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RNases and their role in Cancer

[1,]Eswari Beeram

1. First Author & Corresponding Author Department of biochemistry, Sri Venkateswara University, Tirupati, Andhrapradesh, India. Tel: +91- 97-0027-7136. E-mail: eshu.sonu@gmail.com

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Abstract

RNases plays a pivotal role in biological system 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 proved to improve genome stability in normal cells up to some extent. 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 through processing of Ags. IRE1 RNase acts as both tumour suppressor gene and oncogene in normal and cancer cells and involved in both antitumour and tumorigenic activities. RNase III upregulates miRNA in cancer cells there by acting via posttranscriptional level and proven to be effective against colorectal adeno carcinoma. In addition to this IRE1 RNase is a double edged sword through RIDD pathway in ER (18). 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 through RIDD pathway (18). Thus RNases play vital role in regulating the genome stability.

Keywords: IRE1, RNaseL, RNase MRP, 2',5'- A, IFN

Major classification: Health Science.

1. Introduction

RNase A was a multi functional enzyme which plays key role in gene regulation in cells and its major role in humans is digestion of nucleic acid RNA present in the food and is secreted from pancreas. As the enzyme is involved in gene regulation through digestion of SS RNA and DNA-RNA hybrid and ds RNA its role as antitumor enzyme is as expected. Mainly cancer occurs through genetic mutations, viral infection and through affecting the pathways mainly involved in gene regulation and through gain of function in certain genes and proteins like P53 and loss of function in some of the genes and proteins such as cell cycle proteins like ARK.

Antitumor activity was not only limited to RNase A but many of the RNases like RNase III prevents genetic mutations through mi RNA nucleases Dicer complex, where as RNase L is involved in antitumor protection against prostate cancer. Enzyme's role is not only limited to nuclear material but also to extra chromosomal material of mitochondria through mitochondrial RNase (RNase MRP) . RNase A is mainly involved in protection against RNA viruses that enter through food and tumour causing viruses containing RNA that aid their entry through mucus membranes of digestive tract like 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 genetic material either DNA or RNA.

RNase III is also involved in protection against viruses containing RNA through miRNA and dicer and Drosha complex. miRNA mainly binds the RNA after uncoating of virus in the cell. RNaseIII cleaves the RNA-miRNA complex with the help of dicer and drosha complex thereby preventing viral replication and eliminates tumour inducing virus. Some of the RNases induce apoptosis in cancer cells by targeting stromal environment at post transcriptional level. In physiological conditions cancer cells requires survival proteins like VEGF that serves as proangiogenesis factor. So by deficit of VEGF cancer cells does not form new blood vessels in the tissue there by preventing tumor invasion.

RNases like RNase L also plays important role in eliminating other viral diseases like hepatitis caused by hepatitis virus and also against corona virus (1). RNase along with IRE1α phenocopies SCD (Stearoyl –CoA desaturase) and prevent myc induced development of cancers (2). So, this review mainly focus on RNases involved in inducing cancer, cancer prevention and pathways of RNase in prevention of cancer.

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

CCNB1 is one of the gene expressed in normal cells and promotes cell survival, proliferation and inhibits apoptosis as it is a mitosis regulator (3) and 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 of cir- Ccnb1 with Bclaf1 through H2AX(3). Both normal and cancer cells are resistant to RNase treatment with respect to cirCcnb1 RNA but not to Ccnb1 mRNA as circularisation reduces the accessibility of the RNA to the enzyme proved by the results of Fang, Du, Lyu, Dong, Zhang, Yang, He, Kwok, Ma, Wu, Li, Awan, He, Yang, Peng, MacKay, Yee, and Yang (2018).

CYTOR was the other long noncoding RNA involved in tumour progression and epithelial mesenchymal transition through binding to NCL and Sam68 as they are RNA binding proteins in colorectal cancer cells proved by diminished interaction with CYTOR after treatment with RNase A (4).

