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RNA-binding protein nucleolin in disease

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Abbreviations: ARE, AU-rich element; CR, coding region; RBP, RNA-binding protein; RNP, ribonucleoprotein; UTR, untranslated region

Nucleolin is a multifunctional protein localized primarily in the nucleolus, but also found in the nucleoplasm, cytoplasm and cell membrane. It is involved in several aspects of DNA metabolism, and participates extensively in RNA regulatory mechanisms, including transcription, ribosome assembly, mRNA stability and translation, and microRNA processing. Nucleolin's implication in disease is linked to its ability to associate with target RNAs via its four RNA-binding domains and its arginine/glycin-rich domain. By modulating the post-transcriptional fate of target mRNAs, which typically bear AU-rich and/or G-rich elements, nucleolin has been linked to cellular events that influence disease, notably cell proliferation and protection against apoptotic death. Through its diverse RNA functions, nucleolin is increasingly implicated in pathological processes, particularly cancer and viral infection. Here, we review the RNA-binding activities of nucleolin, its influence on gene expression patterns, and its impact upon diseases. We also discuss the rising interest in targeting nucleolin therapeutically.

Introduction

In coordination with transcription, post-transcriptional mechanisms elicit robust, efficient and dynamic changes to the patterns of expressed proteins, enabling cells to respond to intracellular and environmental stimuli. Transcriptional and post-transcriptional processes are tightly interconnected. Post-transcriptional events are mainly governed by RNA-binding proteins (RBPs) and by noncoding (nc)RNAs, which jointly regulate steps such as mRNA splicing, maturation, transport, editing, stability and translation.[1,2] However, some post-transcriptional regulators perform many functions; for example, the RBP family of hnRNPs (heterogeneous nuclear ribonucleoproteins) is capable of modulating DNA transcription, as well as replication, telomere maintenance, transcription and repair.[3,4]

First described almost four decades ago,[5] nucleolin is one of the most multifunctional RBPs known to-date. It is most abundant in the nucleolus, but is also found in other nuclear regions, as well as in the cytoplasm and the plasma membrane.[6-8] Nucleolin plays key functions in processes such as chromatin remodeling, transcription of ribosomal (r)RNA, rRNA maturation, ribosome assembly, nucleocytoplasmic transport and ribosome biogenesis.[7-10] It binds DNA and RNA, functions as a DNA and RNA helicase, and has self-cleaving activity.[10,11] The multiple functions and subcellular localization of nucleolin reflect its complex structure. Its acidic N-terminal region contains multiple phosphorylation sites, participates in the transcription of rRNA, and interacts with components of the pre-rRNA processing complex.[12] The central region of nucleolin contains four RNA-recognition motifs (RRMs) and mediates the interaction with mRNAs and pre-rRNA.[13,14] The C-terminal region of nucleolin contains an arginine/glycine-rich domain (RGG), through which nucleolin can interact with target mRNAs as well as with other proteins, including ribosomal proteins.[13,15,16]

Nucleolin has been extensively implicated in DNA metabolism. It affects DNA replication, telomere maintenance and DNA repair, and recombination.[17-22] At the level of transcription, it represses the function of RNA polymerase I, thereby lowering rRNA transcription.[7] Nucleolin also modulates the transcription of mRNAs in several ways. It represses RNA polymerase II function and it can affect mRNA transcription both positively and negatively through its interaction with chromatin components like histone H1,[23,24] and chromatin remodeling enzymes such as SWI/SNF.[25] In addition, nucleolin can affect mRNA transcription directly by interacting with DNA by interacting with DNA.[26]

Nucleolin's influence on ribosome biogenesis has also been studied in detail. Nucleolin binds to a stem-loop structure found in nascent pre-rRNA and plays a chaperone function by facilitating the proper folding of pre-rRNA.[14,27] Nucleolin also catalyzes the first processing step of pre-rRNA occurring in the 5' external transcribed spacer (5'-ETS) resulting in cleavage of the precursor transcript of rRNA.[28,29] The affinity of nucleolin for ribosomal proteins suggests that it may also help assemble ribosomal subunits in the nucleus,[15] and likely participates in the transport of these newly assembled ribosomal subunits into the cytoplasm.[30] Through its involvement in rDNA transcription, its association with nascent pre-rRNA, and its assembly and transport of ribosomal particles, nucleolin is believed to assist with every step of ribosome biosynthesis.[31]

The transcriptional and ribosome assembly functions of nucleolin have been known for many years. However, the past

