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PATHOBIOLOGY IN FOCUS

Nuclear functions of NME proteins

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The NME family of proteins is composed of 10 isoforms, designated NME1-10, which are diverse in their enzymatic activities and patterns of subcellular localization. Each contains a conserved domain associated with a nucleoside diphosphate kinase (NDPK) function, although not all are catalytically active. Several of the NME isoforms (NME1, NME5, NME7, and NME8) also exhibit a 3′–5′ exonuclease activity, suggesting roles in DNA proofreading and repair. NME1 and NME2 have been shown to translocate to the nucleus, although they lack a canonical nuclear localization signal. Binding of NME1 and NME2 to DNA does not appear to be sequence-specific in a strict sense, but instead is directed to single-stranded regions and/or other non-B-form structures. NME1 and NME2 have been identified as potential canonical transcription factors that regulate gene transcription through their DNA-binding activities. Indeed, the NME1 and NME2 isoforms have been shown to regulate gene expression programs in a number of cellular settings, and this regulatory function has been proposed to underlie their well-recognized ability to suppress the metastatic phenotype of cancer cells. Moreover, NME1 and, more recently, NME3, have been implicated in repair of both single- and double-stranded breaks in DNA. This suggests that reduced expression of NME proteins could contribute to the genomic instability that drives cancer progression. Clearly, a better understanding of the nuclear functions of NME1 and possibly other NME isoforms could provide critical insights into mechanisms underlying malignant progression in cancer. Indeed, clinical data indicate that the subcellular localization of NME1 may be an important prognostic marker in some cancers. This review summarizes putative functions of nuclear NME proteins in DNA binding, transcription, and DNA damage repair, and highlights their possible roles in cancer progression.
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The NME (NM23/NDPK (nucleoside diphosphate kinase)) family in humans consists of 10 known proteins (NME1–10), possessing NDPKs that exhibit varying levels of catalytic activity. NME1 was the first metastasis suppressor protein described,[1] defined as a protein with the ability to suppress the metastatic phenotype of cancer cells without having an impact on primary tumor growth.

The NME isoforms display different patterns of subcellular localization, found to varying degrees in the cytoplasm, cell membrane, mitochondria, and nucleus.[2] Originally thought to be primarily cytoplasmic proteins, NME1 and NME2 have both been shown to be present in the nucleus under certain conditions. The mechanism underlying nuclear translocation of NME proteins is poorly understood, as they lack a canonical nuclear localization signal. NME2 was shown to reside within the nucleus using conventional immunofluorescence microscopy,[3] a finding later corroborated using confocal microscopy.[4] Immunohistochemistry and subcellular fractionation approaches have since confirmed that NME1 is also present in the nucleus.[5–11] More recent data indicate that the presence of NME1 in the nucleus is induced by DNA-damaging agents (Puts *et al.*, manuscript in preparation),[6,10] demonstrating that the protein can be translocated to the nucleus in response to environmental stimuli. Interestingly, NME4, an NDPK member known to associate with the mitochondria, translocates to the nucleus when the mitochondrial localization signal is deleted.[12]

This review highlights and describes the biochemical functions associated with NME proteins present within the cell nucleus, such as its DNA binding, regulation of transcription, and DNA repair activities. The potential relevance of nuclear localization to the metastasis suppressor function of NME1 is also discussed.

DNA-BINDING ACTIVITY OF NME PROTEINS

DNA-Binding Activity of NME Proteins is Probably Determined by Three-Dimensional DNA Structure, and Not by Primary Nucleotide Sequence

Human NME1 and NME2 share 88% sequence homology and, thus, have similar structural and functional attributes. Both NME1 and NME2 form hexamers made from two pairs

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of stacked trimers, with each hexameric unit forming a compact α/β domain that falls into the category of $\beta\alpha\beta\beta\alpha\beta$ folds.[13] Although the so-called $\beta\alpha\beta\beta\alpha\beta$ motif is associated with many biological functions, it is found in proteins with known DNA-binding activity such as *Escherichia coli* DNA Pol I[14] and HIV I Reverse Transcriptase.[15]

