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Review article

New perspectives of physiological and pathological functions of nucleolin (NCL)

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ABSTRACT

Nucleolin (NCL) is a multifunctional protein that mainly localized in the nucleolus, it is also found in the nucleoplasm, cytoplasm and cell membrane. The three main structural domains allow the interaction of NCL with different proteins and RNA sequences. Moreover, specific post-translational modifications and its shuttling property also contribute to its multifunctionality. NCL has been demonstrated to be involved in a variety of aspects such as ribosome biogenesis, chromatin organization and stability, DNA and RNA metabolism, cytokinesis, cell proliferation, angiogenesis, apoptosis regulation, stress response and microRNA processing. NCL has been increasingly implicated in several pathological processes, especially in tumorigenesis and viral infection, which makes NCL a potential target for the development of anti-tumor and anti-viral strategies. In this review, we present an overview on the structure, localizations and various functions of NCL, and further describe how the multiple functions of NCL are correlated to its multiple cellular distributions.

1. Introduction

Nucleolin (NCL) is one of the most abundant proteins of the nucleolus that is mainly located at the dense fibrillar and granular regions of the nucleolus [1–5]. NCL is highly conserved during evolution, and it has been the focus of much research since it was first described by Orrick et al. in 1973 [6]. NCL is a multifunctional phosphoprotein that ubiquitously distributed in various eukaryotic cell compartments, such as the nucleolus, the nucleoplasm, the cytoplasm and the cell membrane [7–9]. The principal function of the nucleolus is thought to be controlling RNA metabolism and ribosome biogenesis, including rRNA synthesis, pre-rRNA synthesis, rRNA processing, ribosomal assembly and maturation. It also has been implicated in many aspects of cell biology such as gene silencing, senescence, cytokinesis, nucleogenesis, cell proliferation and growth [10–14].

As a multifunctional protein, the analysis of NCL functions is quite challenging due to the broad range of localizations and various corresponding mechanisms. Modifications such as auto-degradation and glycosylation are linked to the localization and biological activities of NCL [15–17]. Moreover, the phosphorylation status and its self-cleaving activity also add much more difficulties in explicating the functions and mechanisms of this protein [15–22].

Numerous studies have demonstrated that NCL is involved in many cellular functions under both physiological and pathological situations, and the subcellular localization of NCL is tightly correlated with its functions [9,23–26]. In this review, we present an overview on the structure, localization and corresponding functions of NCL.

2. The structure and major domains of NCL

The NCL genes have been found in various of species and they are highly conserved across different species [27]. Most animal cells contain one NCL gene per haploid genome, whereas tetraploid species contain up to three NCL genes and plants usually contain at least two NCL genes. The human NCL gene consists of 14 exons and 13 introns on chromosome 2q12-qter [8,28]. The mammalian NCL consists of 707 amino acids and the predicted molecular mass is approximately 77 kDa [29,30]. However, due to the high content of negatively charged amino acids in the N-terminal domain, the practical molecular weight of NCL is usually between 100 and 110 kDa [31–33]. The multifunctionality of NCL mainly results from its multidomain structure. Sequence comparison from different species reveals a high degree of evolutionary conservation of this large protein, and the biophysical and biochemical research have shown that NCL which is composed of three main structural domains: the N-terminal domain, the central domain and the C-terminal domain [11]. The structures and functions of these domains

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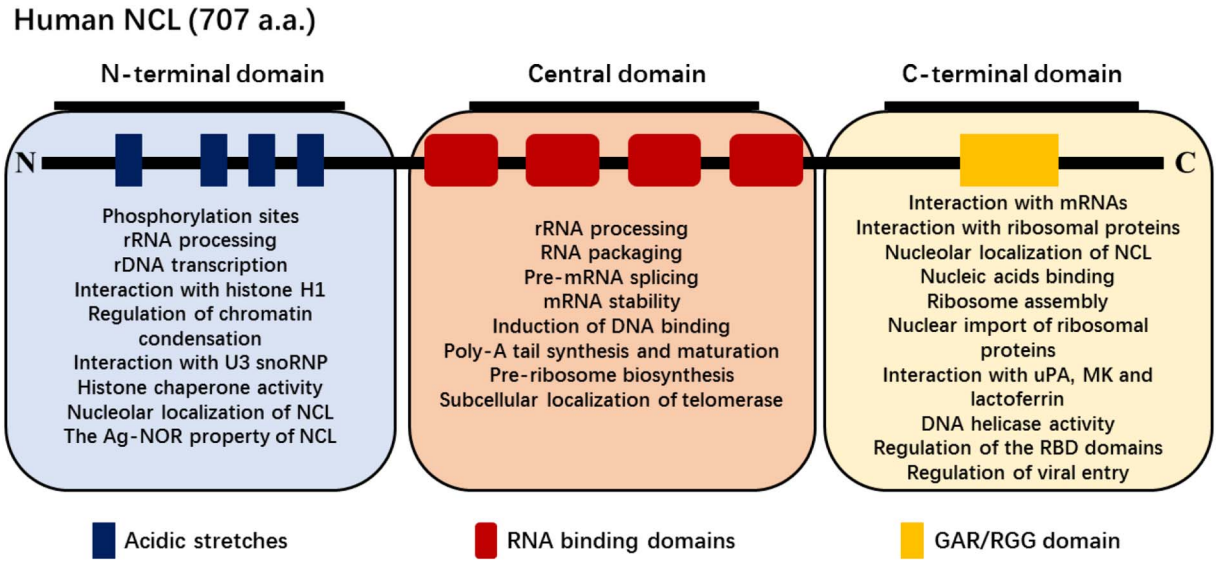

