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Nucleoside diphosphate kinase/Nm23 and Epstein–Barr virus

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Abstract

Nm23-H1 was discovered as the first metastasis suppressor gene about 20 years ago. Since then, extensive work has contributed to understanding its role in various cellular signaling pathways. Its association with a range of human cancers as well as its ability to regulate cell cycle and suppress metastasis has been explored. We have determined that the EBV-encoded nuclear antigens, EBNA3C and EBNA1, required for EBV-mediated lymphoproliferation and for maintenance EBV genome extrachromosomally in dividing mammalian cells, respectively, target and disrupt the physiological role of Nm23-H1 in the context of cell proliferation and cell migration. This review will focus on the interaction of Nm23-H1 with the Epstein–Barr virus nuclear antigens, EBNA3C and EBNA1 and the functional significance of this interaction as it relates to EBV pathogenesis.

Keywords

Nm23-H1; Epstein–Barr virus; NDPK and cell migration

Introduction

Cancer is one of the leading causes of death worldwide. The most deadly aspect of cancer is its ability to spread to the adjoining tissues, a process referred to as metastasis [1]. The first metastasis suppressor gene to be identified was Nm23, also known as NDP kinase. The Nm23 gene family encoding a closely related group of nucleoside diphosphate kinases (NDPKs) of which eight members have been identified so far in humans [2, 3]. The family is characterized by a wide variety of functions including suppression of metastasis, transcriptional regulation, differentiation, and proliferation [4]. The expression of Nm23 is divergent in some malignant tumors; however, there is enough evidence that correlate its reduced expression to an increased metastatic potential in the majority of cancer types [5].

In recent years, many cancers have been linked to viruses including EBV, Kaposi's sarcoma associate herpesvirus (KSHV), human papillomaviruses (HPV), hepatitis B virus (HBV), hepatitis C virus (HCV), and human T lymphotropic virus (HTLV-1). EBV and KSHV belong to genus Lymphocryptovirus of the human gamma herpesvirus family [6]. EBV is the first identified human tumor virus [7, 8]. EBV is a ubiquitous human gammaherpesvirus,

which infects more than 90% of the worldwide adult population. After the initial infection, EBV remains latent, mainly in B-lymphocytes, for life [6]. In most healthy individuals, EBV does not lead to any overt pathogenesis, thus ensuring the survival of both the host and the virus. However, rarely though, EBV contributes to the development of several malignancies, such as Burkitt's lymphoma (BL) [9], nasopharyngeal carcinoma (NPC) [10], natural killer cell lymphoma [11], primary effusion lymphoma [12], Hodgkin's disease [13], and X-linked lymphoproliferative disease [14, 15]. Moreover, immunosuppressed people like AIDS patients or post-organ transplant patients also have a high chance of getting EBV-associated lymphomas.

Like other herpesviruses, EBV's life cycle has a distinct latent (non-productive) and a lytic (productive) phase. In infected cells, EBV can adopt four different latency programs (0, I, II, and III). In latency type 0–II, there is expression of a part of EBV latent proteins, but latency type III shows expression of all known EBV latent proteins including Epstein–Barr virus nuclear antigen (EBNA) 1, 2, 3A, 3B, 3C and LP, and latent membrane protein (LMP) 1, 2A and 2B [6]. This latency type III is seen in AIDS-associated lymphoma, post-transplant lymphoma patients, and laboratory-derived lymphoblastoid cell lines (LCL). EBNA2 and EBNA-LP are the earliest viral proteins expressed in EBV-infected B cells [16]. EBNA1 is essential for the maintenance and segregation of EBV genome [17, 18]. EBNA-LP seems to co-stimulate EBNA2 mediated activation of cellular and viral gene expression, which has been shown to be critical for immortalization of B cells [19]. LMP1, EBNA2, EBNA3A, and EBNA3C have been shown to be absolutely essential for B lymphocyte immortalization [20–23], while EBNA3B enhanced the survival of cells prone to undergo apoptosis [24]. LMP2A has been shown to block normal B cell receptor signaling [25]. The expression of EBNA3A, EBNA3B, and EBNA3C (also known as EBNA-3, EBNA-4, and EBNA-6) against negative selective pressure by cytotoxic T cells in vivo [26] suggests an important role for these genes. All EBNA3 proteins are encoded tandemly in the EBV genome and their mRNAs are initiated at the Cp or Wp promoter. Expression of the individual genes of the EBNA3 family results in transactivation or repression of viral and cellular genes. All three proteins can bind to CBF1 or RBP-J κ , a known cellular transcriptional factor, which is important for the transformation process of B cells [27]. CBF1 and RBP-J κ proteins also bind and target the EBV transactivator protein EBNA2 and the intracellular (IC)-Notch, an effector of the Notch signaling pathway to DNA [28]. In brief, EBNA3 family plays a role as transcriptional regulators in the transformation process [29–31].