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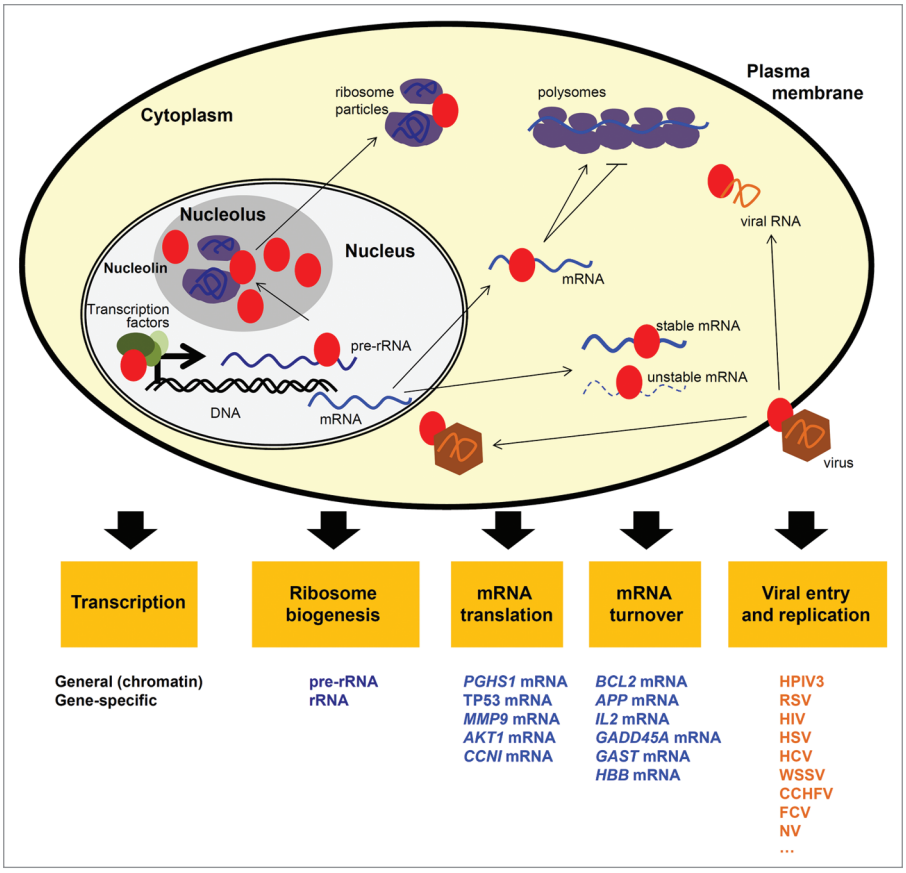

Figure 1. Regulation of mRNA by nucleolin. Schematic representation of nucleolin (red oval) and its influence on the post-transcriptional regulation of mRNA fate (mRNA turnover and translation) in the context of its multiple cellular functions (yellow boxes) and its presence in the nucleolus, nucleoplasm, cytoplasma and cell membrane. The target mRNAs whose regulation by nucleolin has been characterized are indicated under "mRNA translation" and "mRNA turnover."

decade has uncovered many other functions linked to the binding of nucleolin to mRNAs (**Fig. 1**). This review will focus mainly on this relatively new activity of nucleolin, given its direct implication in disease. We will describe the subsets of mRNAs with which nucleolin interacts, the influence of nucleolin on their expression, and the impact of the encoded proteins on pathologies, mainly cancer and viral infections. Finally, we will discuss emerging efforts to target nucleolin for therapeutic intervention.

Nucleolin Target Transcripts

Nucleolin affects the stability and/or translation of target mRNAs in multiple ways. Many of nucleolin target mRNAs bear AU-rich elements (AREs), typically present in their 3'-untranslated region (UTR), and/or G-rich sequences distributed in the 5' UTR, coding region (CR), and 3' UTR.[13,32] In this section, we will discuss those nucleolin target mRNAs which are best characterized, and we will highlight the impact of the encoded proteins in disease processes (**Table 1**).

Nucleolin effect on mRNA turnover. Nucleolin affects mRNA turnover, both increasing and decreasing mRNA half-life, by interacting with the UTRs of target mRNAs. As described below, the regulation of mRNA turnover by nucleolin is often functionally linked to the association of other turnover-regulatory RBPs.