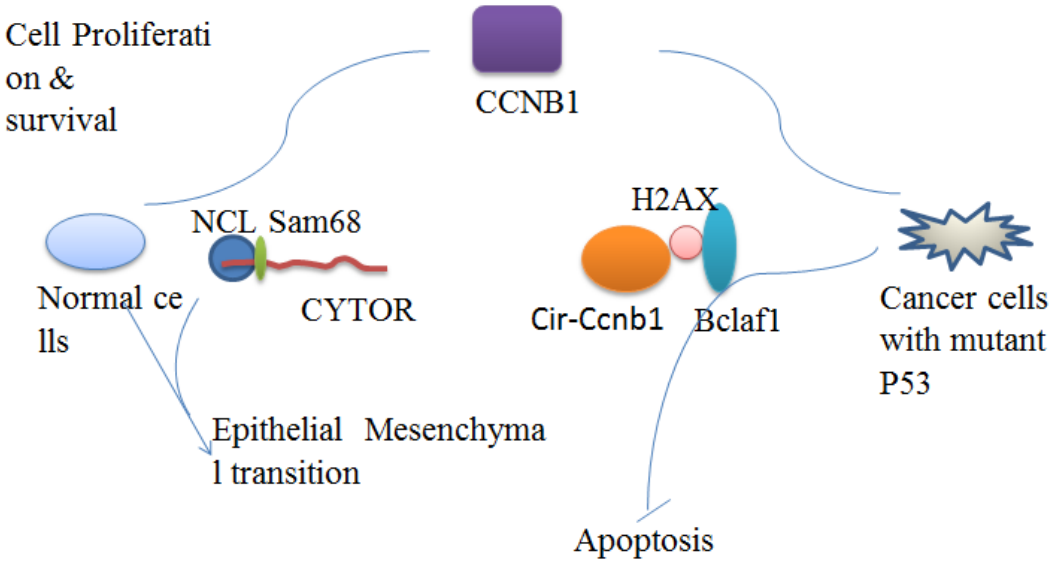

Figure 1: Role of CCNB1 And CYTOR in normal and cancer cells. In normal cells CCNB1 is involved in cell proliferation and survival. In cancer cells with mutant P53 cir-Ccnb1 interaction through H2AX with Bclaf1 induces apoptosis where as CYTOR long noncoding RNA interacts with NCL and sam68 and causes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

RNase L as a tumour suppressor:

First observation of RNase L as a tumour suppressor was made by Bettoun, Scafonas, Rutledge, Hodor, Chen, Gambone, Vogel, McElwee-Witmer, Bai, Freedman, and Schmidt (2005). Dihydrotestosterone is the most potent form of testosterone and binds to Androgen receptor harmone responsive element in the nucleus and mediates its proliferation of cells. RNase L interacts with androgen receptor in a ligand dependent manner and accelerates interferon pathway. When IFN release by effector cells binds to AR and the antagonistic activity of AR- IFN depends on RNase L- 2' oligo adenylate synthase pathway. IFN activates 2'-5' oligo adenylate synthetases synthesising 2'-5' A which activates RNase L. So, as RNase L acts through or guide its own pathway and is unavailable for AR to bind so the IFN binds and antagonises the activity of androgen receptor and RNase L accelerates 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 transcriptional inactivation lead to 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 overexpressing 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 Babaei, Ahmadi, Rezaei, Jalilvand, Ghavami, Mahmoudi, Abiri, Kondori, Nategh, & Azad (2015). Xenotropic Murine Leukaemia Virus related Virus (XMRV) was not associated with prostate cancer(5).

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 RNase L dependent apoptosis . 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 (6).

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 (7). 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, Paranjape, Ganapathi, and 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 (6).

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 another RNase III nuclease Dicer is involved in processing of precursor miRNA in to mature miRNA in the cytoplasm(8). 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 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 and Ribosomal rRNA IlT1(9). 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 due to 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 in those cells but effective targeting of enzyme to cancer cells is equally important.