Fig. 1. Schematic representation of domain diagram of the primary sequence and related functions of human NCL protein. The blue boxes represent the acidic stretches in the N-terminal domain, the red boxes represent the RNA binding domains, and the yellow box represents the GAR domain. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

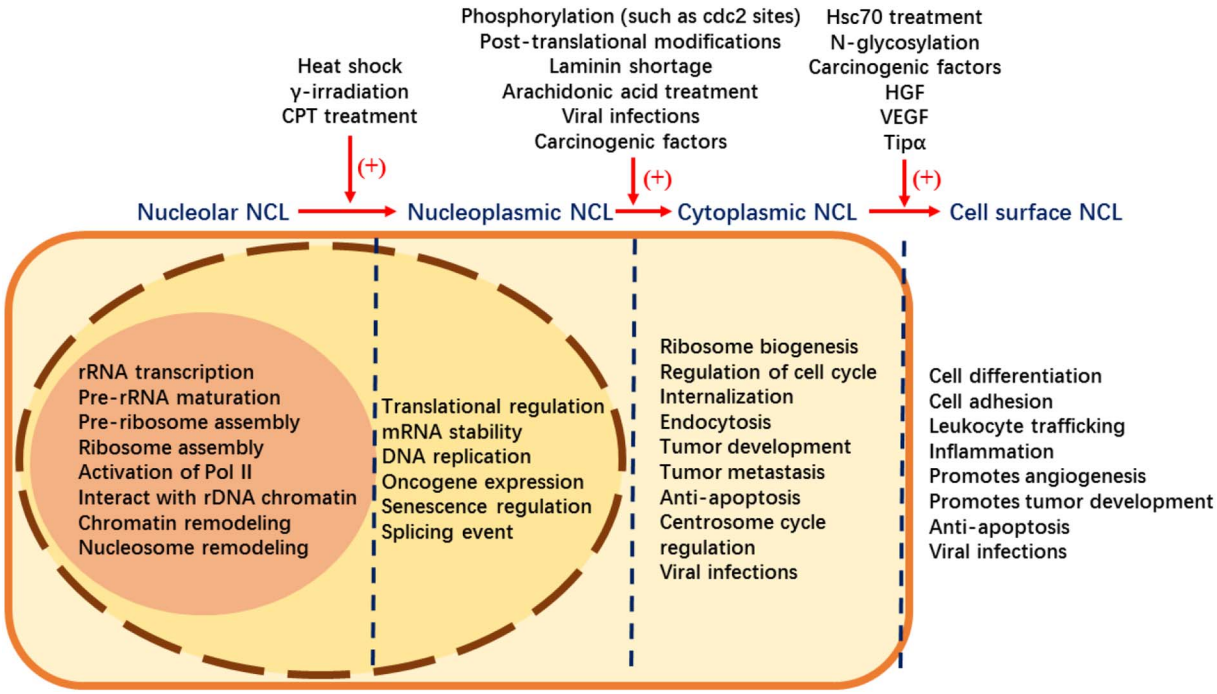

Fig. 2. The stimulation factors that induce the shuttling of NCL and related functions in different cellular compartments.

are summarized in Fig. 1.

The N-terminal domain contains acidic regions (rich in glutamic acid and aspartic acid), which are the sites of multiple phosphorylation by cell division control protein 2 homolog (Cdc2), casein kinase 2 (CK2), protein kinase C (PKC) and cyclin dependent kinase 1 (CDK1), indicating that it may functions during cell cycle [19,20,34]. The N-terminal domain participates in the transcription of rRNA, and interacts with components of the pre-rRNA processing complex. It also regulates rDNA transcription by interacting with chromatin and UTRs [35–42].

The central domain contains four RNA-recognition motifs (RRMs), which are also called RNA-binding domains (RBDs). This domain has been the focus of many studies. Research demonstrated that NCL interacts with the stem-loop structure of 18S and 28S ribosomal RNA through its first two RBDs, and this domain is responsible for the very specific interacts with RNA [43–47]. During pre-rRNA transcription, NCL acts as a chaperone by helping the pre-rRNA to fold correctly [43]. This domain is involved in a variety of biological processes such as RNA packaging, pre-mRNA splicing, poly-A tail synthesis and maturation, translational control and mRNA stability. It also serves as a component of pre-ribosomes [31,48,49]. The RBDs of NCL alter the subcellular localization of telomerase, and it is believed that the RBDs are essential for the nucleolar localization of NCL [50].

The C-terminal domain (GAR or RGG domain) is rich in arginine and glycine residues, which contains many Arg-Gly-Gly (RGG) repeats that interspersed with several aromatic amino acids [11,51,52]. Structural studies of this domain reveals that it can adopt repeated β-turns and it was initially found to be associated with the presence of an RBD. It was shown that the RGG domain is the site of N^G, N^G-

dimethylarginines modifications and interacts with nucleic acids [46,51–54]. It facilitates the interaction of NCL RBD domains with targets located within large RNA [46,54,55]. The RGG domain is also considered as a protein interaction domain, as it is involved in NCL interactions with urokinase-type plasminogen activator (uPA) and its receptor uPAR, midkine (MK) and lactoferrin [56–60]. This domain is also essential for the ribosomal assembly and nuclear import of ribosomal proteins [8].