***BCL2* mRNA.** Nucleolin associates with the 3' UTR ARE of the *BCL2* mRNA, enhances its stability, and thus augments expression of the anti-apoptotic, pro-oncogenic protein B-cell lymphoma 2 (Bcl-2).[32] Accordingly, elevated expression of nucleolin was linked to the ARE-dependent stabilization of *BCL2* mRNA and increased Bcl-2 levels in leukemia cells.[32,33] The positive effect of nucleolin on Bcl-2 expression agrees with the finding that nucleolin inhibits oxidative stress-induced apoptosis in human umbilical vascular endothelial cells.[34] In HL-60 leukemia cells, nucleolin and the RBP HuR bound the *BCL2* ARE concurrently and had a synergistic effect on Bcl-2 expression, as both RBPs stabilized the *BCL2* mRNA, while HuR also enhanced its translation;[35] by contrast, AUF1 antagonized nucleolin binding to the *BCL2* ARE and triggered *BCL2* mRNA decay.[36] Treatments with all-trans retinoic acid, taxol or okadaic acid enhanced nucleolin degradation and promoted *BCL2* mRNA decay.[32,37]

APP mRNA. The amyloid precursor protein (APP) is linked to Alzheimer's disease. The 3' UTR of *APP* mRNA was found to be a substrate for association by nucleolin, as well as by the RBPs hnRNP C and fragile X mental retardation protein (FMRP).[38-41] The helicase activity of nucleolin was proposed to accelerate *APP* mRNA degradation in response to stress, an effect that was counteracted by the stabilizing influence of hnRNP C.[41]

***IL2* mRNA.** Interleukin (IL)-2 is a major cytokine implicated in the response against microbial infection and is used in certain cancer therapies.[42] Unlike nucleolin's binding to the 3' UTR of *BCL2* and *APP* mRNAs, nucleolin binds the 5' UTR of *IL2* mRNA, and this interaction is required for JNK-mediated *IL2* mRNA stabilization during T-cell activation, likely in cooperation with the Y box-binding protein-1 (YB-1).[43]

***GADD45A* mRNA.** The growth arrest- and DNA damage-inducible 45 protein (Gadd45α) is induced under stress conditions.[44] The stress agent arsenite enhances the association of nucleolin with *GADD45A* mRNA, leading to transcript stabilization.[45] Interestingly, *GADD45A* mRNA is also a target of the translational suppressor TIAR and the decay-promoting protein AUF1, two RBPs that dissociate after treatment with the alkylating agent methyl methanesulfonate (MMS).[44] These findings suggest a functional interplay between nucleolin, TIAR and AUF1 to promote the expression of Gadd45α under stress conditions.

Table 1. mRNA targets of nucleolin

mRNA (protein)	Interaction with Nucleolin	Consequences on mRNA	Other factors involved	Implication in disease	References
BCL2 (Bcl-2)	3'UTR ARE	Stabilization	HuR cooperates AUF1 antagonizes	Cancer (anti-apoptotic)	32–36
APP (APP)	3'UTR	Decay	hnRNP C antagonizes	Alzheimer's Disease	38–41
IL2 (IL-2)	5'UTR	Stabilization	YB-1 cooperates	Cancer (immunosurveillance)	43
GADD45A (Gadd45α)	3'UTR	Stabilization	TIAR antagonizes (?) AUF1 antagonizes (?)	Cancer (stress response)	44, 45
GAST (Gastrin)	3'UTR	Stabilization	hnRNP C cooperates PCBP1 cooperates	Cancer (inflammation)	46, 47
HBB (β globin)	3'UTR	Stabilization	hnRNP E cooperates	Thalassemia	48, 49
PGHS1 (Pghs-1)	5'UTR NRE	Translation repression	NF45, NF90 cooperate (?)	Inflammation	50, 51
TP53 (p53)	5'UTR	Translation repression	RPL26 antagonizes	Cancer	52
MMP9 (MMP9)	3'UTR	Translation enhancement	HuR cooperates (?)	Cancer (invasion)	53–55
AKT1 (Akt1)	5'UTR,CR,3'UTR	Translation enhancement	-	Cancer (survival)	13
CCNI (Cyclin I)	5'UTR,CR,3'UTR	Translation enhancement	-	Cancer (anti-apoptotic)	13

The table lists well-characterized nucleolin target mRNAs (column 1), the regions of the mRNA with which nucleolin interacts (column 2), the consequences of these interactions on mRNA stability and translation (column 3), and the participation of other RBPs in this regulation (column 4). Column 5 lists disease processes affected by nucleolin-regulated gene expression. (?) indicates proposed involvement, but not yet demonstrated.

***GAST* mRNA.** The gastrointestinal hormone gastrin, responsible for gastric acid secretion, is highly expressed in malignancies such as pancreatic and colorectal cancers.[46] *GAST* mRNA is co-regulated by nucleolin, PCBP1 [poly(C)-binding protein 1] and hnRNP K, as the three RBPs are required for stabilizing *GAST* mRNA in cells treated with epidermal growth factor (EGF).[47]

***HBB* mRNA.** Dysregulation of β globin, encoded by *HBB* mRNA, can result in pathologies such as thalassemia.[48] Nucleolin binds the *HBB* 3' UTR mRNA and enhances its stability, likely facilitating the binding of hnRNP E.[49]

Nucleolin influence on mRNA translation. Nucleolin can also affect the translation of a subset of associated mRNAs. As described below, binding to the 5' UTR often suppresses translation, while binding to the 3' UTR enhances mRNA translation.