Despite the high degree of sequence similarity between NME1 and NME2, their functions in the nucleus appear to differ. NME2 binds DNA *in vitro* and promotes transcription of several genes, such as *CMYC*.[16] Specifically, NME2 preferentially associates with single-stranded, poly-pyrimidine-rich, DNA sequences.[17] Further analyses with double- and single-stranded oligonucleotides suggested that NME2 bound to DNA in a structural, rather than sequence-specific manner.[18] The nuclease-hypersensitive element ($NHEIII_1$) found in the *CMYC* promoter can form a G-quadruplex that is bound by NME2, but not by NME1.[19] The NDPK activity of NME2 was not necessary for DNA binding or transcriptional activity.[20] Interestingly, NME1 did not transactivate the same genes or share the same DNA-binding properties.[16,17]

Recently, the application of high-quality, large-scale sequencing platforms has enhanced the ability of investigators to interrogate the DNA-binding capability of NME2 *in vivo*. NME2 was identified as a telomere repeat-binding protein using chromatin immunoprecipitation followed by sequencing (ChIP-Seq).[21] The ChIP-Seq approach was also used to demonstrate binding of NME2 to DNA regions associated with open, transcriptionally-active chromatin.[22] NME2 was found to bind thousands of regions in genomic DNA, with a 12-mer consensus motif present in greater than 70% of the identified sequences. The consensus nucleotide sequence motif for DNA-binding activity of NME2 consisted of a core GAGGT region flanked by G-rich sequences.[22] Interestingly, this motif was very similar to previous regions identified in the *CMYC* and *PDGFA* promoters.[16,23] These findings do not contradict the earlier model that NME2 does not bind DNA in a sequence-specific manner, but rather support the idea that some sequences may be prone to secondary structures that are the actual binding cue for NME2. Similar to previous studies that demonstrated NME proteins bound to nuclease-hypersensitive regions, DNA-binding activity of NME2 was associated with a shift in nucleosome position, coupling NME2 binding to transcriptional activation.[22] The degree to which NME1 is similar to NME2 in its sequence and/or structural requirements for DNA binding is yet to be determined.

DNA Cleavage Activity of NME Proteins

In addition to its single-stranded DNA-binding activity, NME1 and NME2 have been shown to cleave DNA. Even when bound to the same DNA elements, NME1 and NME2 appear to have different functions.[23,24] The regions bound by NME1/NME2 in the *PDGFA* gene and by NME2 in the *CMYC* gene are nuclease-hypersensitive (NHE), suggesting that both proteins interact with DNA harboring single-stranded and possibly higher-order structures. When NME1 is provided with single-stranded DNA with a free 3′-hydroxyl group it displays 3′–5′ exonuclease activity.[25] The exonuclease activity of NME1 has no apparent sequence specificity and is dependent on divalent magnesium. The 3′–5′ exonuclease activity was also demonstrated for the human NME5, NME7, and NME8 isoforms.[6] Meanwhile, NME2 does not exhibit exonuclease activity, but instead has been proposed to cleave at internal sites of NHE DNA regions.[26] One study has reported that this nuclease activity can be resolved from recombinant NME2 preparations by chromatography using size exclusion or heparin-containing matrices.[27] To date, no studies have addressed whether NME2 cleaves DNA in the context of living cells.

Site-directed mutagenesis studies suggest the 3′–5′ exonuclease activity of NME1 may be associated with its metastasis suppressor function. Point mutations that specifically disrupt 3′–5′ exonuclease activity also abolish the ability of NME1 to inhibit metastasis of human melanoma cell lines in xenograft models.[28] DNA cleavage activity of NME1 was also implicated in Granzyme A-mediated cytotoxicity,[29,30] with NME1 proposed as a component of the Granzyme A-activated SET complex. NME1 was posited to provide a DNA-nicking activity, acting as an endonuclease in regions of single-stranded DNA, which facilitates TREX1-mediated 3′–5′ exonuclease activity.[29]

