modulators. *Eur J Med Chem*. 2018;144:82-92. https://doi.org/10.1016/j.ejmech.2017.12.026
55. Domachowske JB, Dyer KD, Adams AG, et al. Eosinophil cationic protein/RNase 3 is another RNase A-family ribonuclease with direct antiviral activity. *Nucleic Acids Res*. 1998;26(14):3358-3363. https://doi.org/10.1093/nar/26.14.3358
56. Boix E, Salazar VA, Torrent M, et al. Structural determinants of the eosinophil cationic protein antimicrobial activity. *Biol Chem*. 2012;393(8):801-815. https://doi.org/10.1515/hsz-2012-0160
57. Bystrom J, Amin K, Bishop-Bailey D. Analysing the eosinophil cationic protein-a clue to the function of the eosinophil granulocyte. *Respir Res*. 2011;12(1):1-20. https://doi.org/10.1186/1465-9921-12-10
58. Shamri R, Young KM, Weller PF. PI 3K, ERK, p38 MAPK and integrins regulate CCR 3-mediated secretion of mouse and human eosinophil-associated RNases. *Allergy*. 2013;68(7):880-889. https://doi.org/10.1111/all.12163
59. Becknell B, Ching C, Spencer JD. The responses of the ribonuclease A superfamily to urinary tract infection. *Front Immunol*. 2019;10:2786. https://doi.org/10.3389/fimmu.2019.02786
60. Pulido D, Arranz-Trullén J, Prats-Ejarque G, et al. Insights into the antimicrobial mechanism of action of human RNase6: structural determinants for bacterial cell agglutination and membrane permeation. *Int J Mol Sci*. 2016;17(4):552. https://doi.org/10.3390/ijms17040552
61. Harder J, Dressel S, Wittersheim M, et al. Enhanced expression and secretion of antimicrobial peptides in atopic dermatitis and after superficial skin injury. *J Invest Dermatol*. 2010;130(5):1355-1364. https://doi.org/10.1038/jid.2009.432
62. Koczera P, Martin L, Marx G, et al. The ribonuclease a superfamily in humans: canonical RNases as the buttress of innate immunity. *Int J Mol Sci*. 2016;17(8):1278. https://doi.org/10.3390/ijms17081278
63. Andika IB, Kondo H, Suzuki N. Dicer functions transcriptionally and posttranscriptionally in a multilayer antiviral defense. *Proc Natl Acad Sci USA*. 2019;116(6):2274-2281. https://doi.org/10.1073/pnas.181240711
64. Rademacher F, Simanski M, Harder J. RNase 7 in cutaneous defense. *Int J Mol Sci*. 2016;17(4):560. https://doi.org/10.3390/ijms17040560

65. Kopfnagel V, Wagenknecht S, Harder J, et al. RNase 7 strongly promotes TLR9-mediated DNA sensing by human plasmacytoid dendritic cells. *J Invest Dermatol*. 2018;138(4):872-881. https://doi.org/10.1016/j.jid.2017.09.052
66. Chen LL, Yang L. Regulation of circRNA biogenesis. RNA Biol. 2015;12(4):381-388.
67. Chen YG, Kim M V, Chen X, et al. Sensing self and foreign circular RNAs by intron identity. *Mol Cell*. 2017;67(2):228-238. https://doi.org/10.1016/j.molcel.2017.05.022
68. Hou J, Jiang W, Zhu L, et al. Circular RNAs and exosomes in cancer: a mysterious connection. *Clin Transl Oncol*. 2018;20(9):1109-1116. https://doi.org/10.1007/s12094-018-1839-y
69. Xu Z, Li P, Fan L, et al. The potential role of circRNA in tumor immunity regulation and immunotherapy. *Front Immunol*. 2018;9:9. https://doi.org/10.3389/fimmu.2018.00009
70. Li P, Liu C, Yu Z, et al. New insights into regulatory T cells: exosome-and non-coding RNA-mediated regulation of homeostasis and resident Treg cells. *Front Immunol*. 2016;7:574. https://doi.org/10.3389/fimmu.2016.00574

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РОЛЬ РИБОНУКЛЕАЗ У РЕГУЛЯЦІЇ ІМУННОЇ ВІДПОВІДІ

Рибонуклеази (РНКази) виконують різноманітні функції в живих системах. Вони відповідають за формування та процесинг різних РНК, включаючи мРНК та мікроРНК, та визначають тривалість існування різних РНК в клітині та позаклітинному середовищі. РНКази експресуються повсюдно в тканинах різних типів. В цьому стислому огляді розглянуто основні типи РНКаз та їхні функції, вплив РНКаз на транскрипцію та імуномодулювання, а також роль позаклітинних РНКаз в механізмах імунного захисту.

Ключові слова: РНКази, гомеостатична функція, вплив на транскрипцію, імунний захист.