***PGHS1* mRNA.** Binding of nucleolin to the 5' UTR nucleolin response element (NRE) of the prostaglandin endoperoxide H synthase-1 (*PGHS1*) mRNA reduced translation of the encoded proinflammatory enzyme Pghs-1 in megakaryoblastic cells.[50] Interestingly, NF45 and NF90 also associated with the 5' UTR of *PGHS1* mRNA and repressed its translation,[51] although the possible functional links among these RBPs to control Pghs1 production have not been reported.

***TP53* mRNA.** Nucleolin and ribosomal protein L26 (RPL26) were found to bind the 5' UTR of the *TP53* mRNA, which encodes the tumor suppressor p53. While RPL26 enhanced the translation of *TP53* mRNA in response to DNA damage, nucleolin suppressed *TP53* mRNA translation and prevented the induction of p53 after DNA damage.[52]

***MMP9* mRNA.** Degradation of extracellular matrix (ECM) components by matrix metalloproteinases is essential for processes like wound healing and angiogenesis and is central to pathophysiological conditions such as cancer progression and metastasis.[53] Nucleolin binds the 3' UTR of *MMP9* mRNA and enhances its translation.[54] HuR also binds the 3' UTR of *MMP9* mRNA and increases its stability,[55] although it is not yet known if HuR and nucleolin may regulate MMP9 expression competitively or cooperatively.

***AKT1, CCNI* and other G-rich mRNAs.** Recently, nucleolin was reported to enhance translation of a subset of target mRNAs by interacting with G-rich elements present in the CR and UTRs. These mRNAs included those that encode the prosurvival proteins Akt1 and cyclin I.[13,56,57] Akt is one of the most active kinases in cancer cells, while the anti-apoptotic protein cyclin I is highly expressed in breast cancer and its increased level in serum is associated with pancreatic cancer.[56,58,59]

Nucleolin and microRNA processing. MicroRNAs (miRNAs) are short RNA molecules (~22-nt long) that potently regulate gene expression.[60,61] Primary miRNAs are transcribed and processed into precursor miRNAs in the nucleus; after their export to the cytoplasm, they undergo maturation and are assembled into an RNP silencing complex (RISC) that directs the miRNA to a specific mRNA in order to influence mRNA stability and translation.[62] Altered levels of miRNAs have been implicated in a myriad of physiologic and pathologic processes.[63-65] Recently, nucleolin was reported to interact with the microprocessor complex and thereby regulated the biogenesis of the protumorigenic microRNAs miR-15a and miR-16.[66] It is likely that

nucleolin influences the processing of other miRNAs in a similar manner, although this possibility remains to be investigated.

Nucleolin function on viral RNA. Nucleolin influences multiple aspects of viral infection, including association of the virus with the host cell, insertion of the viral genetic material, and utilization of the host cell to produce viral proteins. Nucleolin was shown to be essential for entry of the human parainfluenza virus type 3 (HPIV3) during infection of lung epithelial cells, and functioned as a receptor for the respiratory syncytial virus (RSV).[67,68] The synthetic peptide HB-19, a specific antagonist that binds the C-terminal RGG domain of nucleolin, inhibited the attachment of human immunodeficiency virus (HIV) to cells, indicating that this domain of nucleolin could be functional during the process of HIV anchorage.[69] Nucleolin is also believed to participate in the infection of Hepatitis C virus (HCV), herpes simplex virus (HSV) type 1, white-spot syndrome virus (WSSV) and the Crimean-Congo hemorrhagic fever virus (CCHFV).[70-73] Interestingly, nucleolin forms RNP complexes with the 3' UTR of feline calicivirus (FCV) and Norwalk virus (NV); in this regard, lowering nucleolin reduced viral protein synthesis and FCV replication, while the mobilization of nucleolin from the nucleolus to the perinuclear region was proposed to enhance viral mRNA translation.[74] The association of nucleolin with the 5' UTR IRES of rhinovirus and poliovirus stimulated the translation of viral proteins in vitro and in vivo.[75] In sum, nucleolin is important for viral entry to the host cell and for assisting viral RNA translation and viral replication (**Fig. 1**).