3. Localization and related functions of NCL

The distribution of NCL is ubiquitous, mainly including the nucleolus, the nucleoplasm, the cytoplasm and the cell membrane. As is shown in Fig. 2, a variety of stimulations could alter the distributions of NCL, and the functions of NCL in different cell compartments are of great diversity.

3.1. The nucleolar NCL

NCL is an ubiquitously expressed protein that is found in various cell compartments, and the nucleolus is the major location. The initiation research of NCL began within this compartment. NCL is mainly observed in the dense fibrillary compartment (DFC) in the nucleolus, which is responsible for transcribing ribosomal DNA (rDNA) genes. The explanation of how NCL accumulates in the nucleolus has been a focus for a long time. Research found that the bipartite nuclear localization signal (NLS) of NCL (KRKKEMANKSAPEAKKKK) is responsible for entering the nucleus, the RBDs and RGG domains also contribute to its nucleolar accumulation via binding to other nucleolar components such as rRNA [9,23,50].

The phosphorylation of NCL by CK2 is involved in the regulation of rDNA transcription [11,61,62]. The argyrophilic property of this protein made it possible to quantify the abundance of NCL. As the hyperactivation of rDNA transcription is a common character of highly dividing cells, NCL is considered to be involved in the tumorigenesis by increasing rRNA synthesis and ribosome assembly [9]. Several studies suggested that NCL contributes to cell proliferation via increasing the transcriptional activity of RNA polymerase I, as the transcriptional activity of RNA polymerase I and the expression of NCL are tightly correlated to the rapidity of cell proliferation [63]. Moreover, the phosphorylation of NCL is closely correlated with increased rRNA transcription and cell proliferation, which confirmed the role of NCL in the regulation of RNA polymerase I transcription. NCL has been shown to interact with rDNA chromatin, promoter and coding region of rRNA genes [38]. Furthermore, NCL could collaborate with the chromatin remodelers and promote the remodeling of nucleosomes [35]. NCL also acts as a histone chaperone, it was found that NCL could directly bind with H2A-H2B dimers and facilitates the assembly of nucleosomes on naked DNA [64].

In addition to its role in the activation of RNA polymerase I transcription, NCL seems to be also involved in many fundamental cellular processes such as pre-rRNA maturation and pre-ribosome assembly. NCL has been shown to interact with an evolutionary conserved RNA sequence in the pre-rRNA 5′ external transcribed spacer (5′ETS), which is essential for the early cleavage of pre-rRNA and thought to be a limiting step in the primary processing reaction [65,66]. As one of the major nonribosomal proteins of the nucleolus, NCL also interacts with several ribosomal proteins through its RGG domain, the interaction between NCL and pre-rRNA is believed to be important for pre-ribosome assembly [12,42]. Interestingly, it has been demonstrated that nucleolar NCL is involved in nucleolar stress in Huntington's Disease (HD), as the mutant Htt transcript interacts with NCL and leads to down-regulation of rRNA transcription [67]. All these demonstrate that NCL is a key factor for the assembly and maturation of pre-ribosomal ribonucleoparticles.

3.2. The nucleoplasmic NCL

Usually, the nucleolar fraction of NCL represents more than 90% of the NCL cellular pool, while the nucleoplasmic compartment only contains no more than 5% of the protein [68]. In the nucleoplasm, NCL has been found to be associated with several genes transcribed by Pol II and with mRNAs, which are important to translational regulation and mRNA stability. Stress conditions such as heat shock, γ-irradiation and CPT (camptothecin) treatment could induce a dramatic redistribution of NCL from the nucleolus to the nucleoplasm in a p53-dependent manner, which may affect DNA replication and repair transiently [69]. The interaction between stress-activated nucleoplasmic p53 and NCL prevents p53 from importing into the nucleolus, resulting in its accumulation around the nuclear matrix [70]. After stress stimulation, NCL may undergo specific post-translational modification such as serine phosphorylation by casein kinase II, which will promote the interaction of NCL with RPA (Replication Protein A), and the nucleoplasmic accumulation occurs as the nucleoplasm contains a high amount of RPA. This redistribution is associated with an increased formation of NCL-RPA complex, which further prevents the initiation and elongation during DNA replication [69,71].

The nucleoplasmic NCL is also involved in the regulation of oncogene expression by interacting with the related miRNAs at a post-transcriptional level, which will subsequently promote the proliferation and aggressiveness of many kinds of tumors [72,73]. NCL may also protect cancer cells from senescence, as it associates with the telomerase reverse transcriptase subunit (TERT) in the nucleoplasm. NCL binds to TERT through interactions with its RBD and RGG domains, and this binding also involves the telomerase RNA subunit TERC. The nucleoplasmic localization of NCL is critical for the specific nucleolar localization of TERT, and the interaction between NCL and TERT participates in the dynamic intracellular localization of telomerase complex, which is important to cellular senescence [74].

The acetylated NCL (NCL-K88ac) has been found in the nucleoplasm, where it colocalized in the nuclear speckles with splicing factor SC35, indicating the nucleoplasmic NCL may be involved in the splicing event [75]. However, further research is still needed to investigate the detailed process and mechanisms.

