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Review Article

Nucleolin: Role in Bacterial and Viral Infections

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Abstract

Nucleolin, also called C23, is a eukaryotic phosphoprotein and 90% is found in dense fibrillary regions of the nucleolus. Additionally, it is located on the cell membrane and within the cytoplasm and performs a myriad of functions including ribosome assembly, rDNA transcription, and RNA metabolism. Nucleolin is involved in disease processes such as viral and bacterial infections, heart disease, cancer proliferation and metastases. Overall, nucleolin tends to be overexpressed in many diseases, such as cancers and viral infections but is diminished in other conditions such as Alzheimer's and Parkinson's disease. In bacterial disease, nucleolin appears to vary from organism to organism. Numerous research studies have shown that targeting nucleolin with an aptamer, such as AS1411 and HB-19, has shown promise in alleviating some of these illnesses. In this paper, we will briefly discuss nucleolin and then review its role in various bacterial and viral infections according to recent research studies.

Keywords: *Nucleolin; Bacterial Infections; Viral Infections*

The structure of nucleolin

The human nucleolin gene is comprised of 14 exons with 13 introns and spans about 11 kb [1]. The intron 11 of the nucleolin gene encodes a small nucleolar RNA, termed U20. Human nucleolin has a molecular mass of 76.3 kDa [1]. Nucleolin maintains a high degree of evolutionary conservation among different species and is comprised of three structural and multifunctional domains: An N-terminal portion that contains several acidic sections; 2 to 4 RNA-binding domains called RNA recognition motifs (RRM) in the center; and a glycine/arginine-rich domain or GAR domain at the C-terminus [2]. The N-terminal acidic and basic region and the C-terminal domain, which is abundant in RGG repeats, mediate protein-protein interactions with histone H1, U3 snoRNP, and ribosomal proteins [3].

The function of Nucleolin

The primary role of nucleolin is rRNA synthesis and ribosome biogenesis, but it has been implicated in many other tasks including gene silencing, senescence, and cell and cell cycle regulation as well as in steps of ribosomal synthesis including transcription of rDNA repeats, modifying and processing pre-rRNA, assembling pre-ribosomal particles and nuclear-cytoplasmic transport of ribosomal proteins and subunits [2-5]. Additionally, it is a DNA-dependent ATPase capable of degrading itself as well as plays a role in the regulation of cell growth, DNA replication and apoptosis [6-10].

Nucleolin in Bacterial Infection

Although the role of nucleolin in bacterial infectious diseases has not been extensively studied, it appears that nucleolin expression varies between bacterial organisms. Certain bacteria increase nucleolin expression, (e.g. *Porphyromonas gingivalis* and wild-type *Enterohemorrhagic Escherichia coli* (EHEC) strain), while others show no change (e.g. *M. paratuberculosis*) or a decrease (e.g. vt2-negative mu-

tant of EHEC O157: H7) in nucleolin expression [11-14]. Nucleolin was additionally found to be involved in the adherence of EHEC O157: H7 via intimin [15-17]. Nucleolin at wound sites was previously identified as docking partners for pathogenic bacteria and viruses [18]. Nucleolin can also be mobilized into the cytoplasm during infection, suggesting an ability to recruit and sequester cell-surface nucleolin into extracellular bacterial micro-colonies [13]. The correlation of nucleolin with bacterial strains studied are only a small percentage of those that exist, and further studies would benefit to find remedies to these unfortunate and uncomfortable illnesses (Table 1). Obtaining further data on the expression levels of nucleolin of various bacteria could allow for the determination of nucleolin-targeted therapy to eradicate certain pathogenic bacterial infections.

