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RNASES AND THEIR ROLE IN CANCER

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ABSTRACT

RNases plays a pivotal role in biological system as an enzyme and different RNases are known for their various functions like angiogenesis, immunological response, antiviral, antitumour activity and apoptosis. In which anti tumour activity of RNase is necessary to improve genome stability in normal cells up to major extent along with other factors. RNases like RNase L shows antiviral and antitumour activities against virus infected cells and cancer cells through 2'-5' oligo adenylate pathway, and induces RNaseL dependent apoptosis. Where as RNase A modulates various proliferative pathways like MAP kinase, JNK, TGF-β and activates apoptosis in cancer cells and promotes immunological response against viruses through processing of Ags. IRE1 RNase acts as tumour suppressor and as well as oncogene in normal and cancer cells. RNase III up regulates miRNA in cancer cells there by acting via posttranscriptional level and proven to be effective against colorectal adeno carcinoma. Recently drugs like metosartan is found to induce deleterious effects in normal subjects compared to hypertensive subjects and most of the work in these days is at the Chemotherapy level in order to patients but targeting of proteins like enzymes together with chemotherapy may be useful and hope to be expected by next century.

KEYWORDS: IRE1, RNase L, RNase MRP, 2', 5'- Oligo A, IFN.

INTRODUCTION

RNase A is a multi functional enzyme which plays a key role in gene regulation, and its major role in humans is to digest nucleic acid RNA present in the food and is secreted from pancreas in to stomach along with pancreatic juice. As the enzyme is involved in degradation of SS RNA and DNA-RNA hybrid and ds RNA its role as antitumor agent is well accepted. Mainly cancer in cells occurs through genetic mutations, viral infection, defects in pathways regulating gene expression, and gain/loss of function with respect to certain genes and proteins, like P53 and ARK.

Antitumor activity was found to be not only limited to RNase A but many of the RNases like RNase III prevents cancer by reducing genetic mutations in cells acting through miRNA nucleases Dicer complex, where as RNase L shows antitumor activity against prostate cancer. Enzyme's role is not only limited to nuclear genome, but also extended to extra chromosomal DNA of mitochondria through mitochondrial RNase, RNase MRP. RNase A mainly protects against RNA viruses that enter through food and tumour causing viruses containing RNA as genetic material that aid their entry through mucus membranes of digestive tract of humans similar to H. pylori. H.pylori entry is mainly through AGS cells and it is a gram negative pathogen that inhabits stomach and causes ulcers. Its genetic material is mainly exchanged through bacteriophage which contains DNA or RNA as genetic material.

RNase III seems to protect against viruses containing RNA as genetic material through miRNA and dicer and Drosha complex. miRNA mainly binds the RNA after uncoating of virus in the cell and RNase III cleaves the RNA-miRNA complex with the help of dicer and drosha complex thereby preventing viral replication and prolongation of disease. Some of the RNases induce apoptosis in cancer cells by targeting stromal environment of them at post transcriptional level, and in physiological conditions cancer cells requires survival proteins like VEGF that serves as proangiogenic factor. So by deficit of VEGF cancer cells does not form new blood vessels in the target tissue There by unable to cause tumor.

RNases like RNase H2 is now very well known to prevent loss of chromatin integrity and RNase A is known to promote apoptosis in neoplastic cells and it is also one of the RNase identified and surely present in testis. Testes also consists of Potent unknown RNase With Potent RNase activity which is inhibited by antihypertensive drug metosartan by both competitively and non competitively. The drug induces apoptosis in normal cells by release of cyt C as the drug act on

disulphide bonds of the protein and whereas RNase A inhibits the release of cyt C induced by metosartan.

RNases like RNase P enhances the mitochondrial expression of protein cytochrome C oxidase (Vilius Stribinskis, Guo-Jian Gao, Steven R. Ellis & Nancy C. Martin (2001) so cyt C is released by this enzyme, Where as oxidative stress in testis mitochondria induce expression of cyt P460 which is mitochondrial specific.

RNases like RNase L also plays important role in eliminating viruses like hepatitis and corona virus (Zhao et al., (2012) where as some RNases together with IRE1α phenocopies SCD (Stearoyl –CoA desaturase) and prevent myc induced development of cancers (Hong Xie, Chih-Chi Andrew Hu & M. Celeste Simon (2018). So, this review mainly focus on RNases that induce cancer, that prevents cancer and pathways that involve RNase role in prevention of cancer.