3.3. The cytoplasmic NCL

Although NCL is mainly localized in the nucleolus, it has been demonstrated that enhanced cytoplasmic NCL is shown under a number of physiological and pathological conditions. The percentage of cytoplasmic NCL varies due to different biological processes. It is well known that ribosomal proteins are synthesized in the cytoplasmic compartment and imported into the nucleus where they are assembled with rRNA to form pre-ribosomal particles. As previously described, NCL is essential for the transcription of rDNA repeats, the modification and processing of pre-rRNA and the assembly of pre-ribosomal particles. By directly interacting with a subset of ribosomal proteins and RNA through different domains, NCL may have a direct role in the assembly of the ribosomal subunits by bringing together ribosomal proteins and RNA [23,76,77]. NCL is also known as a shuttling protein that migrates constantly back and forth between nucleus and cytoplasm [76]. Through this nucleocytoplasmic shuttling property, NCL contributes to the nucleolar-cytoplasmic transportation of ribosomal proteins and subunits [8,10,78].

The phosphorylation conditions of different domains of NCL affect the distribution of this shuttling protein. For example, the cdc2 sites on NCL may play a dual role by enhancing nuclear translocation exclusively in their dephosphorylated state and in promoting cytoplasmic localization when phosphorylated, which links the localization of NCL with cell cycle [79]. Post-translational modification of the GAR domain of NCL is also important to its nucleolar-cytoplasmic shuttling, which deserves to be further investigated. In addition, as a major component

of extracellular matrix, laminin was also found to affect the cytoplasmic localization of NCL. When cells were cultured on laminin-coated plate, NCL was mainly present inside the nucleus, while in the cells cultured without laminin, NCL was mainly observed in the cytoplasm [80].

Due to the shuttling property of NCL between the nucleus and the cytoplasm, the cytoplasmic NCL was initially suggested to be involved in the transportation of diverse molecules (as ribosomal proteins) that were required for ribosome biogenesis in the nucleolus [76]. However, further research has highlighted novel roles for NCL in the cytoplasm compartment. In addition to linking rRNA and ribosomal proteins during ribosome biosynthesis, cytoplasmic NCL has also been reported to be involved in the process of internalization. NCL is detected within cytoplasmic smooth vesicles and colocalizes with EEA1, a marker specifically associated with clathrin in early endosomes. NCL also co-localizes with lactoferrin through vesicles of the recycling/degradation pathway by an active process during internalization. Moreover, due to the property that NCL associates with the actin cytoskeleton and many membrane-anchored proteins, NCL may therefore essential to the classical endocytic pathway [56,81]. During the process of endocytosis, NCL redistributes from the membrane to the cytoplasm or even to the nucleus. Meanwhile, certain modifications of NCL may also induce NCL accumulation from cytoplasm to membrane. For example, it has been reported that the N-linked glycosylation of cytoplasmic NCL is necessary for surface NCL expression in various cells [15].

It has been reported that increased cytoplasmic expression of NCL is associated with worse prognosis for the gastric cancer patients [82]. Further research demonstrated that NCL presented anti-apoptotic and pro-oncogenic properties by regulating the stability and translation rate of mRNAs that involved in tumorigenesis. For example, a key mRNA target of NCL is p53 mRNA. NCL is involved in p53 translation by interacting with its 5′ UTR, which protects tumor cells from apoptosis [83–85]. The cytoplasmic NCL overexpression was also presented in B cells from chronic lymphocytic leukemia patients, which is related to the enhanced stability of Bcl-2 mRNA [86]. The cytoplasmic NCL is important to regulate centrosome cycle during cell proliferation. As the absence of NCL resulted to cell growth arrest, accompanied with defect in the control of centrosome duplication, which may contributes to tumorigenesis as well [87]. In addition, treatment of arachidonic acid induced phosphorylation of NCL and its accumulation from the nucleus to the cytoplasm, where it co-localized with RhoA, indicating that cytoplasmic NCL is involved in tumor metastasis [88].

3.4. The cell surface NCL

As NCL possesses neither a hydrophobic sequence nor a plasma membrane targeting sequence, the cell membrane located NCL has drown a lot of focus since it was first identified in 1990 [81,89–91]. A large number of reports presented enhanced expression of NCL on the surface of activated lymphocytes, angiogenic endothelial cells and many different types of cancer cells. Plasma membrane located NCL serves as a binding partner of several molecules implicated in cell differentiation, adhesion, and leukocyte trafficking, inflammation, angiogenesis and tumorigenesis [92–97].

The mechanism of how NCL is translocated to the plasma membrane remains unclear. Translocation of NCL to the plasma membrane may occur via a secretory pathway, and the process seems to be mediated by a variety of factors. Cell surface NCL may interact with membrane proteins that bind to phosphoinositides [98]. Hsc70 induces distribution of NCL on the cell surface via enhancing its interaction with the actin based motor protein nonmuscle myosin heavy chain (MyH9), which provides a driving force during NCL translocation [99]. Growth factors such as VEGF could induce cell surface NCL localization in a PI3K dependent manner [98,100]. It has been also demonstrated that N-glycosylation may contribute to the expression and functions of surface NCL [101].