DNA-Binding Functions of NME are Well Conserved

DNA-binding activity of NME proteins is evolutionarily conserved. Drosophila NME (Awd) displayed exonuclease activity *in vitro* toward supercoiled plasmid DNA, but not linear dsDNA and ssDNA.[31] Sponges, the simplest of metazoans, also express an NME protein with DNA-binding properties similar to both human NME1 and NME2. Although the NME homolog NmeGp1Sd from the sponge *Suberites domuncula* is most homologous in amino-acid sequence to NME1 in vertebrates, it binds circular, single-stranded DNA like human NME2.[32] However, in a manner more consistent with human NME1, it cannot cleave negatively supercoiled plasmid DNA.[32] Similar to human NME1 and NME2, the homolog found in corn (*Zea maize*) does not require NDPK activity to bind G-quadruplex DNA structures.[33]

ROLES OF NME1 AND NME2 IN TRANSCRIPTIONAL REGULATION

Evidence for Transcription Factor Activities of NME1 and NME2

Binding of NME1 and NME2 to single-stranded regions within the promoters of multiple genes suggests the potential for transcription factor activities. One of the first discoveries of NME involvement in transcription was the cloning and identification of NME2 as the transcription factor PuF, an activator of the *CMYC* gene.[16] As discussed above, NME2 was first discovered to bind NHEs within the *CMYC* promoter.[20] Furthermore, NME2 cleaved regions specifically within the

NHE, resulting in 3′ overhangs.[26] Subsequently, the G-rich NHE region of the *CMYC* promoter was proposed to develop a non-B-DNA confirmation, or a G4/NHEIII$_1$ complex.[19] Binding of NME2 to the G4 motif was shown to be associated with increased *CMYC* expression. NME2 also binds the NHEIII$_1$ sites located at the *CMYC* promoter, resulting in increased *CMYC* expression in a mouse adenocarcinoma cell line,[34] Burkitt's lymphoma cell lines,[35] and human HeLa and HepG2 cells.[36] Furthermore, silencing NME2 expression through siRNA,[27] and disrupting NME2 interaction with the NHEIII$_1$/G4 complex using synthetic compounds, resulted in decreased *CMYC* expression.[37,38] Taken together, these results strongly suggest a direct role of NME2 in regulation of *CMYC* gene transcription.

In addition to their transcription-enhancing functions, NME1 and NME2 act as transcriptional repressors via interactions with silencer elements in the platelet-derived growth factor A gene.[23] Similar to the *CMYC* promoter, the *PDGFA* gene contains NHEs responsible for most of its basal promoter activity. An additional NHE (5′-SHS) was identified upstream of the promoter, which serves as a binding substrate for NME1 and confers silencer activity when linked to either homologous or heterologous promoter elements.[23] ChIP analysis in the chronic myelogenous leukemia cell line K562, and the human melanoma cell line M14, has confirmed binding of NME1 and NME2 to the NHEs in the 5′-SHS region and *PDGFA* promoter region.[39,40]

The promoter region of the *TP53* gene was also identified as a potential binding site for NME proteins through ChIP analysis in the M14 cell line.[40] Although the research did not distinguish between NME1 and NME2, both proteins bind to a G-rich region of the *TP53* promoter, and, in addition, IFI16, a transcriptional repressor, binds the same regions on the *TP53* and *CMYC* promoters.[66] This suggests that transcriptional activity at both the *TP53* and *CMYC* promoters could be determined by competition for promoter occupancy between NME proteins and IFI16.[66] Similarly, the rat homolog of NME1 competes with the YB-1 transcription factor for occupancy of a similar NHE within the promoter of the gelatinase A (*MMP2*) gene.[41] Overexpression of NME1 disrupted the YB-1 interaction with the response elements, resulting in decreased *MMP2* expression in glomerular mesangial and Rat1 fibroblasts.[41] These studies establish a role of NME1 and NME2 proteins in gene regulation, and demonstrate their abilities to bind sites that may be occupied by other transcription factors. Although the mechanisms through which DNA-bound NME proteins modulate gene transcription are not well understood, the proteins may interact with transcriptional co-regulatory molecules that serve to modulate RNA polymerase II activity. Evidence for such an interaction is provided by the recent demonstration that NME1 and NME2 proteins are physically associated with a co-activator complex (OCA-S), which promotes transcription of the histone 2B gene.[42,43]