RNase digestion cannot prevent the role of cir-Ccnb1 in mutant cancer cells:

CCNB1 is one of the gene expressed in normal cells and promotes cell survival, proliferation where as it inhibits apoptosis, (Fang et al., (2018) as these cells contain wild type p53. Where as in cancer cells containing mutant p53 protein the cir-Ccnb1 is down regulated and inhibits apoptosis through interaction with Bclaf1 followed by H2AX(Fang et al., (2018). Both normal and cancer cells are resistant to RNase treatment with respect to cirCcnb1 RNA but not the Ccnb1 mRNA as circularisation reduces the accessibility of the RNA to the enzyme as proved by the results of Fang etal.,(2018).

CYTOR was the other long noncoding RNA involved in tumour progression and epithelial mesenchymal transition through binding to NCL and Sam68, the RNA binding proteins, proved by diminished interaction with CYTOR after treatment with RNase A (Wang et al., (2018).

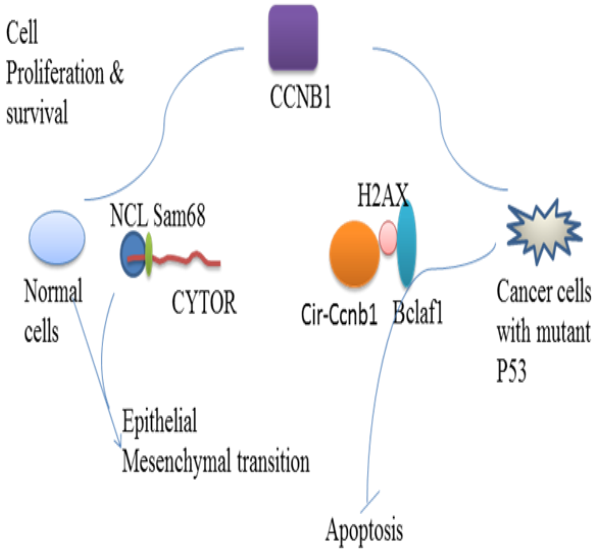

Figure 1: Role of CCNB1 And CYTOR in normal and cancer cells. In normal cells CCNB1 is involved in cell proliferation and survival. In cancer cells with mutant P53 cir-Ccnb1 interaction through H2AX followed by Bclaf1 induces apoptosis where as long non coding RNA CYTOR interacts with NCL and sam68 and causes epithelial mesenchymal transition in normal cells.

Role of RNase L as a tumour suppressor

First observation of RNase L as a tumour suppressor was made and confirmed by Bettoun et al., in 2005. Dihydrotestosterone is the most potent form of testosterone and binds to Androgen receptor harmone responsive element (HRE), in the nucleus and mediates proliferation of cells. RNase L interacts with androgen receptor in a ligand dependent manner and causes up regulation of interferon pathway. IFN release by effector cells leads to binding of IFN to AR and the antagonistic activity of AR- IFN complex which again depends on RNase L- 2’ oligo adenylate synthase pathway. IFN activates 2’-5’ oligo adenylate synthetases synthesising 2’-5’ A which in turn activates RNase L. So, as RNase L acts through or guide its own pathway and is unavailable for AR to Bind where as IFN binds and antagonises the activity of androgen receptor. RNase L causes up regulates IFN so the final effector of RNase L – 2’ oligo adenylate synthetase pathway may activate the IFNɤ Producing effector cells of immune system.

In breast cancer cells androgen receptor regulation through transcriptional inactivation lead to development of breast tumour and the effect was reversible with treatment of DHT which is mainly through AR-DHT-RNaseL- 2’ oligo adenylate synthetase- IFN pathway. In the recent review of AR, receptor phoshorylations at ser 213 and ser 650 was increased in breast cancer cells compared to begnin tumours which indicate AR phosphorylation sequesters the receptor as a part of regulation of AR signaling which is responsible for development of breast cancer.

Further AR over expressing breast cancer cells are tam resistant in which post translational modification of receptor regulation proven to be useful. In breast cancer cells ARK and mTOR pathways are up regulated resulting in up regulation of AR activity as ARK is a survival pathway which involved in proliferation and mTOR in protein synthesis.

RNase L is also studied as an oncogene as mutations in this gene was highly to be expected in prostate cancer caused by XMRV but it is still controversial. In previous reports, XMRV found to be associated with prostate cancer but from recent reports of Farhad Babaei etal., (2015) Xenotropic Murine Leukaemia Virus related Virus (XMRV) was not associated with prostate cancer (Babaei et al., (2015).

RNase L was also found to be effective against EMCV virus through activation of IFN induced synthetases (14) . RNase L activation by 2'- oligoadenylate lead to activation of MAP kinase, JNK phosphorylation which phosphorylates c- jun leading to apoptosis which is RNase L dependent. The target of RNase L is rRNA so protein synthesis is inhibited but basal levels of JNK and c-jun are sufficient to induce RNase L mediated apoptosis (Li et al.,(2004).