Cell surface NCL is involved in a number of signaling pathways related to cell proliferation, cell cycle and apoptosis. NCL has been found to co-localize and interact with Fas at the plasma membrane of tumor cells. The interaction between NCL and Fas blocks Fas-FasL binding, which further prevents Fas induced apoptosis [102]. NCL interaction with Ras at the plasma membrane favors cell proliferation. As one of the most classical signaling pathways related to cell proliferation, the Ras/MAPK cascade has been strongly implicated in tumorigenesis. By binding with Ras via the C-terminal 212 amino acids, NCL significantly promotes cancer cell proliferation and tumor growth [103,104]. Treatment of endothelial cells with an antibody against cell surface NCL induced cell apoptosis and decreased Bcl-2 expression in the mRNA level, while NCL overexpression in endothelial cells significantly inhibited apoptosis and decreased the expression of pro-apoptotic BAX gene [105,106].

Thanks to its shuttling property, cell surface NCL transports its binding partners by internalization, which may account for the fact that many growth factors and their receptors related to angiogenesis and tumor growth have been found in the cell nucleus [26,107]. NCL thus act as a bridge between the cell surface and the nucleus. The interaction between cell surface NCL and its partner proteins is mutual, as the partner proteins induce cell surface accumulation of NCL, while NCL transports its partner proteins to the nucleus.

The expression of NCL at the plasma membrane is up-regulated in many tumor cells, as well as endothelial cells during angiogenesis [92,96,106,108,109]. A number of proteins that involved in tumorigenesis and angiogenesis have been shown to interact with cell surface NCL, such as hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF) and tumor necrosis factor alpha inducing protein (Tipα) [94,109,110]. Therefore, NCL might serves as a potential biomarker for cancer diagnosis and a target for cancer treatment.

4. The roles of NCL in cancer

The role of NCL in the development of cancer has received much attentions these years. Disordered accumulation of NCL is observed in various of cancers, and NCL has been demonstrated to play an important role during tumorigenesis [92,111,112].

The large nuclei are commonly seen in many cancerous cells, which indicates increased mitotic activity and are usually used for the diagnosis of tumors. To sustain a high level of protein synthesis in highly dividing cells, hyperactivation of rDNA transcription and ribosome synthesis is required [113]. Up-regulated NCL may contribute to tumorigenesis by increasing rRNA synthesis and the assembly of functional ribosomes [7–9,12,104,114]. NCL is also involved in regulating the transcription of oncogenes and tumorigenic miRNAs [115–117]. As an anti-apoptotic molecule, NCL plays an important role in cancer cell proliferation and survival [16,118–121]. NCL cooperates with a number of growth factors such as HDGF and VEGF, and subsequently activate several classical signaling pathways that involved in tumorigenesis. Moreover, NCL is highly expressed in angiogenic endothelial cells and is involved in regulating angiogenesis and lymphangiogenesis, which is essential for the metastasis of tumors [26,94,95,110,122,123]. All these properties make NCL a key factor in tumorigenesis and progress of tumors, which have been summarized in Fig. 3.

It has been demonstrated that NCL expression significantly up-regulated in a number of tumor tissues such as gliomas, thyroid cancer, breast cancer, lung cancer, gastric cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer, renal cancer, prostate cancer, cervical cancer and melanomas [82,120,122–146]. The expression and roles of NCL in different cancers are summarized in Table 1. Higher NCL expression is also observed in leukemia cells [86,147,148]. The up-regulated NCL expression, especially cytoplasmic and cell surface located NCL, is associated with worse prognosis in several tumors, while high levels of nucleolar NCL has been demonstrated to be an independent prognostic marker for better survival [82,129,149]. Moreover, research found that NCL staining of circulating tumor cells (CTCs)