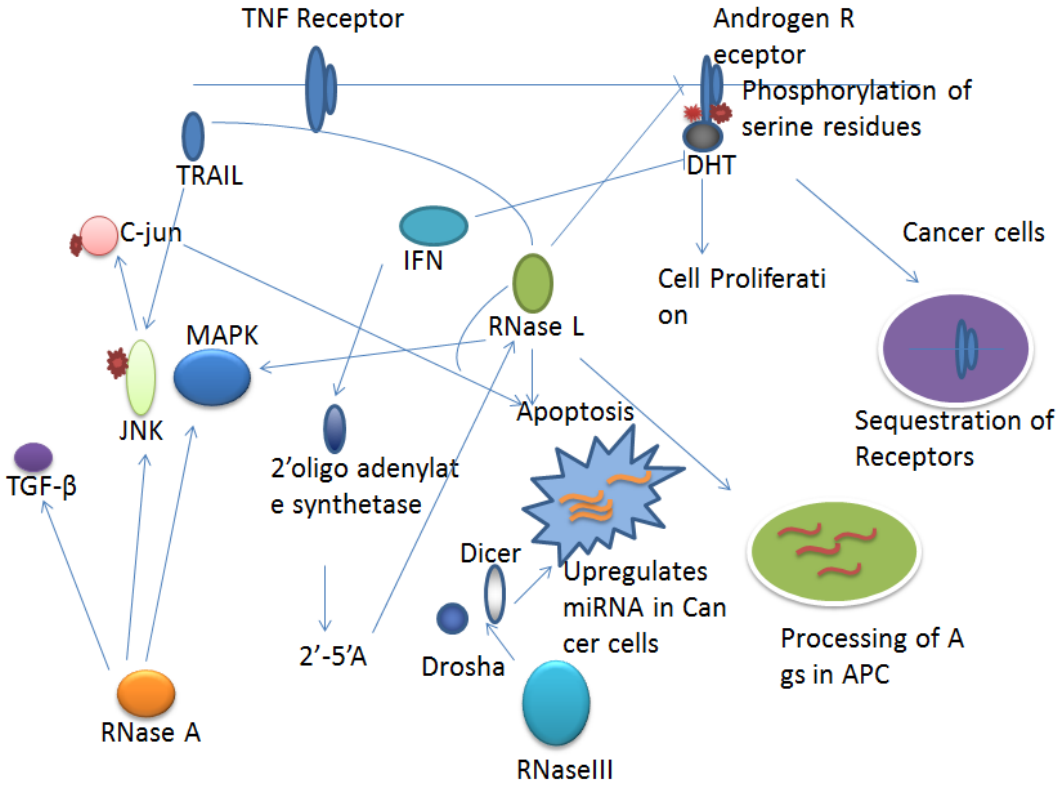

Figure 2: Role of RNases in normal and cancer cells: IFN binds to Androgen receptor so RNase L is unable to bind to receptor where as IFN binds to AR and inhibits binding of DHT. In cancer cells AR transcriptional inactivation is necessary for tumour progression. Phosphorylation of ser residues causes sequestration of AR in breast cancer cells and prevents its activity. RNase L is also involved in processing of Ags in APC. 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 activating them through phosphorylation and finally to RNase L dependent apoptosis. 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

RNase P core subunits Rpp21 and Rpp29 function 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 repair. Homology dependent repair is an error free repair and involves recruitment of Rpp21 and Rpp29 in PARP dependent manner (10). 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 invasion of tumour

and malignancy. Where as in normal cells the recruitment is maintained and rescued from death of these cells. 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 (11).

2. RNase A as onconase:

niger RNase acts as an anti invasive and anticytostatic agent in breast cancer cells through inhibiting formation of actin-angiogenin complex (12). Similarly RNase A exerts apoptosis of cancer cells and inhibits apoptosis in normal cells From the results of Fiorini, Gotte, Donnarumma, Picone, and Donadelli (2014), BS- RNase but not RNase A induces autophagic cell death in pancreatic adenocarcinoma (13). oligomerisation of BS-RNase is necessary for cytotoxic property of the enzyme. Absence of oligomerisation of BS-RNase in cancer cells is ananother problem to be rectified. Inside environment of cancer cells is more redoxive compared to normal cells (14). 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 antineoplastic drugs that produce oxidative stress as a mechanism of survival.

RNase A is a monomer and bound RI is scavenged by the protein Angiogenin in cancer cells (15). From the results of Dickson, Haigis, and Raines (2005), Angiogenin also has proven to possess RNase activity and required for angiogenesis (16). So, RNase A can form oligomers by domain swapping and can form dimers, trimers and can induce apoptosis. Cytotoxicity of RNase A is arrested by RI as proved by the results of Rybak, Saxenat, Ackermant, and Youle (1991), where as BS-RNase is a dimer so not accessible to RI. But RI and RNase L does not change in cancer cells and normal cells (7). RNase L is also proven to protect organisms against hepatitis caused by carona virus (17).

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 induction of apoptosis in lung carcinoma (16) .

3. IRE1 RNase as double edged sword:

IREα1 RNase is the one of the downstream regulator of c-myc and N- myc through SCD1 protein (2). MYC deregulation in breast cancer cells includes mRNA and protein stabilisation, gene amplification, 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 from the results of Xie, Tang, Song, Mancuso, Del Valle, Cao, Xiang, Dang, Lan, Sanchez, Keith, Hu, and Simon (2018). Cycloheximide treatment may be expected to cause cellular death in c-myc cells but other downstream targets of c-myc make 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 tumourigenic properties with upregulating the genes required to cause epithelial mesenchymal transition and by degrading mRNAs and miRNAs targeted to ER (23). IRE1 dependent splicing of XBP1s requires N-glycosylation of protein which is prevented by tunicamycin treatment (18,19-23).

Cisplatin resistant cancer cells can be targeted by metformin through inhibition of IGFR-1. But the IGFR1 mRNA levels increase may indicate c-myc and N- myc overexpresses in resistant cells along with JNK (24).

4. Discussion:

RNases plays an important role in maintaining genome integrity. So, these are the enzymes at least its downstream regulators which 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 death of those cells. RNase catalytic subunit M1RNA has also antitumour 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 (17). 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 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 necessary for their survival (17). 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 also in spirochete Borrelia burdgoferi (25). RNase III family members recognise and cleave ds RNA and participates in immune surveillance in both eukaryotes and prokaryotes (26) and functions as principle regulator of gene expression by indulging in maturation of rRNAs and other structural RNAs (27).

Myc is a protooncogene in B- cell chronic lymphocytic leukaemia involving translocations like t(8;12)(q24;q22) with BTG1 amplification and as downstream regulators of some effectors(28). 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 as c-myc plays similar role so, RNase III may be the downstream regulator of c-myc in c-myc overexpressing cancers.

In addition to this IRE1 RNase is a double edged sword through RIDD pathway in ER (18). 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 through RIDD pathway (18). Thus RNases play vital role in regulating the genome stability.

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