RNase L-/- mice is found to be resistant to graft rejection and also alpha virus vaccination may be due to impairment in processing of antigens in APC negotiating immune response in cell system (Krishnamurthy Malathi, Jayashree M. Paranjape, Ram Ganapathi, & Robert H. Silverman (2004). Viruses use host machinery for synthesis of viral proteins. so RNase dependent cleavage of rRNA may prevent the assembly of coat proteins in virus there by producing defective phages which are immunogenic.

From work of Krishnamurthy Malathi, Jayashree M. Paranjape, Ram Ganapathi, & Robert H. Silverman (2004) it was found that TRAIL induced apoptosis require RNase L and JNK activation. TRAIL is a death receptor TNF ligand so, RNaseL activates both extrinsic and intrinsic pathway of apoptosis (Geqiang Li, Ying Xiang, Kanaga Sabapathy, & Robert H. Silverman (2004).

RNase III Nucleases Drosha and Dicer role in Colorectal Cancer

RNase III nuclease Drosha is involved in processing of primary miRNA in to precursor miRNA and where as Dicer is involved in processing of precursor miRNA in to mature miRNA in the cytoplasm (Olivier Preynat-Seauve, Sylvia Coudurier, Alain Favier, Patrice-Noël Marche and ChristianVilliers (2003). These two RNase III nucleases are upregulated in colorectal cancerous tissues compared to non neoplastic tissues. The reason for this may be the expression of tumour suppressor gene mRNAs are down regulated in cancerous cells compared to normal tissues but how the cancerous tissue mRNAs are protected is an unsolved question but one negative mutation in cancerous tissues is solved by other gain in functions like mutations and Epigenetic regulations like DNA methylation, Post translational regulation, change in expression levels of long non coding RNA etc.

RNase MRP Role in regulating the Cyclin B levels during cell cycle

RNase MRP plays an important role in maintainance of Cyclin B in cell cycle through degradation of CLB2 mRNA during the mitosis in mitochondria (Kim et al., (2017). Normally cyclins are periodically cycled between synthesis and degradation to control the activity of CDKs. Inorder to progress and exit through mitosis of cell cycle cyclin B levels should be reduced which requires RNase MRP. RNase MRP mutants suffer from mitosis exist delay due to inability to exit from mitosis caused by late anaphase delay. So, in cancer tissues RNase MRP mutation can be used to induce apoptosis in cancer cells as these cannot exit mitosis and results in large size cells which results in apoptosis of those cells but effective targeting of enzyme to cancer cells is equally important.