The ability of NME proteins to regulate transcription of multiple cancer-associated genes (*CMYC*, *PDGFA*, *TP53*, and *MMP2*) strongly suggests that their transcriptional functions may contribute to metastasis suppressor function. Additional transcriptional targets of NME2 were identified in the A549 adenocarcinoma cell line using ChIP–chip analysis.[43] Both vinculin (involved in the focal adhesion complex) and histone H2B were identified as potential transcriptional targets of NME2. NME2 directly binds to the vinculin promoter region, resulting in transcriptional silencing, and reducing metastatic potential of lung cancer cells.[43] The analysis also detected regulation of histone 2B expression by NME2, and binding of NME2 was localized to sequences within the histone 2B promoter region.[42,43] Taken together, these results suggest that NME1 and NME2 may regulate gene transcription via control of epigenetic mechanisms.[42]

Potential Co-regulator Functions of NME1 and NME2

NME1 and NME2 have been shown to interact physically with other transcription factors.[44] A recent study proposes that NME2 activates *CMYC* transcription not by binding the *CMYC* promoter directly, but indirectly through binding to the zinc-finger-binding protein, CNBP,[45] which has been shown to bind and stabilize G-quadruplex structures adopted by NHEIII$_1$ regions in the *CMYC* promoter. NME1 has been reported to inhibit cyclin D1 expression indirectly through physical interactions with the transcription factor AP1, leading to cell cycle arrest and TP53-dependent apoptosis in B cells.[46] Both NME1 and NME2 associate with estrogen receptors in the ERα-positive breast cancer cell line MCF7, resulting in differential regulation of estrogen-responsive genes.[47,48] The NME1–ERα interaction was shown to facilitate interactions with estrogen response elements, resulting in decreased expression of Bcl-2, cathepsin D, and cyclin D1. NME2 specifically binds estrogen receptor β, and a synergistic decrease in cell migration was observed with both NME2 expression and estradiol treatment.[48] Taken together, these studies demonstrate that NME1 and NME2 are able to interact not only with transcriptional elements but other transcription factors as well, perhaps as either transcriptional co-activators or co-repressors.

Interactions of NME1 with transcription factors may influence the expression of genes associated with metastasis. NME1 interacts with oncogenic viral antigens of the Epstein-Barr virus.[49] NME1 interactions with the EBNA3C viral antigen resulted in increased translocation of NME1 from the cytoplasm to the nucleus, leading to increased transcription of the tumor-associated gene COX-2, through interactions with transcription factor-binding sites NF-κB and CREB/Ap-1.[49] NME1 and EBNA3C binding allows NME1 to bind transcription factor GATA-1, and EBNA3C to bind transcription factor SP-1, in a transcription factor complex.[50] Collectively, this complex induces transcriptional expression of alpha V integrin, associated with highly migratory cancer cells. In the absence of EBNA3C, NME1 is still able to bind

GATA-1, but alpha V integrin expression is repressed, suggesting a decrease in cell migration.[50] While the studies show that interactions of NME1 with oncogenic viral antigens can lead to expression of genes that regulate metastasis, they also demonstrate a very complex role of NME1 and NME2 in transcriptional regulation of genes that may be context- and cancer cell-type-specific. Table 1 summarizes the direct and indirect functions of NME1 and NME2 on transcription. The target genes of NME1 and NME2 are suggestive of a transcriptional program by which these proteins may suppress metastasis.