Genetic studies have identified EBNA3C as one of the genes that is absolutely required for primary B cell transformation [32]. EBNA3C is expressed in lymphoblastoid cell lines (LCLs). The basic structure of the protein sequence shows a large polypeptide of 992 amino acids with nuclear localization signals, leucine zipper domain, acidic domain, proline-, and glutamine-rich domains. EBNA3C primarily functions as a transcriptional regulator by interacting with various cellular and viral factors. It has been shown to act both as a transcriptional activator and as a repressor in transient reporter assays [33]. It inhibits EBNA2-activated transcription by direct interaction with CBF-1/RBP-J κ , a cellular transcriptional factor while it activates latent membrane protein-1 (LMP-1) promoter in the presence of EBNA2 through Spi-1/Spi-B binding sites [34]. Work from our lab implicates EBNA3C's involvement in the regulation of chromatin remodeling by targeting acetylase,

deacetylase, or other factors associated with these complexes. EBNA3C binds to transcriptional repressor complex that include histone-modifying deacetylase enzyme HDAC-1 and HDAC-2 [35]. Moreover, EBNA3C interacts with prothymosin α (ProT α) and transcriptional coactivator (p300), and these interactions modulate histone acetylase transferase activity [35]. EBNA3C has also been shown to interact with the transcriptional corepressor C-terminal binding protein-1 (CtBP-1) in vitro and in vivo [36]. These interactions with corepressors and coactivators suggest that EBNA3C can modulate gene expression (Fig. 1).

EBV and Nm23-H1

Nm23-H1 is the first known gene that regulates tumor metastasis and was identified using differential hybridization analysis [37]. The nm23-H1 gene product Nm23-H1 is the 'A' subunit of nucleoside diphosphate kinase (NDPK-A) [38]. Its expression at protein or RNA level has shown an inverse association with the metastatic potential and the patient survival index in several human cancers [39–42]. However, there are contradictory reports that positive association between Nm23-H1 level and metastatic potential was seen in neuroblastoma, osteosarcoma, and pancreatic carcinoma [43–46]. Nm23-H1 is known to form homo- and hetero-random hexamers with Nm23-H2, which is located in the nuclei and associated with chromatin [47]. Nm23-H2 binds DNA and acts as a transcriptional activator of c-myc oncoprotein [48–51]. Nm23-H1 is known to have DNA transactivation activity in the nucleus [52]. Although, it may act as a DNA transactivator, the signaling pathways and the exactly functions of Nm23-H1 in the nucleus are not clear.