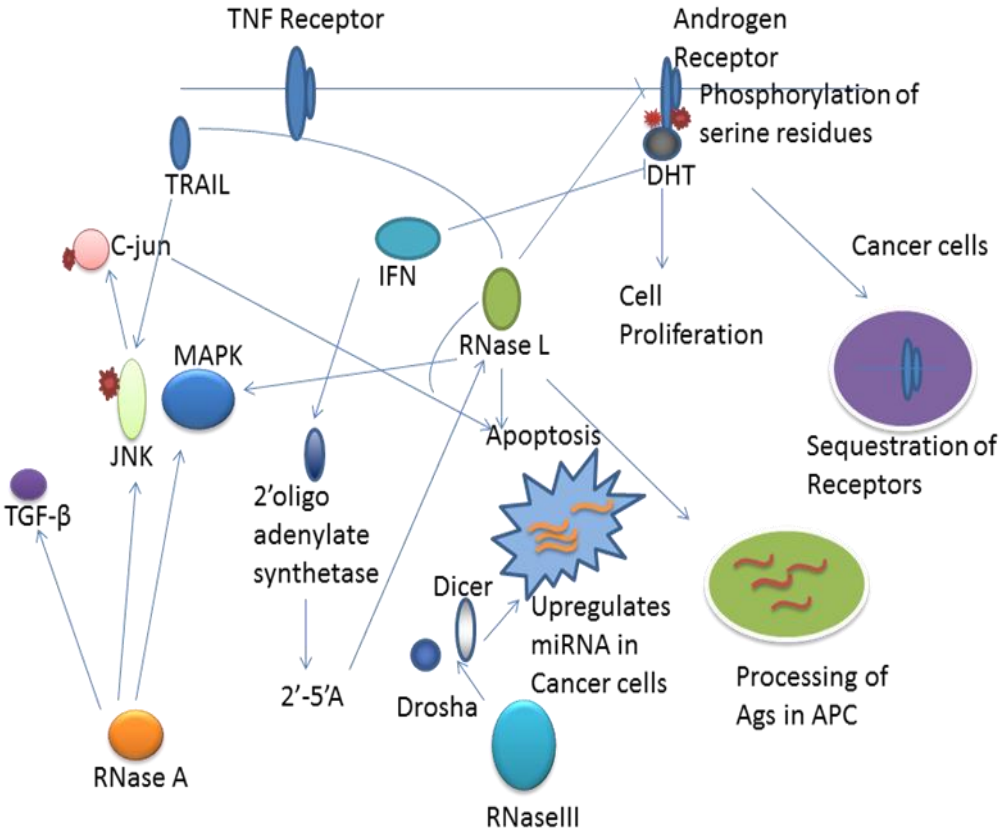

Figure 2: Role of RNases in normal and cancer cells: IFN binds to Androgen receptor so RNase L is unable to bind to receptor resulting in binding of IFN to AR and inhibits binding of DHT. In cancer cells AR transcriptional inactivation is necessary for tumour progression. Phosphorylation of ser residues causes sequestration of AR in breast cancer cells and prevents its activity. IFN is also involved in activation of 2'oligo adenylate synthetases which synthesise 2'-5' A that binds to RNase L which activates upstream regulators of MAPK and JNK finally through phosphorylation causing RNase L dependent apoptosis. Another nuclease RNase III upregulates miRNA through upregulation of drosha and dicer in cancer cells where as RNase A modulates MAPK, JNK, TGF-β pathways in cancer cells. TRAIL is another downstream regulator of RNase L. DHT- Dihydro testosterone, IFN- Interferon,APC- Antigen Presenting cell,2'-5'A- 2'-5' oligo adenylates, TRAIL- TNF related apoptosis inducing ligand, TNF- Tumour necrosis factor, MAPK- MAP kinase, JNK-Janus Kinase, TGF-β – Transforming growth factor β

Role of RNase P core subunits Rpp21 and Rpp29 in normal cells and cancer cells

In normal cells the DNA damage normally recruits several proteins of homology dependent repair and non homology end joining improve genome integrity after repair. Homology dependent repair is an error free repair and involves recruitment of Rpp21 and Rpp29 in PARP dependent manner (Tina Gill, Ti Cai, Jason Aulds, Sara Wierzbicki, and Mark E. Schmitt (2004). In case of both normal and cancer cells irradiation causes recruitment of both RNase P core subunits, and these components are over expressed in cancer cells especially to maintain their genome integrity. So, after radiation exposure they need RNase P core components for their survival. So, preventing the recruitment of these core components in cancer cells implies negative impact on tumour invasion and malignancy. Where as in normal cells the recruitment is maintained and rescued from death. Another approach of Charles olea etal., towards use of L-RNA aptamers to inhibit RNase, can support the use of L- RNA aptamers against RNase P core components to target cancer cells. Similarly RNase P catalytic subunit M1 RNA can be used to target breast cancer cell lines with chromosomal abnormalities like BCR-ABL fusion (Cobaleda and Gracia (2000).

RNase A as onconase

RNase of A.niger acts as an anti invasive and anti cytostatic agent in breast cancer cells through inhibiting formation of actin-angiogenin complex (Enas R. Abu-Zhayia, Hanan Khoury-Haddad, Noga Guttmann-Raviv, Raphael Serruya, Nayef Jarrous & Nabieh Ayoub (2017). Similarly RNase A exerts apoptosis of cancer cells and inhibits apoptosis in normal cells From the results of Fiorini et al., (2014) BS- RNase but not RNase A induces adenocarcinoma(13) andoligomerisation of BS-RNase is necessary for cytotoxic property of the enzyme. Absence of oligomerisation of BS-RNase in cancer cells is an another problem to be rectified. Inside environment of cancer cells is more redoxive compared to normal

cells (Ravi kumar et al., (2012). So, as BS-RNase is native dimer where as RNase A is a monomer and bind by RI in normal cells. Cancer cells maintain high reducing environment to resist the ROS produced due to required increased energy demands by the cancer cell and also to resist the oxidative stress caused by antineoplastic drugs as a mechanism of survival.

RNase A is a monomer and bound RI, but it is scavenged by the protein namely Angiogenin in cancer cells (Asha Acharya, Ila Das, Des Chandhok & Tapas Saha (2010). From the results of Dickson et al., (2005) Angiogenin also has proven to possess RNase activity and also required for angiogenesis. So, RNase A can form oligomers by domain swapping and can induce apoptosis. Cytotoxicity of RNase A is arrested by RI as proved by the results of Rybak et al., (1991) where as BS-RNase is a dimer so not accessible to RI. Levels of RI and RNase L does not change in cancer cells and normal cells (Krishnamurthy Malathi, Jayashree M. Paranjape, Ram Ganapathi, & Robert H. Silverman(2004). RNase L is also proven to protect organisms against hepatitis caused by carona virus (Susanna M. Rybak S, Shailendra K. Saxenat, Eric J. Ackermant, & Richard J. Youle S (1991) and RNase A is involved in antitumorigenic properties through miRNA expression. It downregulates TGF-β, MAPK, PI3-AKT, and also inhibits cell proliferation and invasion, and causes apoptosis.(Kimberly A. Dickson Marcia C. Haigis & Ronald T. Raines (2005).