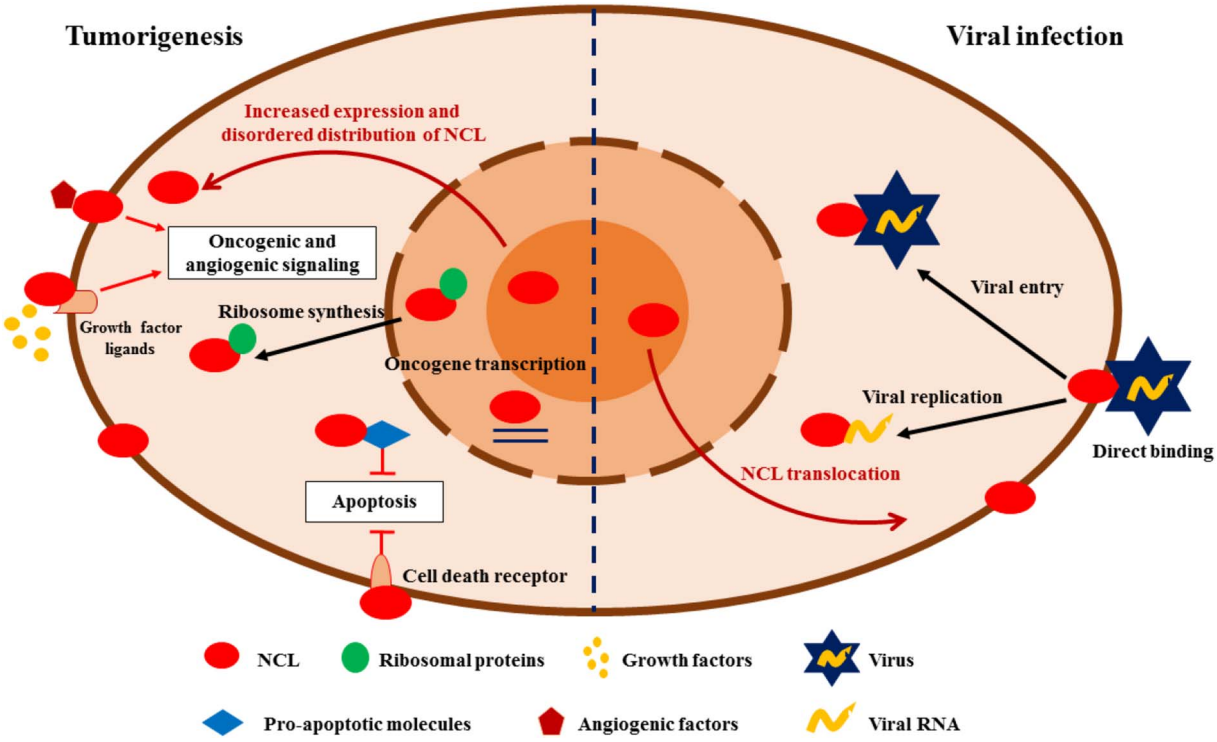

Fig. 3. The roles of NCL in tumorigenesis and viral infection. Increased expression and disordered distribution of NCL are usually shown during tumorigenesis. NCL mainly contributes to the development and progression of tumor via promoting oncogene transcription and ribosomal protein synthesis, activating oncogenic and angiogenic signaling, inhibiting apoptosis and cooperating with various of growth factors. Translocation of NCL also occurs during viral infection. NCL is involved in promoting the entry of virus and viral replication by binding with viral proteins directly.

is useful for the detection of prostate cancer CTCs [150]. Overexpressed NCL contributes to the malignant behaviors such as proliferation, invasiveness, angiogenesis and metastasis of tumor cells by activating oncogenic signaling pathways and preventing apoptosis [72,73,124,132,140,146].

The detection of AgNOR proteins by silver staining has been used for predicting the outcome of some cancer diseases for many years [151–153]. NCL is one of the most abundant silver stained protein, and its nucleolar expression is significantly up-regulated during cell proliferation [8,16,28]. Moreover, the cell surface NCL expression is increased in numerous tumor cells and in angiogenic endothelial cells [8,9,26,108,154]. Therefore, NCL is believed to be a useful biomarker in the diagnosis of tumors and a potential target for the treatment of tumors.

The clinical use of NCL for the diagnosis and treatment of tumors mainly derives from the cell surface NCL of tumor cells and endothelial cells [155–157]. Its property of tumor-specific uptake of targeted ligands is useful for the development imaging tools for the diagnosis of cancer and for the targeted release of chemotherapeutic drugs. Drugs could easily target the cell surface NCL of tumor cells and inhibit the malignant behaviors of tumor cells without affecting the physiological functions inside the cell. The multifunctional property of cell surface NCL leads to a multi-inhibitory effects during tumorigenesis and angiogenesis.

Using several in vivo and in vitro methods, several molecules with potential pharmaceutical activities targeting NCL have been developed. For instance, the AS1411 aptamer (also known as AGRO100) is G-rich oligonucleotides that can form G-quartet structures. It binds to cell surface NCL of cancer cells and subsequently suppresses NCL function by inhibiting DNA replication. The AS1411 aptamer is currently being tested in phase I study with patients with kidney and lung cancers, after it was demonstrated to significantly reduce tumor growth in xenograft models of both renal and lung cancers [137,147,158–160]. AS1411 labeled with a PET isotope can be explored as a potential diagnostic imaging agent as well. It has been demonstrated that aptamer imaging with (64) Cu-CB-TE2A-AS1411 is feasible in the detection of lung cancer [161].

Another clinical application of NCL derives from the interaction between NCL and blood vessel-specific endostatin (ES). NCL has been demonstrated to be a receptor of ES that transports ES into the nucleus, where ES suppresses NCL phosphorylation and subsequently inhibits cell proliferation [93]. The NCL-ES interaction is also implicated in the lymphangiogenesis and angiogenesis. In order to identify cancer patients who are susceptible to cancer therapies employing ES, a diagnostic kits that include antibodies against NCL are patented [95]. In addition, the cell surface NCL induces the production of specific antibodies, which might be useful in the diagnosis and treatment of high NCL expressed tumors [162].

Taken together, NCL is involved in a variety of processes during tumorigenesis. NCL serves as a promising biomarker in the diagnosis of several kinds of tumors and targeting NCL might be a potential strategy for the treatment of tumor patients.

5. The role of NCL in viral infection

Drastic reorganization of the nucleus often occurs after viral infections, which leads to the formation of viral replication compartments. The interactions between protein and nucleic acid within subcellular compartments are required during the process of viral genome replication.

A number of viral proteins have different subcellular localization and exhibit different functions, which is closely similar to that of the major multifunctional nucleolar protein NCL. Adenovirus protein V was the first protein demonstrated to be capable of inducing the nucleolar NCL accumulate in the cytoplasm, and NCL also relocated to the cytoplasm during poliovirus infection, indicating that the cytoplasmic redistribution of NCL is tightly related with virus infection [163,164]. Human cytomegalovirus viral replication factor UL84 exhibits a

Table 1
Expression conditions, functions and corresponding signaling pathways of NCL in human cancers.