We identified Nm23-H1 as a binding partner for EBV nuclear antigen EBNA3C in a yeast two-hybrid screening using EBNA3C carboxy terminus as a bait for screening [53]. The binding site identified on the EBNA3C is located within the proline- and glutamine-rich domains [33]. We tested the expression levels of Nm23-H1 in EBV-negative and -positive cells by Northern blot and Western blot analysis but did not find any significant difference [53]. Typically, EBNA3C is expressed in lymphomas associated with AIDS patients or immunocompromised post-transplant patients. However, EBNA3C has not been detected in EBV-associated carcinomas, including NPC, gastric carcinomas, Hodgkin's lymphomas, and BL. However, Dr. Kelly et al. [54] reported that about 15% of EBV positive BL biopsies and cell lines express EBNA3C. On the other hand, EBNA1, another latent antigen, which is responsible for tethering the virus episome to chromosomes, is present and can be detected in all the major EBV latent infection [6]. We hypothesized that EBNA1 may also be another binding partner for Nm23-H1. In order to confirm our hypothesis, we performed binding assays and found that EBNA1 and Nm23-H1, in fact, do interact in EBV-infected cells in vitro, as well as in vivo in LCLs [55]. Coexpression of EBNA1, along with Nm23-H1 in BJAB cells rescued the suppressive effect of Nm23-H1 in cell migration assays [55]. These interaction studies between EBNA3C-Nm23-H1 and EBNA1-Nm23-H1 provided some interesting observations. One of those was the translocation of the cellular protein Nm23-H1. Nm23-H1 primarily localizes in the cytoplasm but surprisingly when EBNA3C or EBNA1 was co-expressed with Nm23-H1, most of the Nm23-H1 translocated to nucleus and co-localized with the EBV nuclear antigens [53, 55]. This translocation was visualized in EBV-infected LCLs as well as in vitro assay. Nm23-H1 was found to bind amino acid

residues 637–675 of EBNA3C, which is flanked by the proline- and glutamine-rich domains [33]. These interactions and translocation might influence the downstream signaling pathways or affect Nm23-H1's enzymatic activities such as NDP kinase and histidine kinase activity [56–58]. These data, which EBV nuclear antigens translocate Nm23-H1, might indicate that EBV infection brings to Nm23-H1 acting as a DNA transactivator in the nucleus.

EBNA3C regulates cell cycle and Nm23-H1

EBV is a very successful pathogen with a seroprevalence of about 90% in adult population. It has evolved several strategies to subvert the cell cycle machinery. It promotes cell cycle progression following the initial infection of primary resting B-lymphocytes and can cause cell cycle arrest at the onset of the viral replicative cycle [59]. The EBV-encoded latent nuclear antigen EBNA3C has been shown to function as an oncoprotein that can cooperate with activated (Ha-) ras to transform rat embryo fibroblasts (REFs), with efficiency comparable to human papilloma viral protein, E7 [60]. It was also found that EBNA3C could rescue the suppression of this transformation by cyclin D-dependent kinase inhibitor (CDKI) p16^{INK4A} [60, 61]. It is noteworthy that viral oncoproteins E1A and E7 antagonize Rb function and are resistant to suppression by p16. This suggested that EBNA3C interacts directly or indirectly with retinoblastoma (Rb) [62]. A weak in vitro interaction between GST-Rb and EBNA3C was seen in pull down assays. However, no association was seen in in vivo experiments [60]. The molecular mechanism by which EBNA3C regulates the Rb pathway is not fully elucidated. A recent study by Knight et al. [62] showed that EBNA3C can form a stable complex with Rb in cells when the proteasome machinery is inhibited. This study also showed that EBNA3C could influence the stability of Rb by recruiting a cellular ubiquitin ligase, Skp1/Cul1/F-box complex (SCF/^{Skp2}) [63]. In contrast to this, Parker et al. [64] showed previously that EBNA3C has not role in Rb phosphorylation status and degradation pathway.