Bacteria Type	NCL Expression	Bacteria's Association with Nucleolin	References
Enterohemorrhagic Escherichia coli O157: H7		Adherence via intimin	[16,17]
Wild-type *enterohemorrhagic Escherichia coli* strain (EHEC)	Increased		[13]
A vt2-negative mutant of *EHEC* O157: H7	Decreased		[13]
M. paratuberculosis	No change		[11]
Porphyromonas gingivalis	Increased	Inflammatory response	[12]
L. monocytogenes or an inert particle	Not present	Nucleolin was present in the phagosomal compartment of macrophages and confirmed the importance of nucleolin expression for LVS binding, but not in an attempt of another intracellular pathogen such as L. monocytogenes or an inert particle	[14]
F. tularensis		Acts as a surface receptor for *F. tularensis* LVS on human monocyte-like THP-1 cells	[14]
Pathogenic bacteria and viruses		Docking partners with nucleolin	[18]
Enteropathogenic E. coli		Nucleolin mobilized and recruited into the cytoplasm	[13]

Table 1: *Association of Nucleolin and bacterial infection.*

Nucleolin in viral infection: More research is available on nucleolin in various viral infections compared to bacterial infections. There is a generalized process of how nucleolin helps viruses to bind and replicate within a cell. The virus can bind to translocated cell-surface nucleolin directly and then enter into the cell and replicate (Figure 1). Nucleolin can be modified via phosphorylation, methylation, and ADP ribosylation, which can alter the function of nucleolin [19].

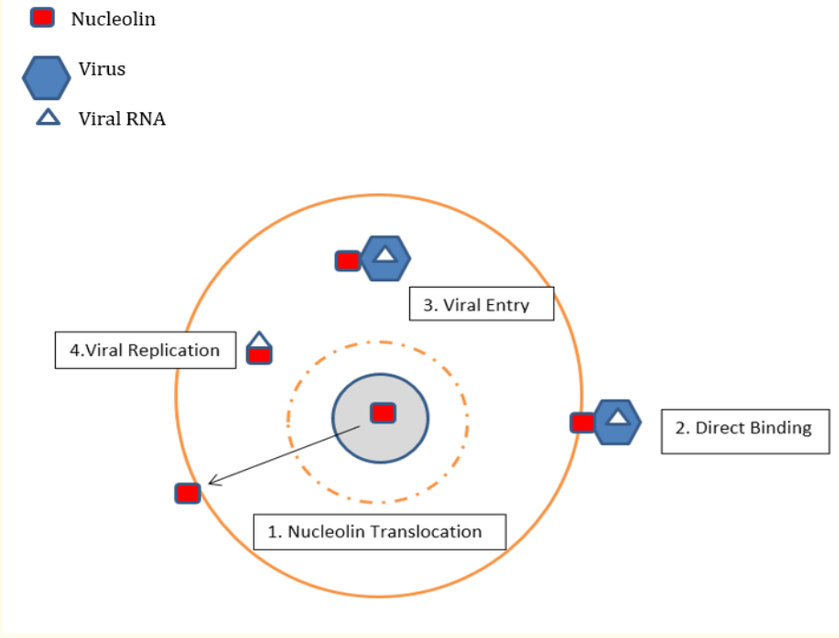

Figure 1: *Nucleolin in viral infection of a cell. During viral infection, translocation of nucleolin can occur (1), to create cell-surface nucleolin (2), and then nucleolin can promote viral entry via direct binding (3), after which, viral replication takes place and viral infection ensues (4). (Orange circle with solid line = cell membrane; orange circle with dotted line = nuclear membrane; blue circle = nucleolus).*

Currently bacterial infections can be controlled via antibiotic treatment; however, majority of viral infections often have no treatment available. Thus, studying nucleolin involvement in viruses can be beneficial to finding and creating better pharmacologic therapies for their eradication.

Nucleolin as a viral target to facilitate viral attachment in Human Immunodeficiency Virus-1 (HIV-1)

HIV is a lentivirus, which is a subtype of the family *Retroviridae*, transmitted as a single-stranded positive-sense enveloped RNA virus, which is reverse-transcribed into double-stranded DNA via a viral reverse transcriptase. HIV-1 group M viruses, which are more virulent than HIV-2 viruses, are the predominant HIV types and have caused the AIDS epidemic. The HIV-1 virus causes immunodeficiency which can cause subsequent death by cancer and/or opportunistic infections. Nucleolin appears to be a viral target, assisting viruses in attachment, and an anti-viral target.

