MINIREVIEW

Nm23/NDP kinases in hepatocellular carcinoma

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Abstract One of the most aggressive cancers is hepatocellular carcinoma, which is associated with a very poor patient outcome due to a high recurrence rate and metastatic spread. NM23, the first metastasis suppressor gene to be identified, has been widely studied in human cancers. However, conflicting results have been obtained depending on the tumor type and the evaluation protocol. The current knowledge of NM23 as a diagnostic and/or prognostic marker in hepatocellular carcinoma is reviewed herein. Most studies demonstrate an inverse association between the expression of NM23-H1 and the metastatic potential, which is not observed with the closely related NM23-H2 isoform. Transfection of metastatic hepatoma cells with NM23 reduced their metastatic potential, as for other tumor cell lines. The demonstration of a causative role of NM23 in metastatic dissemination in a mouse model of hepatocarcinoma suggests that hepatocarcinoma-derived cells could be good models for the analysis of the molecular mechanisms involved in NM23 action.

Keywords Hepatocellular carcinoma · Nucleoside diphosphate kinase · Nm23 · Metastasis · Liver cancer

Introduction

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide with a prevalence which is high in Asia and Africa and is still lower but increasing in North America and Europe (El-Serag, 2004). HCC is associated with a very poor patient outcome (less than 20% five-year survival) due to late detection, a high recurrence rate after surgery, intrahepatic metastases and less common dissemination to other organs. The dominant etiologies of HCC include chronic infection by hepatitis B and C viruses, dietary exposure to aflatoxin and excess alcohol intake (Buendia, 2002). There is a direct link between HCC development and chronic inflammation of the liver, which leads to fibrosis and, in most cases, to cirrhosis but the mechanisms are still poorly understood. Stepwise changes occur during hepatocarcinogenesis *i.e.* alterations in the liver structure generating necrosis, regeneration and genetic alterations leading to foci and nodules of dysplastic and then malignant hepatocytes. The high rate of recurrence and the very low survival rate of HCC patients render urgent the development of prognostic and diagnostic markers. The many studies reporting genetic alterations accompanying HCC development point to a high genomic heterogeneity (Thorgeirsson and Grisham, 2002). Many genes are altered but the frequency of individual gene mutation is low. However, most HCC are due to mutations or loss of heterozygosity (LOH) in genes controlling four main regulatory pathways namely p53, beta-catenin, TGF-β and RB1 (Ozturk, 1999) and also to deregulation of the insulin and insulin-like growth factor (IGF) pathways (Scharf and Braulke, 2003; Boissan et al., 2005a).

NM23

It is now assumed that metastasis can be controlled by two categories of genes, metastasis promoters and suppressors. A dozen metastasis suppressor genes (Shevde and Welch, 2003) have been reported since the discovery of the first one, NM23, in 1988 (Steeg et al., 1988). Up to now, few studies had focused on deregulation of metastasis suppressors in

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HCC. Examples are NM23 which is the object of this review and, more recently, the tetraspanin KAI1 (Guo et al., 1998) which suppresses integrin induced invasion (Sridhar and Miranti, 2005) and HTPAP, a phosphatidic acid phosphatase of a still unknown role in metastasis (Wu et al., 2005). TIP30 was reported as a metastasis suppressor in a small cell lung carcinoma cell line (v-SCLC) in which its ectopic expression induced NM23-H2 (Xiao et al., 2000) but in HCC, TIP30 was rather a suppressor of tumorigenesis (Ito et al., 2003) and its relationship to NM23-H1 expression is not known.

In humans, there are now nine genes encoding Nm23 related proteins (reviewed in: Lacombe et al., 2000; Sadek et al., 2003) but the two most abundantly expressed and the most studied genes are NM23-H1 and NM23-H2, also named NME1 and NME2. They encode, respectively the A and B subunits of nucleoside diphosphate kinase (NDPK), which possess 88% identity in their amino acid sequences. The murine orthologs NM23-M1 and NM23-M2 encode proteins sharing, respectively 94 and 98% identity with their human counterparts. Since their discovery, clinical studies concerning NM23 expression, mainly NM23-H1, at the protein or mRNA levels in different types of cancer have been widely reported. An inverse association between its level of expression and the metastatic potential was observed for some types of human solid tumors such as melanoma and breast cancer, colon and liver carcinoma (for reviews: Hartsough and Steeg, 2000; Ouatas et al., 2003; Steeg, 2003). However, other studies into these tumor types failed to show such a relationship. On the contrary, either no correlation or a positive association between tumor aggressiveness and NM23 expression has also been reported for several cancers such as testicular, prostate, thyroid, endometrial and renal cell carcinoma, hematologic malignancies and neuroblastoma. The metastasis-suppressive activity of NM23H1/M1 was confirmed in aggressive tumor cell lines forced to overexpress NM23-H1 or NM23-M1, which displayed reduced metastatic potential in experimental models (Leone et al., 1991; Suzuki et al., 2004). Several studies point to a dual role for NM23-H1 in tumor progression, with early overexpression in the primary tumor (Lacombe et al., 1991), and a loss of expression at later stages, associated with metastatic spread (Martinez et al., 1995; Bertucci et al., 2004).