EBNA3C can also regulate cyclin/cdk complexes. Cyclin-dependent kinases (cdk) are serine/threonine protein kinases that are expressed throughout the cell cycle but their catalytic activity depends on binding with cyclins, whose levels oscillate during the cell cycle [65]. These cdk complexes phosphorylate various substrates including pRb for the progression of cell cycle. EBNA3C was shown to bind cyclin-A in in vitro pull down assays and also in in vivo coimmunoprecipitation assays in B cell line expressing EBNA3C [66]. There was enhanced cyclin A-associated kinase activity for the substrate histone H1 in cyclin A immune-complexes isolated from EBNA3C expressing U2OS cells [67]. In EBNA3C expressing BJAB cells, there was a decrease in the association of p27 and cyclin A in coimmunoprecipitation experiments compared to the control BJAB cells. This suggested that EBNA3C rescues p27-mediated inhibition of cyclin A/Cdk2 kinase activity by decreasing the molecular association between cyclin A and p27 [67]. On another cell cycle checkpoint G2/M, Krauer et al. [68] showed that EBNA-3 gene family protein expression also disrupted the G2/M checkpoint. Recently, Choudhuri et al. [69] identified the mechanism that EBNA3C disrupts G2/M checkpoint by the directly interacting with Chk2, an ATM/ATR signaling effector. Nm23-H1 can bind cellular partner STRAP (serine-threonine kinase receptor-associated protein) and interact with p53. The p53 activation was

mediated by removing Mdm2, a negative regulator of p53 from the p53-Mdm2 complex by Nm23-H1 and STRAP [70]. Nm23-H1 positively regulates p53-induced apoptosis and cell cycle arrest. Since, EBNA3C regulates and interacts with these proteins, therefore, EBNA3C plays important role for cell immortalization.

EBNA3C rescues Nm23-H1 cell migration and transcription activities

EBNA3C and EBNA1 can affect metastasis through its interaction with Nm23-H1 [53, 55]. In in vitro migration assay, EBNA3C reverses the ability of Nm23-H1 to suppress the cell migration of BJAB, a BL cell line and MDA-MB-435, a breast carcinoma cell line, when Nm23-H1 is overexpressed [53]. Detailed investigation led to the finding that this interaction is responsible for increased expression of matrix metalloproteinase-9 (MMP) and α -V integrin in promoter assays [71, 72]. MMP family proteins are involved in the degradation of basement membrane and extracellular matrix while integrins are a family of heterodimeric, transmembrane glycoprotein receptors that mediate cell-matrix and cell-to-cell interactions [73, 74]. Both proteins, MMP-9 and α -V integrin are implicated in tumor progression and metastasis [75, 76]. Complexes of EBNA3C and Nm23-H1 interact with AP1 and NF- κ B transcription factors to upregulate transcription and gelatinolytic activity of MMP9 function. Importantly, there was increased expression of MMP-9 and α -V integrin in EBV-infected B cells [77, 78]. Another EBV oncoprotein, LMP1, was also shown to increase the expression of α -V integrin and MMP-9 in LCLs [77, 79]. Therefore, it is quite possible that EBNA3C may play a delicate role in this intricate but finely tuned system that involves Nm23-H1 and is responsible for modulating metastasis.

Tumorigenesis EBV nuclear antigens and Nm23-H1

A widely accepted definition of a metastasis suppressor gene states that such a gene when expressed can inhibit the spread of cancer cells to secondary sites without affecting tumorigenicity [80]. Re-expression of a metastasis suppressor gene in a highly metastatic tumor cell line results in a significant reduction in metastatic behavior with no effect on tumorigenicity [81]. Nm23-H1, however, has also been shown to affect the growth rate of EBV latent proteins expressing cancer cells in addition to suppressing their metastasis potential [82]. Since Nm23-H1 does not appear to affect growth of tumors on its own [83], it is possible that interaction with viral proteins can play role in affecting the tumorigenic potential of Nm23-H1.