Cancer types	NCL level	Sample size	Detection methods	Functions	Signaling pathways	Ref.
Glioma	Increased	Tumor tissues (n = 93) and normal adjacent tissues (n = 15)	IHC	Promotes tumor cell proliferation, colony formation in vitro and tumor growth in vivo	N.A.	[128]
Brain cancer	Increased	Primary culture of human glioblastoma cells (n = 15)	IF	Promotes cell proliferation and inhibits autophagy	Induction of G1/S transition and up-regulates cyclin D1 and B2 expression; down-regulates the expression of p62 and LC3II	[130]
Glioblastoma	N.A.	N.A.	N.A.	Promotes the proliferation, migration and tumor growth of tumor cells both in vitro and in vivo	Activates ErbB1 and cooperates with Ras	[146]
PTC	Increased	Tumor tissues (n = 100)	IHC	Promotes cell growth, migration and invasiveness	Activates CXCR4 signaling via 212 C-terminal domain	[145]
Breast cancer	Increased	Tumor tissues (n = 64)	IF	Correlates with ER expression in tumor cells	N.A.	[135]
Breast cancer	Increased	Tumor cell lines (MCF-7 and MDA-MB-231)	IF and Western blot	Protects tumor cells from death	Stabilizes Bcl-2 messenger RNA	[120]
Breast cancer	Increased	Tumor tissues (n = 332) and tumor cell lines (MCF-7 and T47D)	IHC, qRT-PCR and Western blot	Regulates the transcription of tumor suppressor RARB2	Interacts and regulates COUP-TFII	[139]
Breast cancer	Increased	Breast cancer cell lines (MCF-7, MDA-MB-231 and MDA-MB-435S)	qRT-PCR	Regulates the stem cell phenotype	N.A.	[142]
Breast cancer	Increased	Tumor tissues and tumor cell line (SKBR3)	IF and Western blot	Promotes the proliferation and colony formation of tumor cells; associates with poor prognosis of patients	Activating ErbB2	[144]
NSCLC	Increased	A549 cell line	Western blot	Induces the transformed growth of NSCLC cells	Binding with the Sp1 promoter and regulates c-Jun/Sp1-activated genes, which is essential for the PMA-regulated cPLA2α gene expression	[136]
NSCLC	Increased	Tumor tissues (n = 146)	IF	NCL expression correlates to the endothelial marker CD31 and serves as an independent biomarker to predict worse survival of NSCLC patients	N.A.	[140]
Lung cancer	Increased	A549 and NCI-H460 cell lines	qRT-PCR and Western blot	Contributes to the radio-resistance of NSCLC cells	Promotes the activity of DNA-PKcs phosphorylation sites at the S2056 and T2609	[141]
NSCLC	Increased	Tumor tissues and adjacent non-cancerous tissues (n = 225)	IHC	Cytoplasmic NCL positively correlates with DNA-PKcs and associates with worse prognosis	N.A.	[143]
Gastric cancer	Increased	Tumor tissues (n = 90) and gastric cancer cell lines (n = 5)	IHC and qRT-PCR	NCL expression is associated with metastasis, stage and differentiation, and portended poor survival outcome of gastric cancer patients	Promotes BMP2-mediated EMT via upregulating Erk1/2 and Akt	[133]
Gastric cancer	Increased	Gastric cancer cell lines (MKN-45, KATOIII, MKN-74, and AGS cells)	Cell fractionation and flow cytometry	Promotes the proliferation of gastric cancer cells	Translocating to cell surface and binds with Tipalpha during carcinogenesis	[138]
Gastric cancer	Increased	Tumor tissues and corresponding non-malignant tissues	IHC	Cytoplasmic NCL is associated with worse prognosis for gastric cancer patients	N.A.	[82]
HCC	Increased	Tumor tissues and adjacent normal tissues (n = 130)	IHC, qRT-PCR and Western blot	NCL expression is associated with aggressive characteristics and serves as a biomarker for the poor prognosis of HCC patients	N.A.	[129]
HCC	Increased	Tumor tissues and non-tumorous tissues (n = 147), HCC cell lines (n = 6)	IHC, IF and Western blot	Cell surface NCL is correlated with aggressive characteristics and poor prognosis of HCC patients; NCL promotes the proliferation, invasion and colony formation of HCC cells	NCL promotes HDGF uptake and PI3K/Akt signaling in HCC cells	[123]
PDAC	Increased	Tumor tissues (n = 47) and endothelial cells	IHC	NCL expression correlates with poor prognosis of PDAC patients; Promotes tumor growth and liver metastasis in vivo; Promotes angiogenesis	Increase the secretion and expression of angiopoietin-2 in endothelial cells	[131]
Colorectal carcinoma	Increased	Tumor tissues (n = 30) and colorectal carcinoma cell lines (HCT116 and DLD-1 cells)	IHC and Western blot	Promotes the metastatic potentials in colorectal carcinoma	VEGF induces the cell surface distribution of NCL via PI3K/Akt pathway, which promotes the EMT process of colorectal cancer cells	[122]
Cervical cancer	Increased	Tumor tissues (n = 56) and normal tissues	IHC and Western blot	Promotes the growth and invasion of cervical cancer cells	Activates EGFR signaling	[134]