Immunodeficiency viruses have been found to affect the nucleolin of different species of monkeys in various ways. Complex cell cycle dysregulation was reported to be associated with dysregulation of nucleolin turnover, and this was also present during simian immunodeficiency virus (SIV) infection of rhesus macaques; however, naturally, SIV-infected sooty mangabeys show normal regulation of cell cycle control that includes preserved nucleolin turnover [20]. Significant changes in nucleolar structure and post-translational regulation of nucleolin have been described in HIV [21].

Various studies have shown that nucleolin inhibitors can also block HIV replication (Table 2). Such inhibitors include V3 loop-mimicking pseudopeptide 5[Kpsi(CH2N)PR]-TASP]psi(CH2N), HB-19, and AS1411 [22-24]. There are preferential uptake and stability of HB-19 in lymphoid organ sites of HIV propagation [25]. These HIV inhibitors may one day be used as potent medications to combat HIV disease.

HIV Target	Function	References
V3 loop-mimicking pseudopeptide 5[Kpsi(CH2N)PR]-TASP]psi(CH2N)	Specifically binds to the surface of monocyte-derived macrophages and forms a stable complex with the cell surface-expressed nucleolin, as has been demonstrated to be the case in peripheral blood mononuclear cells.	[22]
HB-19	Forms an irreversible complex with cell-surface expressed nucleolin, and eventually results in degradation of these cells, implying that nucleolin is involved in the process of HIV attachment to target cells.	[23]
AS1411	Cell-surface-expressed nucleolin was observed to be an antiviral target, opening the way for the use of AS1411 as a potent and safe anti-HIV-1 agent.	[24]

Table 2: *Nucleolin and Human Immunodeficiency Virus (HIV).*

Nucleolin's involvement in the spread of Herpes Simplex Virus-1 (HSV-1)

HSV-1 is a member of the *Herpesviridae* family and is a contagious virus that produces cold sores in humans. They consist of a double-stranded linear DNA genome encapsulated in a protein capsid shaped like an icosahedron. There are two regions, the unique extended region (UL) and the short unique region (US). It is apparent via the current research that HSV-1 uses nucleolin for attachment, and viral replication and specific genes help to disperse nucleolin.

Researchers found that UL24 is involved in the HSV-1 dispersal of nucleolin, while cells infected with a UL24-deficient virus retained foci of nucleolin staining [26]. This indicates that the 24th gene of the UL may encode a gene that disperses nucleolin. VP22, a protein found in HSV-1, was found to target and surround areas of dispersed nucleolin during productive HSV-1 infection; however, altered nucleolin and marginalized chromatin were detected using a VP22-null virus, which indicated that VP22 was not responsible for the nuclear architecture alterations [27]. For active HSV-1 infection, nucleolin is required [28]. Viral replication required high levels of nucleolin expression, indicating for the first time that there is a direct role for nucleolin in HSV-1 infection [28]. A genetic link was discovered between UL24 and HSV-1-induced dispersal of nuclear nucleolin and subsequently found that the conserved N-terminal domain of HSV-1 UL24 protein is enough to induce spatial redistribution of nucleolin [29]. Fibrillarin was independent of UL24, which affects nucleolin localization [30]. Conserved residues in the UL 24 protein of HSV-1 were determined to be essential for dispersal of nuclear nucleolin [31]. Nucleolin interacted with the US11 protein of HSV-1 and is involved in its trafficking [32]. With all of this data regarding HSV-1 and nucleolin, it is apparent that a nucleolin inhibitor, such as those used in HIV-1 infection, would be of benefit to fight off HSV-1 infection.