IRE1 RNase as double edged sword

IREα1 RNase is the one of the downstream regulator of c-myc and N- myc through SCD1 protein (Xie et al., (2018). MYC deregulation in breast cancer cells occurs through mRNA and protein stabilisation, gene amplification and transcriptional regulation. In c-myc cells misfolded or unfolded proteins are more inducing ER stress response which is supported by high levels of bip protein (Hong Xie et al., (2018). Cycloheximide treatment may be expected to cause cellular death in c-myc cells but other downstream targets of c-myc made it difficult. But restoration in viability in myc transformed cancers with hydroxy tamoxifen treatment along with CHD implies reduction in ER stress response in treated cells and maintainance of ER receptor mRNA. Recent work on IRE1 RNase has showed tumorigenic properties with upregulated genes required to cause epithelial mesenchymal transition and by degrading mRNAs and miRNAs targeted to ER (Saxena et al., (2002). IRE1 dependent splicing of XBP1s requires N-glycosylation of protein which is prevented by tunicamycin treatment (Mironova et al.,(2017), Lhomond et al.,(2018) Goparaju et al., (2011), Ardelt et al., (2009), Saxena et al., 2002).

Cisplatin resistant cancer cells can be targeted by metformin through inhibition of IGFR-1 But increased levels of IGFR1 mRNA may indicate that c-myc and N-myc overexpresses in resistant cells along with JNK (Zhao H, Ardelt B, Ardelt W, Shogen K & Darzynkiewicz Z).

Role of function of RNases in other than cancer

RNase 9 is one of the testis specific RNase present in ejaculated spermatozoa and participitates in host defense mechanism. Chromatofocussing of testis fraction resulted in two RNases one with pI 9.2,and along with RNase A with pI 9.6. HSV-1 replicates in host by suppressing the RNase activity of IRE1 α but how the kinase activity of same protein promotes replication of virus (Su et al., (2017) is not understood. May be unfolded protein response which depends on RNase activity suppressed by the HSV-1 pathogen is responsible for it.

Some of the specific RNases like RNase E can act as target for bacterial diseases like diarrheoa as the enzyme is specific to the pathogen (Kime et al., (2015). Where as RNase 1 of Human is similar to RNase A of bovine pancreas and involved in clearing the cellular debris by degrading RNA in it. It also activates signalling pathways and involved in response to cell injury and inflammation causing tissue remodelling and repair (Lu Lu, Jiarui Li, Mohammed Moussaoui and Ester Boix (2018).

Research contribution of scientists from past few years and what we know up to now prove that RNases have anti tumor property but RNases role in chemotactic response which results in recruition of macrophages to the target tissue was not known and may be it is one of the reason for antitumorigenic property (Acquati et al., (2013).

In Trypanosoma brucei virus surface glycoprotein is mainly necessary for host invasion by transcription and recombination. RNase H is well known for removal of R loops in DNA – RNA hybrids in Trypanosoma and the non functional enzyme results in R loop formation in Expression sites of virus, damaging genome and preventing route of infection (Briggs E, Crouch K, Lemgruber L, Lapsley C, McCulloch R (2018).

In cancer progress and invasion, stromal environment plays an important role. Secretions from one cell targeted to another through exosomes is majorly responsible for tumor invasion. From the recent reports, unshielded RNA RN7SL1 secreted as exosomes causes immune reactions in host cell and the exosomes secreted from cancer cells causes decrease in innate response and also responsible for metastasis progession through Pattern Recognition Receptor (PRR) Retinoic acid inducible gene. From these studies we may conclude that by sheilding the RNA RN7SL1 we can reduce the metastatic progression of cancer (Paul Kurywchak, Jena Tavormina and Raghu Kalluri l (2018).

DISCUSSION

RNases plays an important role in maintaining genome integrity. So, these are the enzymes or at least its downstream regulators are the agents that are frequently mutated in cancer cells. RNases like RNase P is mainly involved in the editing of 5' sequence of tRNA and also a ribozyme. RNase P core components are mainly involved in Homology dependent repair so targeting this enzyme leads to genome instability in cancer cells and finally causing death of the cells. RNase catalytic subunit M1RNA has also show anti tumour effect on cells exhibiting BCR-ABL fusion.