Abbreviations: IHC, immunohistochemistry; IF, immunofluorescence; ER, estrogen receptor; NSCLC, non-small cell lung cancer; PTC, papillary thyroid cancer; PMA, phorbol 12-myristate 13-acetate; BMP2, bone morphogenetic protein-2; EMT, epithelial-mesenchymal transition; Tipalpha, tumor necrosis factor-alpha-inducing protein; HCC, hepatocellular carcinoma; HDGF, hepatoma-derived growth factor; PDAC, pancreatic ductal adenocarcinoma; VEGF, vascular endothelial growth factor; EGFR, epidermal growth factor receptor.

dynamic subcellular localization during infection, which is highly dependent on direct or indirect interactions with NCL [25]. NCL can also interact with lyssaviruses and plays an important role in lyssavirus infection, as the depletion of NCL inhibited viral protein expression and infectious virus production [165]. The Dengue virus capsid protein (DENV C protein) is a structural component of the infectious virion and is essential in the virus replicative cycle. Research found that the DENV C protein interacts and co-localizes with the multifunctional protein NCL during viral replication, and treatment of AS1411 or NCL siRNA results in a significant reduction of viral titers after DENV infection [166]. NCL is involved in the organization of proteins within the viral replication compartments as it is required for efficient viral DNA synthesis and interacts with the viral DNA polymerase [167]. It also acts as a transporter for the nucleocytoplasmic trafficking of viral proteins during viral infection [168].

Cell surface NCL has been shown to be involved in viral infections by promoting either virus initial attachment to the cell surface or their entry in the host cell [168–170]. It has been found that NCL serves as a cellular receptor for human respiratory syncytial virus during viral infection [171]. Cell surface NCL also mediates the binding and infection of EV71 to cells [172]. By targeting cell surface NCL, HB-19 pseudopeptides inhibit HIV attachment to the cell surface as well as subsequent viral entry into the host cells [173]. Cell surface NCL ligands such as midkine and lactoferrin also have the similar effects during viral infection [56,174]. NCL serves as a conserved cellular factor that required for the entry of multiple influenza A viruses such as H1N1, H3N2, H5N1, and H7N9. As suppression the expression or function of cell surface NCL by siRNA or blocking antibody substantially reduced influenza virus internalization [169]. The roles of NCL during viral infection were summarized in Fig. 3, and all these indicated that cell surface NCL may serve as a potential target for designing novel antiviral strategies.

6. Conclusions and perspectives

NCL is conserved in all eukaryotic organisms and distributes within various of cell compartments such as nucleus, cytoplasm and cell membrane. The high level of evolutionary conservation suggests that NCL is involved in many essential structural and functional processes [8,11]. NCL is a multifunctional protein that has been shown to interact with a variety of cell components and plays important roles in different cellular aspects such as ribosome biogenesis (including rDNA transcription, pre-rRNA synthesis, rRNA processing, ribosomal assembly and maturation), chromatin organization and stability, DNA and RNA metabolism, cytokinesis, cell proliferation, signaling transduction, stress response etc. [9,10]. It is obvious that the multifunctionality of NCL favors the cell a lot during evolution, as cells can utilize the single protein for more than one function. The multifunctionality of NCL mainly derived from its unusual multi-domain structure, post-translational modifications and its shuttling property [8,11,62].

The classical function of NCL is ribosome biogenesis, as NCL is involved in multiple steps of this biosynthetic process, revealed its key role in this highly integrated process [31,42]. The unique tripartite structure allows the interaction of NCL with different proteins and RNA sequences [12,42]. It has been demonstrated that the post-translational modulation such as phosphorylation by cdc2, CK2, p38 could regulate the distribution and functions of NCL significantly [7,8,19]. Thanks to its shuttling property, which not only transfers related proteins between the nucleus, cytoplasm and plasma membrane, but also contributes to the multi-location of NCL.

Recently, the increased expression of NCL in cancer cells, especially the apparent preferential expression of NCL on the cell surface has drawn a lot of attention [9]. Cell surface NCL leads to the development of novel strategies for the diagnosis and treatment of a number of tumors [157,175–177]. Several molecules with potential pharmaceutical activities targeting NCL related pathways have been also developed [26,92]. In addition, targeting NCL also serves as a potential method for the treatment of viral infection as NCL was demonstrated to be involved in several processes during viral infection, including the attachment and engulfment of virus, viral replication, viral protein translocations etc. [172,178].

There are still a number of interesting questions that deserved to be further investigated, such as how these multifunctions are regulated systematically? What is the detailed mechanism of the shuttling process? What is the difference between NCL that from different cellular pools and how these NCLs are well organized during specific pathological processes? Besides directing targeting cell surface NCL, chemical inhibitors target its post-translational regulators and RNA interference targeting intracellular NCL have also been proved to be effective [26,137,160]. Which is the best selection for targeting NCL? Further experimental research, as well as animal studies and clinical trials are needed to evaluate the effectiveness and safety for the anti-cancer and anti-viral treatment that targeting NCL. In closing, what about the role of NCL in other basic cellular physiological processes such as glucose and lipid metabolism? In summary, NCL is a key molecule that involved in so many important aspects that certainly worth intensive further study.

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Author contributions

Ling Gao and Wenyu Jia conceived and designed the outline of the review; Zhenyu Yao and Qingbo Guan contributed to make the table and figures; Wenyu Jia wrote the paper; Ling Gao and Jiajun Zhao revised the paper.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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