Nucleolin as a facilitator for viral binding to host cells in Respiratory Syncytial Virus (RSV)

RSV is a syncytial virus that causes infections of the respiratory system, especially in young children. It is an enveloped virus with an RNA genome. RSV seems to bind to nucleolin and helps viral and host cell membranes to join together, and without nucleolin, RSV has difficulty infecting a host. Nucleolin was identified as a cellular receptor for human RSV [33]. RSV was found to interact with host-cell nucleolin through the viral fusion envelope glycoprotein and binds specifically to nucleolin at the apical cell surface [33]. Mouse knockdown of lung nucleolin was associated with significantly reduced RSV infection, which confirmed that nucleolin is a functioning RSV receptor *in vivo* [33]. Evidence of a cell-surface nucleolin in the respiratory tract was seen, as well as in tissues outside the respiratory tract, relating to RSV clinical manifestations [34]. The RSV glycoprotein was found to mediate the attachment of RSV to the cell membrane, which in turn improves the interaction of the RSV fusion protein with nucleolin, which helps to fuse the viral and host cell membranes [35]. Since nucleolin is a receptor for RSV, potentially, nucleolin inhibitors can be developed to prevent or even alleviate RSV infection.

Nucleolin's involvement in replication of Human Cytomegalovirus (CMV) infection

Human CMV is a member of the *Herpesviridae* family and is enveloped. It primarily infects immunocompromised hosts. Nucleolin is involved in the replication of CMV. Nucleolin was found to associate with UL44, which is a CMV DNA polymerase accessory subunit and is necessary for viral replication efficiency [36]. Nucleolin was identified as one of the nucleolar partners of CMV pp65 [37]. Host cell nucleolin is essential to maintain human CMV compartment architecture. It was shown that nucleolin bound to purified UL44 and that nucleolin is thus involved in protein organization within replication compartments [38]. Dynamic and nucleolin-dependent localization of human CMV UL84 at the periphery of nucleoli and viral replication compartments was noted [39]. Thus, blocking the UL44 subunit of CMV or nucleolin itself appears to be a potential target for pharmacological therapy.

Overexpression of Nucleolin significantly reduces the viral titers of the Influenza A virus

Influenza viruses are in the *orthomyxovirus* family, which are RNA viruses. Types A, B, and C can infect humans and can cause myalgias and upper respiratory symptoms. Influenza binds to nucleolin, and this is necessary for replication. Alternatively, nucleolin overexpression reduces the infection abilities of Influenza A. A non-structural protein 1 (NS1) of influenza A virus binds and interacts with nucleolin during the infectious process [40]. Researchers sought to investigate whether human influenza virus infection mid-pregnancy alters brain development [41]. Nucleolin mRNA was significantly decreased day 0 and day 35 in the neocortex and was drastically increased in day 35 in the cerebellum, which suggests that influenza viral infection mid-pregnancy in mice causes long-term changes in nucleolin levels [41]. Host nucleolin was discovered to be a novel partner in interaction to influenza A virus nucleoprotein [42]. Depletion of nucleolin in A549 cells followed by influenza A virus infection caused increased expression of viral protein transcripts, matrix (M1) and hemagglutinin in infected cells, while overexpression of nucleolin in cells followed by influenza A virus infection significantly reduced late viral gene transcripts as well as the viral titers [42]. Therefore, in Influenza A infection, nucleolin inhibitors may be useful to eradicate or at least reduce the progression of this disease.