RNases like RNase L can act as tumour suppressor by mediating its action through IFN dependent pathway and active against various tumour causing viruses. Viruses like carona virus inhibits IFN dependent pathway to cause hepatitis in organisms (Rybak etal., (1991). Apoptosis of cancer cells by RNase L is mediated through JNK pathway and TNF death receptor pathway as these are downstream regulators of RNase L. RNase A is well known for its effects like inhibition of cell proliferation, angiogenesis and degradation of mRNA and miRNAs there by preventing ER stress by RIDD pathway. In cancer cells most of pathways like MAP Kinase, Wnt pathway, PI3K/AKT, TGF-β, JAK/STAT are either upregulated or down regulated as they are necessary for their survival (Rybak etal., (1991). RNase A as a tumour suppressor modulates these pathways and triggers cell death.

RNase III not only involved in processing of miRNAs but also involved in rRNA processing in spirochete Borrelia burdgoferi (Mitkevich et al., (2010) and recognise and cleave ds RNA. The enzyme participates in immune surveillance in both eukaryotes and prokaryotes (Liu et al.,(2017) and functions as principle regulator of gene expression by indulging in maturation of rRNAs and other structural RNAs (Nicholson (2014)).

Myc is a protooncogene in B- cell chronic lymphocytic leukaemia involved in translocations like t(8;12)(q24;q22) with BTG1 amplification and as downstream regulators of some effectors (Court etal., (2013). In addition to RNase III c-myc is involved in micro RNA regulation by upregulating mi RNA processing enzyme Drosha by directly binding to it. As RNase III is also involved in upregulation of Drosha and Dicer similar to c-myc, So, RNase III may be the downstream regulator of c-myc in c-myc overexpressing cancers.

In addition to this IRE1 RNase acts as a double edged sword through RIDD pathway in ER (Donald M. Miller Shelia D. Thomas Ashraful Islam David Muench & Kara Sedoris (2012). To some of the cancers expressing c-myc IRE1 acts as tumour suppressor where as in cancers where myc is downregulated IRE1 acts as tumour provoking gene through RIDD pathway (Bettoun et al., (2005). Thus totally RNases play vital role in regulating the genome stability.

REFERENCES

1. Allen W. Nicholson Ribonuclease III mechanisms of double-stranded RNA cleavage WIREs RNA, 2014; 5: 31–48. doi: 10.1002/wrna.1195.
2. Ardelt W, Ardelt B, Darzynkiewicz Z. Ribonucleases as potential modalities in anticancer therapy. Eur J Pharmacol, 2009; 625: 181–189.
3. Asha Acharya, Ila Das, Des Chandhok and Tapas Saha Redox regulation in cancer A double-edged sword with therapeutic potential Oxidative Medicine and Cellular Longevity, 2010; 3(1): 23-34.
4. C. Cobaleda and I. Sa´nchez-Garcı´a In vivo inhibition by a site-specific catalytic RNAsubunit of RNase P designed against the BCR-ABL oncogenic products: a novel approach for cancer treatment; BLOOD, 2000; 95(3): 731-37.
5. Claudia Fiorini , Giovanni Gotte , Federica Donnarumma , Delia Picone , Massimo Donadelli (2014) Bovine seminal ribonuclease triggers Beclin1-mediated autophagic cell death in pancreatic cancer cells. Biochimica et Biophysica Acta, 1843; 976–984.
6. Donald L. Court, Jianhua Gan, Yu-He Liang, Gary X. Shaw, Joseph E. Tropea, Nina Costantino, David S. Waugh, and Xinhua Ji RNase III Genetics and function structure and mechanism Annual Review of Genetics, 2013; 47: 405-431.
7. Donald M. Miller Shelia D. Thomas Ashraful Islam David Muench and Kara Sedoris. c-Myc and Cancer Metabolism Clin Cancer Res., 2012; 18(20): 5546–5553.
8. David J. Bettoun, Angela Scafonas, Su Jane Rutledge, Paul Hodor, Oliver Chen, Carlo Gambone, Robert Vogel, Sheila McElwee-Witmer, Chang Bai, Leonard Freedman, and Azriel Schmidt. Interaction between the Androgen Receptor and RNase L Mediates a Cross-talk between the Interferon and Androgen Signaling Pathways. THE Journal Of Biological Chemistry, 2005; 280(47): 38898–38901.
9. Enas R. Abu-Zhayia, Hanan Khoury-Haddad, Noga Guttmann-Raviv, Raphael Serruya, Nayef Jarrous & Nabieh Ayoub A role of human RNase P subunits, Rpp29 and Rpp21, in homology directed-repair of double-strand breaks. Scientific Reports, 2017; 7: 1002. DOI:10.1038/s41598-017-01185-6.
10. Farhad Babaei,Ali Ahmadi, Farhad Rezaei, Somayeh Jalilvand, Nastaran Ghavami, Mahmoud Mahmoudi, Ramin Abiri, Nasim Kondori, Rakhshande Nategh and Talat Mokhtari Azad Xenotropic Murine Leukemia Virus-Related Virus and RNase L R462Q Variants in Iranian Patients With Sporadic Prostate Cancer. Iran Red Crescent Med J., 2015; 17(12): e19439.
11. Gene ID: 11727, Ang angiogenin, ribonuclease, RNase A family, 5. [*Mus musculus* (house mouse)]
12. Geqiang Li, Ying Xiang, Kanaga Sabapathy, and Robert H. Silverman An Apoptotic Signaling