NME PROTEINS AND DNA REPAIR

The 3′–5′ exonuclease activity of NME1[25] suggests that it may contribute to DNA recombination and repair. Exonucleases are usually associated with proofreading of DNA, either during replication by polymerases that possess exonuclease activity, or by autonomous exonucleases such as RAD1, RAD9, MRE11, and TP53 during DNA repair.[51] The 3′–5′ exonuclease activity of NME1 was extended to the NME5, NME7, and NME8 isoforms, particularly in the presence of the base excision repair proteins APE1, UDG, and NTH.[6] Exonucleases are responsible for excision of misrepaired and damaged nucleotides, permitting resumption of stalled DNA replication or repair.[51] Consistent with this, 3′ single-stranded overhangs provided the strongest substrate for NME1.[6,25]

NME1 is translocated to the nucleus in response to DNA damage induced by cisplatin or etoposide,[6,52] UV irradiation,[6,10] bleomycin, and gamma irradiation (Puts *et al.*, manuscript in preparation), further suggesting a role in the DNA damage response. In addition, when NME1 expression was forced in melanoma cell lines with low expression of endogenous NME1, expression of many DNA repair genes was downregulated in response, including RAD51, HUS1, MLH1, BRCA1, PCNA, FEN1, POLθ, and MBD.[52]

Our laboratory reported that NME1 promotes repair of UV-induced DNA lesions, particularly the removal of 6-4 photoproducts, to which NME1 translocates.[10] This process is mediated almost exclusively by the nucleotide excision repair (NER) pathway, providing evidence of a role for NME1 in the repair of single-stranded DNA lesions. Mutations disrupting both the 3′–5′ exonuclease and NDPK activities of NME1 inhibited repair of UV-induced 6-4 photoproducts. Moreover, NME1 suppressed the incidence of both spontaneous and UV-induced mutations in cultured cells. Importantly, mice deficient in NME1 and NME2 are sensitized to UV-induced melanoma *in situ*, consistent with its contribution to NER.[10]

We are currently investigating the role of NME1 in DNA double-stranded break repair (DSBR), given its requirement for 3′–5′ exonuclease activity. In this regard, 3′–5′ exonucleases, such as Mre11, are known to be required for both the non-homologous end-joining (NHEJ) and homologous recombination (HR) pathways of DSBR.[53] We have recently obtained evidence for DSB-induced association of NME1 with

Table 1 Direct and indirect transcriptional targets of NME1 and NME2

NME isoform	Gene target	DNA-binding target	Interacting protein(s)	Mechanism	Regulation	Ref.
1	*PDGFA*	NHE Promoter, 5′-SHS silencer	–	Direct	Activation, repression	23,24,39,40
1	*TP53*	Promoter	–	Direct	Activation	66
1	*MMP2*	Promoter	Blocks YB-1	Direct	Repression	41
1	*CCND1*	Promoter AP1 element	AP1	Indirect	Repression	46
1	*CTSD*	ERE	Enhances ERα–ERE interaction	Indirect	Suppresses ERE activity	47,48
	BCL2					
	CCND1					
2	*CMYC*	NHEIII$_1$ Promoter	CNBP	Direct	Activation	16,19,34–36,45
2	*PDGFA*	NHE promoter, 5′-SHS silencer	–	Direct	Activation, repression	23,24,39,40
2	*VCL*	Promoter		Direct	Repression	43
2	*CTSD*	ERE	ERβ	Indirect	Enhances ERE activity	47,48
	BCL2					
	CCND1					
2	*PTGS2*	NF-κB, CREB, AP1 motifs	NF-κB, CREB, AP1 via EBNA3C	Indirect	Activation	7
2	*MMP9*	NF-κB, AP1 motifs	NF-κB, AP1 via EBNA3C	Indirect	Activation	67
2	*ITGAV*	GATA-1, SP1 motifs	GATA-1, SP1 via EBNA3C	Indirect	Activation	50
2	*ITGAV*	GATA-1 motifs	GATA-1 alone	Indirect	Repression	50

factors involved in DSBR, and have demonstrated direct recruitment of NME1 to DSBs (Puts *et al.*, manuscript in preparation).