Regulation of Nucleolin Function, Implication in Disease

Regulation of nucleolin abundance. It is well established that nucleolin promotes cell proliferation and survival linked to disease processes like carcinogenesis, but the mechanisms that control nucleolin abundance are not well understood. In phorbol ester-treated peripheral blood mononuclear treated cells, the levels of *NCL* mRNA, which encodes nucleolin, increased transcriptionally via the activity of extracellular-regulated kinase (ERK).[40] At the post-transcriptional level, HuR was found to interact with the 3' UTR of *NCL* mRNA and promoted its translation, while miR-494 competed with HuR and repressed nucleolin translation.[13] Post-translationally, nucleolin abundance was shown to be controlled by proteolysis. Oxidative stress increased the cleavage of nucleolin and lowered the levels of intact nucleolin; in laryngeal squamous cell carcinoma (LSCC), the 70-kDa heat shock protein (HSP70) inhibited the cleavage and degradation of nucleolin, likely impacting on LSCC radiotherapy resistance, and in lung cancer cells, HSP90 protected nucleolin stability during mitosis.[76,77] The self-cleaving activity of nucleolin was significantly decreased in dividing T lymphocytes, likely due to the increased concentration of proteolytic inhibitors in the nuclei of these cells.[78] LYAR, a zinc finger nucleolar oncoprotein that is highly expressed in undifferentiated embryonic stem cells (ESCs), associated with nucleolin, prevented its self-cleavage and elevated nucleolin concentration.[79] It is not yet known if the truncated nucleolin is functional.

Control of nucleolin localization. Nucleolin is ubiquitously expressed in proliferating tissues and is primarily localized in the nucleolus. Although it contains a specific bipartite nuclear localization signal, its accumulation in the nucleolus is thought to depend on its affinity for nucleolar components.[7] Phosphorylation by Cdc2 (also known as Cdk1) promotes the cytoplasmic localization of nucleolin, while dephosphorylated nucleolin resides in the nucleus.[80] Under stress conditions such as heat shock, ionizing radiation and treatment with camptothecin, nucleolin is mobilized from the nucleolus to the nucleoplasm in a p53-dependent manner, likely exerting a transient influence on DNA replication and repair.[81]

Although in lesser abundance than in the nucleolus, nucleolin is also localized in the cytoplasm and on the cell membrane. In the cytoplasm, nucleolin binds mRNAs to influence their stability and translation, as described above. However, the function of nucleolin on the plasma membrane is less clear. Perhaps nucleolin transports RNA molecules to the cell membrane in order to affect cell fate, is mobilized to the cell membrane for transient repression of its nuclear and cytoplasmic functions, or functions as a receptor for extracellular RNA that needs to be internalized. The latter putative activity is reminiscent of the actions of the glucocorticoid receptor, which associates with a subset of cytoplasmic mRNAs and regulates their turnover rates.[82] It also resembles the function of the transmembrane receptor DCC (deleted in colorectal carcinoma), which recruits translational components and retains them in an inactive state; in neurons, association of netrin-1 with DCC led the the release of the translation initiation machinery and promoted translation.[83]

The cell surface localization of nucleolin has received considerable attention in the past few years. Its high expression on the surface of cancer cells is believed to facilitate processes that affect the fate of the cancer cell.[84,85] In this regard, reducing the levels or activity of cell-surface nucleolin inhibited the growth of cultured hepatocellular carcinoma cells and triggered endothelial cell apoptosis.[86,87] Cell-surface nucleolin also mediated signaling events such as calcium entry and calcium-regulated pathways, lipopolysaccharide-stimulated expression and secretion of TNFα and IL-1β and P-selectin-induced pathways that regulate cell adhesion and spreading.[88-90] Nucleolin was found to be the receptor of endostatin and peptides F3 and N6L.[91-93]

Besides tumorigenesis, angiogenesis and signaling pathways, cell-surface nucleolin also participates in viral and bacterial infection. For example, HIV inhibitors such as pleiotrophin (PTN), the pseudopeptide HB-19, and the cytokine midkine bind specifically to cell surface-expressed nucleolin and inhibit HIV entry, indicating that nucleolin facilitates viral entry to the host cell.[94] In addition, nucleolin plays an important ligand-binding role in *Francisella tularensis* bacterial infection, facilitating host tissue invasion.[95]

Regulation of nucleolin by phosphorylation. Nucleolin is phosphorylated by numerous kinases, notably Cdc2, casein kinase II (CKII), protein kinase C (PKC)ζ, and the stress-activated protein kinase (SAPK) p38;[8,10,96-98] additional kinases include the nucleolar-type NII protein kinase, casein kinase-like ectoprotein kinase, phosphatidylinositol-3-kinase (PI3K),

Akt and Rho-associated kinase. A number of these phosphorylation events were linked to cellular processes and diseases associated with changes in the subcellular localization of nucleolin, as well as to the interaction of nucleolin with several target mRNAs.