Pathway in the Interferon Antiviral Response Mediated by RNase L and c-Jun NH2-terminal Kinase. The Journal of Biological chemistry 2004; 279(2): 1123–1131.
13. Goparaju CM, Blasberg JD, Volinia S, Palatini J, Ivanov S, Donington JS, Croce C, Carbone M, Yang H, Pass HI. Onconase mediated NFKβ downregulation in malignant pleural mesothelioma. Oncogene, 2011; 30: 2767–2777.
14. Gundampati Ravi Kumar & Rajasekhar Chikati & Santhi Latha Pandrangi & Manoj Kandapal & Kirti Sonkar & Neeraj Gupta & Chaitanya Mulakayala & Medicherla V. Jagannadham & Chitta Suresh Kumar & Sunita Saxena & Mira Debnath Das(2012).Molecular docking and dynamics simulations of A.niger RNase from Aspergillus niger ATCC26550: for potential prevention of human cancer. J Mol Model; DOI 10.1007/s00894-012-1587-9.
15. Hong Xie, Chih-Chi Andrew Hu, M. Celeste Simon IRE1a RNase–dependent lipid homeostasis promotes survival in Myc-transformed cancers. J Clin Invest., 2018; 128(4): 1300-1316.
16. Kimberly A. Dickson Marcia C. Haigis and Ronald T. Raines Ribonuclease Inhibitor: Structure and Function Prog Nucleic Acid Res Mol Biol., 2005; 80: 349–37.
17. Krishnamurthy Malathi, Jayashree M. Paranjape, Ram Ganapathi, and Robert H. Silverman HPC1/RNASEL Mediates Apoptosis of Prostate Cancer Cells Treated with 2_,5_-Oligoadenylates, Topoisomerase I Inhibitors, and Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand CANCER RESEARCH, 2004; 64: 9144–9151.
18. Ling Zhao, Babal K. Jha, Ashley Wu, Ruth Elliott, John Ziebuhr, Alexander E. Gorbalenya, Robert H. Silverman, and Susan R. Weiss Antagonism of the Interferon-Induced OAS-RNase L Pathway by Murine Coronavirus ns2 Protein Is Required for Virus Replication and Liver Pathology Cell Host & Microbe, 2012; 11: 607–616.
19. Ling Fang, William W. Du, Juanjuan Lyu, Jun Dong, Chao Zhang, Weining Yang, Alina He, Yat Sze Sheila Kwok, Jian Ma, Nan Wu, Feiya Li, Faryal Mehwish Awan, Chengyan He, Bing L. Yang, Chun Peng , Helen J. MacKay, Albert J. Yee, , Burton B. Yang. Enhanced breast cancer progression by mutant p53 is inhibited by the circular RNA circ-Ccnb1Cell Death & Differentiation https://doi.org/10.1038/s41418-018-0115-6, 2018.
20. Mitkevich VA, Tchurikov NA, Zelenikhin PV, Petrushanko IY, Makarov AA, Ilinskaya ON. Binase cleaves cellular noncoding RNAs and affects coding mRNAs. FEBS J., 2010; 277: 186–196.
21. Nadezhda Mironova, Olga Patutina, Evgenyi Brenner, Alexander Kurilshikov, Valentin Vlassov and Marina Zenkova The systemic tumor response to RNase A treatment affects the expression of genes involved in maintaining cell malignancy Oncotarget, 2017; 8(45): 78796-78810.
22. Olivier Preynat-Seauve, Sylvia Coudurier, Alain Favier, Patrice-Noël Marche and Christian Villiers Oxidative Stress Impairs Intracellular Events Involved in Antigen Processing and Presentation to T Cells. Cell Stress & Chaperones, 2003; 8(2): 162-171.
23. Susanna M. Rybak S, Shailendra K. Saxenat, Eric J. Ackermant, and Richard J. Youle S Cytotoxic Potential of Ribonuclease and Ribonuclease Hybrid Proteins, 1991; 266(31): 21202-21207.
24. Stéphanie Lhomond et al., Dual IRE1 RNase functions dictate glioblastoma development EMBO Molecular Medicine e7929, 2018.
25. Saxena SK, Sirdeshmukh R, Ardelt W, Mikulski SM, Shogen K, Youle RJ. Entry into cells and selective degradation of tRNAs by a cytotoxic member of the RNase A family. J Biol Chem. 2002; 277:15142–15146.
26. Shin Kim, Mei Ling Song, Hyeonji Min, Ilseon Hwang, Seong Kyu Baek, Taeg Kyu Kwon And Jong-Wook Park miRNA biogenesis-associated RNase III nucleases Drosha and Dicer are upregulated in colorectal adenocarcinoma. Oncology Letters, 2017; 14: 4379-4383.
27. Tina Gill, Ti Cai, Jason Aulds, Sara Wierzbicki, and Mark E. Schmitt RNase MRP Cleaves the CLB2 mRNA To Promote Cell Cycle Progression: Novel Method of mRNA Degradation Molecular And Cellular Biology, 2004; 24(3): 945–953.
28. Vilius Stribinskis, Guo-Jian Gao, Steven R. Ellis and Nancy C. Martin Rpm2, the Protein Subunit of Mitochondrial RNase P in Saccharomyces cerevisiae, Also Has a Role in the Translation of Mitochondrially Encoded Subunits of Cytochrome c Oxidase GENETICS, 2001; 158(2): 573-585.
29. Xue Wang, Hongfei Yu, Wenjie Sun, Jianlu Kong, Lei Zhang, Jinlong Tang, Jingyu Wang, Enping Xu,Maode Lai and Honghe Zhang. The long non-coding RNA CYTOR drives colorectal cancer progression by interacting with NCL and Sam68. Molecular Cancer., 2018 (17): 110.
30. Zhao H, Ardelt B, Ardelt W, Shogen K, Darzynkiewicz Z. The cytotoxic ribonuclease onconase targets RNA interference (siRNA). Cell Cycle, 2008; 7: 3258–3261.
31. Zhen-Chuan Liu, Kuo Cao, Zhao-Hua Xiao, Liang Qiao, Xue-Qing Wang, Bin Shang, Yang Jia and Zhou Wang. VRK1 promotes cisplatin resistance by up-regulating c-MYC via c-Jun activation and serves as a therapeutic target in esophageal squamous cell carcinoma. Oncotarget, 2017; 8(No. 39): 65642-65658.
32. Airong Su ,Huanru Wang,Yanlei Li ,Xiaohui Wang, Deyan Chen and Zhiwei Wu Opposite Roles of RNase and Kinase Activities of Inositol-Requiring Enzyme 1 (IRE1) on HSV-1 Replication