Virus Type	NCL expression	Virus association with NCL	References
HIV-1		Cell-surface NCL has been recognized as a low-affinity co-receptor for human immunodeficiency virus type 1 (HIV-1) anchorage on target cells	[24]
Induced SIV infection		Dysregulation of nucleolin turnover	[20]
Naturally infected mangabeys with SIV		Preserved nucleolin turnover	[20]
HSV-1		UL24- assists in the dispersal of nucleolin	[26]
HSV-1	Increases	Nucleolin Required for efficient HSV infection	[28]
RSV		Facilitates RSV binding to host cells. It is a cellular receptor for RSV	[33]
CMV		Nucleolin was found to associate with UL44, which is a CMV DNA polymerase accessory subunit and is necessary for viral replication efficiency.	[36]
Influenza A		Influenza A virus was found to be a non-structural protein 1 (NS1) binds and interacts with nucleolin during the infectious process.	[40]
		Overexpression of nucleolin in cells followed by influenza A virus infection significantly reduced late viral gene transcripts as well as the viral titers.	[42]
		Nucleolin is a host cell surface protein for entry	[43]
Coxsackie B		Coxsackie B virus-binding protein was found to be nucleolin.	[44]
Poliovirus		Nucleolin was previously shown to translocate in the cytoplasm after infection of cells	[45]

parainfluenza virus (HPIV-3)		Cell surface-expressed nucleolin was identified as a cofactor required for efficient entry into human lung epithelial A549 cells	[46]
Hepatitis C Virus (HCV)	Elevated in Huh 7-HCV cells		[47]
Adeno-associated virus (AAV2 capsids)		Nucleolin was previously shown to interact with Adeno-associated virus (AAV2 capsids) and showed that knockdown of nucleolin mobilized capsids to the nucleoplasm and increased transduction by 10 to 30-fold.	[48]
Crimean Congo Hemorrhagic Fever Virus (CCHFV)		Human cell surface nucleolin was a putative Crimean Congo Hemorrhagic Fever Virus (CCHFV) entry factor, and it was expressed on all susceptible cells tested, but not on cell surfaces resistant to CCHFV	[49]
Feline calicivirus		Viral replication	[50]
Recombinant Norwalk virus		Viral replication	[50]
Feline calcivirus		Nucleolin is part of the feline calicivirus RNA translational complex, and for efficient feline calicivirus replication, the N-terminal region of nucleolin is required.	[51]
Japanese Encephalitis		Binding protein	[52]
Dengue virus		Nucleolin interacts with dengue virus capsid protein and is involved in the formation of infectious virus particles and that this interaction is disrupted via adding nucleolin binding aptamer (AS1411).	[53]
Enterovirus 71		Cell surface nucleolin was found to improve enterovirus 71 binding and infection as a novel binding receptor for EV71 and knockdown of cell surface nucleolin reduced EV71 binding, infectivity, and production in human cells.	[54]

Rabies virus		Mostly nuclear rabies virus phosphoprotein (P-protein) isoform P3 can localize to nucleoli and interact with nucleolin and be depleting nucleolin expression prevents viral protein expression and infectious production of the virus.	[55]
Kaposi's Sarcoma-Associated Herpes Virus		The presence of cytoplasmic nucleolin is required for protection from Kaposi's Sarcoma-Associated Herpes Virus	[56]
Epstein Barr Virus		Epstein Barr Virus uses nucleolin to establish persistent B-lymphoblastoid cell infection	[57]

Table 3: *The nucleolin role for attachment of other viruses.*

Conclusion

In conclusion, nucleolin appears to be tied to viral and sometimes bacterial survival. In viruses, nucleolin is used for entry as well as replication. Very little research has been done on nucleolin in bacterial infection and there is not enough to draw apparent correlations. However, the current research shows that nucleolin inhibitors can possibly be used pharmacologically, since most viruses and some bacteria need nucleolin to survive and replicate. Nucleolin is not a widely studied molecule, and many questions are still unanswered and further research is needed. We do not yet know the full mechanism of what causes nucleolin to, in a sense, "turn it's back" on a healthy cell and help viruses replicate. Possibly phosphorylation or methylation, or such, may ignite it. We also do not know which type of nucleolin is better to target-cell-surface vs. intracellular vs. nucleolar nucleolin. Use of nucleolin inhibitors in HIV-1 as discussed above appears to be a potential success, but clinical trials are still needed, so we still have a long way to go before it can be proven. Overall, nucleolin seems to be a promising target in viral infections and more research is needed to figure further out what this fascinating molecule can do.

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