Cdc2. Nucleolin is phosphorylated by Cdc2 during mitosis and associates with metaphase chromosomes; in addition, Cdc2-phosphorylated nucleolin is enriched in cytoplasmic neurofibrillary tangles found in neurons from Alzheimer's disease patients, suggesting that Cdc2-phosphorylated nucleolin may link two distinct processes, mitosis and neurodegeneration.[21] In *Xenopus laevis*, phosphorylation by Cdc2 promotes the cytoplasmic localization of nucleolin, while unphosphorylated nucleolin was preferentially nuclear;[99] an opposite scheme was seen for HuR, whose phosphorylation by Cdc2 promoted its nuclear localization, affecting its RNA-binding activity and its anti-apoptotic function.[100,101]

p38. Phosphorylation by p38 increased the RNA-binding activity of nucleolin following exposure to stresses like UV light (UV) and ionizing radiation, leading to enhanced interaction of nucleolin with a subset of mRNAs encoding stress-response proteins (e.g., glutathione peroxidase, peroxiredoxin 1 and HSP90).[21] This regulation also recapitulates the increased affinity of HuR for *CDKN1A* mRNA (encoding the cdk inhibitor p21) after phosphorylation by p38 following ionizing radiation.[102]

CKII. Phosphorylation by CKII and cdc2 promoted nucleolin's helicase activity on different double-stranded nucleic acids, including RNA-RNA and RNA-DNA duplexes. This activity was linked to nucleolin's influence on cell cycle progression, embryonic development and tumorigenesis.[103-105] The proteolytic cleavage of nucleolin into 30- and 72-kDa peptides was also enhanced by CKII.[106]

PKC. Phosphorylation of nucleolin by PKCζ reportedly mediated the effects of nerve growth factor (NGF) on rat pheochromocytoma PC12 cells, transmitting NGF signaling from the cell membrane to the inside of the cell.[107] Activation of PKC leading to nucleolin phosphorylation was proposed to mediate the transcriptional activation of the cytosolic phospholipase A_2 ($cPLA_2$) by transcription factors c-Jun and Sp1 and to affect NFκB transcriptional activity.[107-109]

Other post-translational modifications of nucleolin. Nucleolin is also post-translationally modified via methylation, glycosylation and ADP-ribosylation. With approximately one-third of its arginine residues methylated, nucleolin is one of the most highly methylated nuclear proteins.[110] Recently, the RIO kinase 1 was shown to recruit nucleolin to the arginine methyltransferase (PRMT5) complex, suggesting that PRMT5 could be responsible for methylating nucleolin.[111] Nucleolin methylation appeared to affect its interaction with DNA and RNA,[112,113] but its influence upon mRNA stabilization or translation has not yet been examined. Nucleolin is glycosylated in Chinese hamster ovary cells (CHO) and in the lymphoma-derived cell line U937.[114,115] Although N- and O-glycosylation of nucleolin promotes its localization and function on the plasma membrane,[116] it also remains to be studied whether it affects its RNA-binding activity. Nucleolin is modified by ADP-ribosylation,[117] but the consequence of this modification upon nucleolin's RNA-binding function is unknown.

The mechanisms that mediate nucleolin glycosylation and recruitment to the plasma membrane are still ill-defined. In this regard, nucleolin does not have a signal peptide sequence that would target it to the endoplasmic reticulum, where glycosylation and protein targeting to the membrane are initiated. It is possible that nucleolin overexpression in pathologic states results in its localization in unusual sites like the plasma membrane.

Nucleolin and the Hallmarks of Cancer

Nucleolin is highly expressed in proliferating cells, including stem cells and cancer cells. The oncogenic effect of nucleolin appears to be multifactorial, in keeping with the many functions of this protein. Cells acquire a number of features in order to become malignant, including the abilities to grow and proliferate, overcome senescence, evade apoptosis and the immune system, invade and metastasize other tissues and promote angiogenesis.[118,119] Nucleolin can enable these traits through its RNA-binding activity, as elaborated below.

Toward implementing an anti-apoptotic phenotype, nucleolin modulates the expression of several proteins that influence the survival of malignant cells during cell damage. As explained above, nucleolin binds to *BCL2* mRNA and promotes the expression of proto-oncogene Bcl-2 (explained above), which blocks apoptosis in cancer cells,[120] and it binds to *AKT1* mRNA and enhances translation of Akt1, another potent pro-survival protein.[56] Additionally, nucleolin associates with the 5' UTR of *TP53* mRNA and reduces the translation of the pro-apoptotic tumor suppressor p53,[52] further promoting an anti-apoptotic cell phenotype.