EBV infection interferes with the transactivation activity and phosphorylation of Nm23-H1

EBNA3C can regulate Nm23-H1 by enhancing its trans-activation activity [33]. Nm23-H1 has a low level of intrinsic transactivation activity when targeted to the Gal4 promoter through a Gal4 DNA-binding domain in HEK 293T cells. This activation was increased in the presence of EBNA3C [33]. Thus, the ability of EBNA3C to rescue the ability of Nm23-H1 to suppress metastasis and increase its transactivation potential is likely to be differentially regulated.

In vitro both Nm23-H1 and Nm23-H2 can be phosphorylated on S122 residue by casein kinase II (CKII) [84, 85]. Phosphorylation of Nm23-H1 induces phosphor-Nm23-H1 to make complex with H-prune and promotes cell motility [86]. These functions are all related to their NDPK activity. H-prune, which is the human homolog of the *Drosophila* prune protein known as the Killer of prune phenotype, shows a phosphodiesterase (cAMP-PDE) activity. The inhibition of this PDE activity with dipyridamole has been shown to suppress cell motility [87]. H-prune interacts with Nm23-H1 and GSK-3 β and the resulting Nm23-H1–h-prune complex have a positive influence on cell motility [88]. Another interesting function of Nm23-H1 is its ability to nick DNA after it is released from the SET complex [89].

Inflammation EBV and Nm23-H1

The latent and lytic life cycles of EBV are a result of a highly regulated interaction of EBV with its host that can be divided into three phases: (i) EBV infects human B lymphocytes and induces proliferation of the infected cells, (ii) it enters into a latent phase in vivo that follows the proliferative phase, and (iii) it can be reactivated resulting in the production of infectious viral progeny for the reinfection of other cells or transmission of the virus to another individual [90]. In healthy people, these processes take place simultaneously in different anatomical and functional compartments and are linked to each other in highly dynamic steady-state equilibrium [90]. Like other pathogenic viruses, EBV-encoded genes also have been shown to be involved in immune evasion and in the regulation of various cellular signaling cascades. One of the enzymes, which have been reported to be expressed in EBV associated tumors, is Cyclooxygenase-2 (COX-2) [91]. These authors and others have previously reported that COX-2, a key mediator of inflammatory processes, is frequently expressed in EBV-positive nasopharyngeal tumors as well as detected at higher levels in EBV positive LCLs on lipopolysaccharide (LPS) induction, when compared to EBV negative nasopharyngeal tumors or LPS-induced EBV-negative BL cell lines. These results suggest a role for COX-2 in EBV pathogenesis [82, 91]. Increased expression of COX-2 has been reported in a variety of cancers including colon cancer [92], lung cancer [93], breast cancer [94], gastric cancer [95], esophageal cancer [96], and head and neck cancer [97]. Therefore, COX-2 may play critical role in carcinogenesis. Interestingly, selective COX-2 inhibitors have been shown to reduce tumorigenesis or tumor cell growth [98–100]. Upregulation of COX-2 in cancer cells has also been linked to increased angiogenesis and metastasis [101–103]. EBV latent membrane protein antigen (LMP1) has been shown to induce COX-2 in a NF- κ B-dependent manner [91]. We have previously reported that EBV latent nuclear antigen EBNA3C in conjunction with the metastasis suppressor Nm23-H1 can modulate the expression of COX-2 through the cyclic AMP response element, and NF- κ B [82]. Prostaglandin (PG) G/H endoperoxidase synthase, also known as COX, is a key enzyme in synthesis of prostanoids (PG and thromboxanes) [104]. Of the two isoforms of cyclooxygenase, COX-1 is the constitutively expressed form and COX-2 is the inducible form [104]. The PG products derived from COX-1 activity are thought to facilitate many physiological processes [105]. In contrast, COX-2 is highly induced in a variety of inflammatory diseases and in response to cytokines, growth factors, and other tumor inducers [106–108]. COX-2 has been shown to play role in de novo infection of various