In addition, we are investigating which enzymatic activity of NME1 is predominantly responsible for the role of the protein in DSBR, and are using mutants to both the 3′–5′ exonuclease and NDPK activities to study the impact on our DNA repair assays. The obvious candidate is the 3′–5′ exonuclease activity, given the well-documented role of these enzymes in DSBR.[51] The NDPK activity of NME1 may also contribute by ensuring that NTPs are replenished and maintained during DSBR. Ribonucleotide reductase protein (RNR) is recruited to sites of DNA damage and is required for maintenance of dNDP supply during DNA repair.[54] NME3 has been shown to associate directly with the RNR complex via a physical interaction with TIP60, a histone acetyltransferase, and to be recruited to sites of DNA damage.[55] This complex was proposed to maintain local concentrations of dNTPs for repair of DNA damage. It remains to be seen whether NME1 is also recruited to the RNR complex, and, if so, whether this is indicative of a role for NDPK activity in DSBR. It will be of interest to determine whether NME proteins are recruited to the nucleus to provide 'fuel' in the form of NTPs for DNA repair, gene transcription, and other processes within the nucleus. In this regard, NME1, NME2, and NME4 interact with dynamin family proteins to provide GTP as fuel for activation of endocytosis and mitochondrial fusion.[56]

Given that the 3′–5′ exonuclease activity of NME1 has been implicated in its suppression of metastasis,[28] a fundamental question that remains is whether the DNA repair function of NME1 is necessary for inhibition of metastasis. Reduced expression of NME1 could lead to accumulation of mutations and increase in genomic instability through disruption of DSBR pathways, eventually leading to metastasis-driving mutations.

POTENTIAL MECHANISMS OF NME TRANSLOCATION TO THE NUCLEUS

Although nuclear localization of both NME1 and NME2 has been demonstrated, the mechanism by which the proteins move from the cytoplasm to the nucleus is yet to be determined. NME4 is localized to the mitochondria via an N-terminal-specific sequence,[57] and also contains an RRK motif that is responsible for the binding of NME4 to phospholipid membranes.[58] Acetylation of this motif promotes localization of NME4 to the mitochondria, whereas a deacetylated form of NME4 no longer moves to the mitochondria, but rather is found in the nucleus.[12] Therefore, post-translational modifications to NME1 and NME2 could promote nuclear translocation in a similar manner.

Alternative mechanisms have been proposed for the nuclear translocation of NME2, including association with carrier proteins that do possess a nuclear-localization signal.[4] In addition, as mentioned above, the interaction of NME1 with the viral antigen EBNA3C resulted in increased translocation of NME1 from the cytoplasm into the nucleus.[49] Given that NME2 was found to bind DNA as a dimer of just 35 kDa,[59] it was further postulated to freely diffuse through the nuclear pore complex, which is permissible for proteins smaller than 40 kDa.[59,60]

NME1, NME2, and NME4 have all been identified in association with artificial membranes, which in theory could promote their ability to translocate into various organelles. Structural determinants of the membrane-associating activities of NME1, NME2, and NME4 were recently described.[61] NME2 was able to bind negatively charged lipid membranes, and NME4 could bind both negatively charged and zwitterionic lipid membranes. However, NME1 was unable to bind to these lipid membranes, which was attributed to a higher ratio of negatively charged amino acids present at the surface of the conserved membrane-binding domain. Furthermore, NME1 demonstrated lower hydrophobicity at the surface than NME2 and NME4, which could lower its affinity for hydrophobic components in cellular membranes.[61] These results strongly suggest that nuclear translocation of NME1 requires active transport via physical interactions with other proteins (eg, Ran cycle proteins and NLS-containing proteins such as importins) and possibly lipids within the nuclear envelope.

NUCLEAR NME1 AS A POTENTIAL PROGNOSTIC MARKER IN CANCER

High levels of NME1 protein expression in specific cancer types (eg, melanoma, liver, and breast) correlate with low metastatic potential.[62,63] However, in some cancer types (eg, gastric and neuroblastoma) an increase in NME1 expression correlates with more aggressive tumors.[64,65] Localization of NME1 in these and other cancers may be a useful indicator of tumor prognosis.[9]

Nuclear localization of NME1 has been demonstrated in several different cancer types using immunohistochemical analysis. In prostate cancer cell lines, higher levels of nuclear NME1 correlated with lower metastatic potential,[9] suggesting that the extent of nuclear NME1 may affect cancer progression. However, NME1 expression seemed to be a marker for poor overall prognosis regardless of cellular location.[9] Nuclear NME1 was observed at a higher frequency in invasive ductal carcinoma and invasive lobular carcinoma node-positive patients compared with node-negative patients, suggesting that nuclear NME1 may be a useful prognostic marker for poor outcome in breast cancer.[8] The contribution of nuclear NME1 to the poor prognosis of breast and prostate cancer[8,9] patients is currently unclear. In contrast, nuclear NME1 correlates with a favorable prognosis in laryngeal carcinoma patients.[11]