Another protein under positive regulation by nucleolin, gastrin, is highly expressed in gastrointestinal cancers and functions as a pro-survival factor that enhances cancer cell proliferation, angiogenesis and migration.[46,47] Indeed, enhanced expression of gastrin by nucleolin is directly relevant to the tumorigenicity of human colon cancer cells and upregulates cyclooxygenase-2 (COX-2), which in turn catalyzes prostaglandin E2 production and promotes tumor cell proliferation.[121,122] Nucleolin may also assist cancer cells in overcoming cellular senescence, as it associates with the enzyme telomerase (TERT) and its RNA template (TERC) in the nucleoplasm. Through these interactions, nucleolin may assist in the localization, assembly, and/or maintenance of telomeres,[123] whose compromised integrity can trigger senescence. In keeping with this broad influence on cancer gene expression programs, a subset of nucleolin-associated mRNAs encoding tumor-related proteins were recently identified in mitotic cells.[21,77]

Degradation of the extracellular matrix (ECM) is essential for angiogenesis and metastasis.[124,125] Since nucleolin associates with *MMP9* mRNA and enhances its translation, it may help cancer cells to invade and metastasize. This effect on the ECM could be further amplified by nucleolin's influence on gastrin, itself an inducer of MMP9 expression.[126]

Nucleolin can also enhance oncogenesis in ways that are independent of its mRNA-binding activity. For instance, nucleolin transcriptionally promotes expression of the vascular endothelial growth factor (VEGF) and the interferon regulatory factor-2 (IRF-2), other proteins that are highly expressed in cancers and are potent regulators of cancer cell growth.[127-129] In addition, as explained above, cell-surface nucleolin functions as a receptor for tumorigenic factors like the carcinogenic factor released from *Helicobacter pylori* Tipα (the TNFα-inducing protein); nucleolin shuttles Tipα from the cell membrane to the cytosol and the nucleus, where it induces the expression of TNFα and chemokines and promotes inflammation.[130]

Targeting Nucleolin for Therapy

Nucleolin is an attractive target for therapy in cancer and viral infection given its high abundance, its multifaceted influence on oncogenesis, and its selective presence on the plasma membrane of cancer cells, but not untransformed, normal cells. A number of therapeutic efforts have been directed at controlling nucleolin levels and activity.

Nucleolin-directed anticancer aptamers. Aptamers are short, stable DNA or RNA molecules that can target specific cellular and extracellular targets with high affinity.[131,132] The aptamer AS1411, also known as AGRO100, a 26-mer unmodified guanosine (G)-rich oligonucleotide [5'-d(GGT GGT GGT GGT TGT GGT GGT GGT GG)-3'], is among the aptamers most extensively studied and used. Nucleolin has high affinity for AS1411, in agreement with the strong binding of nucleolin to G-quadruplex DNA sequences.[133,134] AS1411 may directly inhibit the RNA-binding activity of nucleolin, as AS1411 reduced nucleolin binding to *BCL2* mRNA resulting in *BCL2* mRNA destabilization, decreased Bcl-2 protein levels, apoptotic death of cultured human breast cancer cells, and inhibition of cancer cell growth in xenografts.[135,136] Other effects of AS1411 include the inhibition of NFκB via the formation of a complex containing nucleolin and the NFκB essential modulator (NEMO).[137] Cell-surface nucleolin mediates the effects of this aptamer through binding and internalization leading to inhibition of cell growth. The promising effects of this aptamer have led to several clinical trials in patients with advanced solid tumors.[138]

Nucleolin-directed anticancer peptides. As explained above, the synthetic peptide HB-19 specifically antagonizes the C-terminal RGG domain of nucleolin and inhibits cell membrane-associated nucleolin function, thereby preventing the growth, angiogenesis and tumorigenicity of numerous cancer cells using different assays.[139,140] The V3 loop-mimicking pseudopeptide 5[Kpsi(CH2N)PR]-TASP binds to the cell-surface nucleolin in monocyte-derived macrophages and synergizes with the inhibitory effects of β-chemokines on HIV infection.[141] Another synthetic ligand targeting cell-surface nucleolin, N6L, also displays potent anti-tumor activities, enhances apoptosis, blocks angiogenesis and prevents tumor growth.[92] Cell-surface nucleolin was found to be the receptor of a specific tumor-homing peptide, F3, which is internalized by vascular endothelial cells and by some tumor cells.[91] Although these ligands can impair nucleolin binding to target mRNAs, it is not yet known if their antitumor actions are explained by nucleolin's altered RNA-binding activity.