Viruses, 2017; 9(9): 235; 1-17. doi:10.3390/v9090235.

33. Louise Kime , Helen A. Vincent , Deena M. A. Gendoo , Stefanie S. Jourdan , Colin W. G. Fishwick, Anastasia J. Callaghan & Kenneth J. McDowall The First Small-Molecule Inhibitors of Members of the Ribonuclease E Family SCIENTIFIC REPORTS | 5 : 8028 | DOI: 10.1038/srep08028, 2015.
34. Lu Lu, Jiarui Li, Mohammed Moussaoui and Ester Boix Immune Modulation by Human Secreted RNases at the Extracellular Space; Frontiers in Immunology, 2018; 9: 1-20.
35. Francesco Acquati, Marta Lualdi, Sabrina Bertilaccio, Laura Monti, Giovanna Turconi, Marco Fabbri, Annalisa Grimaldi, Achille Anselmo, Antonio Inforzato, Angelo Collotta, Laura Cimetti, Cristina Riva, Laura Gribaldo, Paolo Ghia, and Roberto Taramelli Loss of function of Ribonuclease T2, an ancient and phylogenetically conserved RNase, plays a crucial role in ovarian tumorigenesis PNAS, 2013; 110(20): 140-8145.
36. Briggs E, Crouch K, Lemgruber L, Lapsley C, McCulloch R Ribonuclease H1-targeted R-loops in surface antigen gene expression sites can direct trypanosome immune evasion. PLOS Genetics, 2018; 14(12): e1007729.
37. Paul Kurywchak, Jena Tavormina and Raghu Kalluri l The emerging roles of exosomes in the modulation of immune responses in cancer. Genome Medicine, 2018; 10: 1-4.