DNA and RNA viruses including herpesviruses, such as herpes simplex virus (HSV), human cytomegalovirus (HCMV), EBV, and murine gammaherpesvirus 68 (MHV-68) [109]. Rhesus cytomegalovirus encodes a COX-2 homolog emphasizing the importance of this enzyme [110]. De novo infection of herpesviruses MHV-68 and KSHV in NIH 3T3 cells and HMVEC-d cells, respectively, results in early induction of COX-2 [111, 112]. Moreover, the presence of COX-2 specific inhibitors (indomethacin) reduces viral protein expression, which can be rescued by the addition of exogenous PGE₂, a downstream product of COX-2 suggesting that the elevated levels of COX-2 in response to de novo infection can play a role in supporting viral gene expression [111, 112].

In addition to its role in de novo infection and in latent cells, recent studies from our laboratory showed that COX-2, a multifunctional moderator protein, is also capable of inducing lytic reactivation of EBV in latently infected cells. Our studies show that COX-2 induction in LCLs with LPS resulted in EBV reactivation, whereas the effect was reduced in the presence of specific COX-2 inhibitors confirming that it was not a nonspecific effect of LPS induction on other pathways. On further investigations, we found that PG receptors EP1 and EP4 are upregulated during this process suggesting a role of EP1/EP4 activated pathways. Ligand binding of EP1 is associated with protein kinase C (PKC) pathway activation, whereas EP2 and EP4 are coupled to protein kinase A/adenyl cyclase (PKA/AKT) pathway [113]. 12-*O*-tetradecanoylphorbol-13-acetate (TPA) and sodium butyrate, which are known to induce lytic reactivation of EBV also act via PKC and PKA/AKT pathway, respectively [114]. These studies points toward a similar mechanism of EBV reactivation by COX-2.

Taken together, our results demonstrate that COX-2 can activate lytic reactivation of EBV by PGE₂ pathway. Similarly, Kaufman and colleagues [115] have shown that inhibition of COX-2 synthesis also suppresses the reactivation of HSV type 1 in trigeminal nerve ganglion indicating the role of COX-2 in virus reactivation. These finding may provide an explanation as to what causes the increased risk of lymphoma in people who develop rheumatoid arthritis considering that chronic inflammation and not the anti-inflammatory treatments using COX inhibitors has been found to be connected to lymphoma risk in rheumatoid arthritis patients [116, 117]. However, the more detailed mechanism for COX-2 regulating EBV reactivation needs to be further addressed.

Conclusion

Nm23-H1 is a multifunctional protein that regulates several important cellular processes besides being a bonafide metastasis suppressor. Several studies have implicated this “master regulator” controlling cell cycle, differentiation, development, DNA regulation, and caspase-independent apoptosis. Nm23-H1 has been shown to interact with several proteins. Identifying new binding partners and discerning biological significance of their interaction is an area of active research. Recently, we reported that Nm23-H1 interacts with oncoprotein Dbl-1 [118] and the Rho family member Cdc42 [119]. Besides cellular oncoproteins, Nm23-H1 can also bind to viral oncoproteins like EBV encoded EBNA1 and EBNA3C and human papilloma virus-16 encoded E7 [120]. These interactions with viral oncoproteins suggest that impairing or undulating Nm23-H1-related functions might be critical for the

development of tumors. Future studies will focus on identifying the novel signaling pathways viruses utilize to disrupt Nm23-H1 signaling pathway. Understanding these interactions could lead to targeted therapies effective in the treatment of virally induced cancers.

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Fig. 1.

Model of Nm23-H1 and EBV nuclear antigen 3C associations. Under the Nm23-H1 existence condition, Nm23-H1 associates with many cellular proteins. However, in an EBV-infected cell environment, EBNA3C recruit several cellular proteins such as Prothymosin alpha (ProTa), p300 transcriptional coactivator for leading the immortalization, and transformation of primary cell. In EBNA3C co-expression condition, the cells showed rescue the cell migration. The example of these mechanisms is transcriptional activation of MMP9 or αV integrin