Nucleolin ligand endostatin. The anticancer drug endostatin potently reduces endothelial function and lowers angiogenesis in tumor tissues, in part by inhibiting the action of VEGF.[142] Nucleolin expressed on the surface of lymphangiogenic endothelial cells functions as a receptor of endostatin and mediates its anti-metastatic actions and its inhibitory influence on lymphatic angiogenesis.[143] Interestingly, VEGF itself stimulates the mobilization of nucleolin to the cell surface via the action of the cytoskeletal motor MyH9 (nonmuscle myosin heavy chain 9), suggesting a possible negative feedback mechanism.[144]

Nucleolin-directed siRNA and microRNA therapy. MicroRNAs play important roles in gene regulation through binding and regulating target mRNAs and thus influencing protein levels. The fact that many miRNAs are dysregulated in cancer and elicit tumor suppressive or oncogenic functions has stimulated efforts toward miRNA-based therapy.[145,146] Recently, miR-494 was found to bind the *NCL* 3' UTR and repressed nucleolin expression, an effect that was competed by HuR, which also bound the *NCL* 3' UTR and instead elevated nucleolin abundance. Similar to AS1411 and N6L, miR-494 significantly reduced the survival of cancer cells.[147] Future studies will determine if miR-494 might have therapeutic value by targeting nucleolin in cancer cells. Small interfering (si)RNA approaches aimed at reducing nucleolin levels are also emerging; for example, treatment of nasopharyngeal carcinoma (NPC) cells with antisense phosphorothioate-modified oligodeoxynucleotides (S-ODNs) directed at *NCL* mRNA triggered NPC apoptosis, while administration of NCL S-ODNs to mice suppressed the growth of NPC tumor xenografts.[148]

Nucleolin-based viral therapy. HIV inhibitors such as pleiotrophin (PTN), the pseudopeptide HB-19,[69] and the cytokine midkine bind specifically to cell surface-expressed nucleolin and inhibit HIV entry, indicating that nucleolin facilitates viral entry into host cells.[94] A receptor for human RSV, nucleolin reduction by RNA interference (RNAi)-mediated knockdown lowered RSV infection in mice.[68]

Concluding Remarks

Through functions independent of sequence-specific RNA-binding, including transcriptional regulation and ribosome biogenesis, nucleolin is a long-recognized inducer of cell proliferation. However, over the past decade, nucleolin has established a solid presence as a sequence-specific RNA-binding protein with key roles in disease. Via the direct interaction of nucleolin with subsets of target mRNAs, typically bearing AU- or G-rich sequences, nucleolin modulates the stability or translation of transcripts encoding several cancer-related proteins, including Bcl-2, MMP-9, gastrin, PGHS1, p53, Akt1 and cyclin I. These associations have strengthened nucleolin's pro-growth and pro-survival function. Nonetheless, it will be important to identify the complete set of nucleolin target RNAs, including coding and non-coding transcripts. The use of techniques such as PAR-CLIP

(photoactivatable-ribonucleoside-enhanced crosslinking and immunoprecipitation),[149] can provide a catalog of nucleolin-target RNAs and uncover a more complete spectrum of nucleolin actions.

As the analysis of nucleolin's RNA-binding activity progresses, it will be particularly interesting to investigate if cell-surface nucleolin binds RNA. Positioned on the plasma membrane, nucleolin can serve as a receptor for extracellular RNA, perhaps RNA actively released by neighboring cells as extracellular RNPs or possibly RNA remnants from lysed cells. Thus, the selective identification of RNA present in cell-surface nucleolin may yield exciting new insight on nucleolin function.

Cell-membrane nucleolin serves as a receptor for a number of viruses and is a strong diagnostic marker of cancer cells, as described above. Thus, its accessible plasma membrane localization has been exploited in different ways. It is the target of aptamers, including the G-rich oligonucleotide AS1411 that is presently in cancer clinical trials; in this regard, perhaps other G- or AU-rich oligonucleotides could be identified with superior inhibitory actions. Additional anti-cancer and anti-viral approaches directed at cell-membrane nucleolin include artificial and endogenous peptides. Chemical inhibitors directed toward nucleolin or its many post-translational regulators (e.g., cdc2, CKII, p38) may also prove therapeutically viable. Moreover, targeting intracellular nucleolin through the use of RNAi, miRNA (particularly miR-494) or intracellularly delivered G-rich RNA, may also prove to be effective.

Besides cancer and viral infection, nucleolin inhibition could be beneficial for treating inflammation. Since nucleolin promotes expression of gastrin, an inducer of COX-2 expression, efforts to inhibit the RNA-binding activity of nucleolin might be particularly helpful in treating inflammatory diseases of the gastrointestinal system. Furthermore, nucleolin mediates the effects of Tipα on TNFα, and thus modulates inflammation in the cancer microenvironment.[130,150] Thus, the impact of the RNA-binding activity of nucleolin upon inflammation warrants future investigation. Finally, the association of nucleolin with the microprocessor and its influence on microRNA biosynthesis sets the stage for future work to investigate if some of nucleolin's effects are elicited via microRNAs. In closing, despite the knowledge accumulated for this long-known multifunctional protein, many questions still remain, particularly regarding nucleolin's impact on protein expression programs. As we strive to answer them, we will gain critical insight into nucleolin's role in tumorigenesis, infection and inflammatory diseases, and will be better able to target nucleolin therapeutically.

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