SUMMARY AND PERSPECTIVE

NME proteins are not only able to translocate to the nucleus, but also perform specific functions in the nuclear compartment. A summary of putative functions of nuclear NME

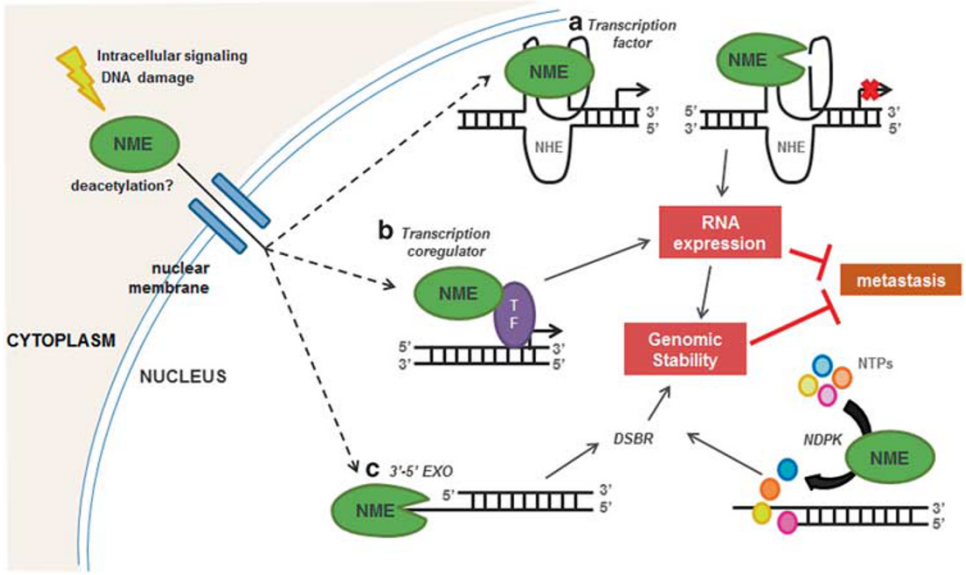

Figure 1 Summary of nuclear functions of NME proteins. In response to environmental stimuli, such as DNA damage, NME proteins translocate into the nucleus via an as yet unknown mechanism. Nuclear NME proteins may execute a variety of functions, including (**a**) direct binding and cleavage of DNA in promoter regions of genes with specific secondary structure, such as nuclease-hypersensitive elements (NHE), to either promote or inhibit transcription; (**b**) binding to transcription factors to indirectly influence gene expression; and (**c**) recruitment to double-stranded breaks, either contributing to end resection via 3′–5′ exonuclease activity (3′–5′ EXO), or contributing via nucleoside diphosphate kinase (NDPK) activity to the local pool of nucleoside triphosphates (NTPs) required for polymerase-mediated 'fill-in' steps of double-stranded break repair (*DSBR*).

proteins is shown in Figure 1. Both NME1 and NME2 bind DNA, with NME2 exhibiting putative cleavage activity against double-stranded DNA substrates, whereas NME1, NME5, NME7, and NME8 possess 3′–5′ exonuclease activity with a preference for single-stranded DNA. A body of evidence implicates both NME1 and NME2 as transcriptional regulators, acting directly as DNA-binding transcription factors, as well as displaying indirect effects on gene expression programs. Furthermore, both NME1 and NME3 are involved in DNA repair, being specifically recruited to sites of DNA damage. Clinical data imply that the subcellular localization of NME1 could be an important prognostic marker in cancers, at least in a context-specific manner. Taken together, these observations of the nuclear functions of NME proteins may provide important insights into the mechanism underlying its metastasis suppressor function.

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DISCLOSURE/CONFLICT OF INTEREST

The authors declare no conflict of interest.

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