This review will now focus on the significance of the expression pattern of NM23 in hepatocellular carcinoma, one of the most fatal cancers worldwide.

NM23 in hepatocellular carcinoma

Clinical studies

Most HCC cohort studies, summarized in Table 1, have been published by laboratories in Asia due to the high incidence of liver cancers in this region. NM23-H1 and sometimes NM23-H2 expression have been assayed at the mRNA level (by RT-PCR, Northern blot or *in situ* hybridization) and/or at the protein level (determined by immunohistochemistry or Western blotting). The metastatic potential has been defined in several ways, by patient survival, disease recurrence, clinical prognosis, presence of metastases (lymph nodes, intrahepatic or distant metastases) or by histopathological characteristics of the primary tumor. Thirteen out of the 16 studies that we found, to the best of our knowledge, reported an inverse association between NM23-H1 expression and the metastatic potential of HCC.

The first study on the relationship between NM23 and HCC was performed by Nakayama et al. (1992). They reported that, when considering cases with and without distant metastases (mainly to the lung and bones), the Nm23 protein in primary sites was significantly less expressed in patients with distant metastases than in patients free of distant metastases (Nakayama et al., 1992). The staining was also less intense at metastatic sites than in primary sites. The study of Yamaguchi et al. (1994) reported that patients with Nm23-H1 negative tumors had a greater relative risk of death compared with those with Nm23-H1 positive tumors. Another report has shown that most of patients without disease recurrence during a 30-month median follow-up showed an overexpression of the NM23-H1 mRNA levels in HCC compared with the non-tumoral surrounding liver (Boix et al., 1994). A positive association of Nm23 protein level with good prognosis of HCC patients was reported by Tang et al. (1998) and by Xiao et al. (2002). Five studies concerned the relationship between NM23 expression and the incidence of intrahepatic metastases (Yamaguchi et al., 1994; Iizuka et al., 1995, 2003; Zheng et al., 1998; Fujimoto et al., 1998). All these studies have shown an inverse relationship between NM23-H1 expression (mRNA and protein) at primary sites and the rate of intrahepatic metastases, which is one of the most important prognostic factors of HCC. In addition, Nm23 was expressed at a significantly lower level in metastatic sites than in primary sites. Huang et al. (1998) considered dissemination of tumor emboli in the portal vein, metastases in portal lymph nodes and in lungs while Xiao et al. (1998) considered tumor emboli in the portal vein and lymph nodes. These authors showed that the expression level of Nm23 was significantly lower in cases of HCC with metastatic dissemination than without. In a study involving 81 patients, Nanashima et al. (2004) observed that the disease-free survival after hepatic resection of HCC patients with a low Nm23 expression in the tumor sample was significantly shorter compared to those with high Nm23 expression. In accordance with this study, Liu et al. (2005) reported that 63% of patients with a low tendency of recurrence showed high expression of Nm23-H1 whereas only 21% of patients with a high tendency of recurrence showed such high Nm23 expression. From these

Table 1 NM23 in human hepatocellular carcinoma

Refs	N^a	Methodology^b	Isoform^c	Inverse association with metastatic potential
Nakayama et al. (1992)	30	IHC	H1	Yes
Yamaguchi et al. (1994)	25	IHC	H1 and H2	Yes (H1)
Boix et al. (1994)	17	NB	H1	Yes
Iizuka et al. (1995)	30	RT-PCR, WB	H1 and H2	Yes (H1)
Fujimoto et al. (1998)	34	NB, IHC	H1	Yes
Huang et al. (1998)	24	IHC	NS	Yes
Lin et al. (1998)	18	RT-PCR	H1	No
Shimada et al. (1998)	27	IHC	NS	No
Tang et al. (1998)	87	IHC	NS	Yes
Xiao et al. (1998)	33	ISH	H1	Yes
Zheng et al. (1998)	25	RT-PCR	H1	Yes
Xiao et al. (2002)	57	IHC	NS	Yes
Iizuka et al. (2003)	24	IHC	H1 and H2	Yes (H1)
Nanashima et al. (2004)	81	IHC	H1	Yes
Liu et al. (2005)	33	IHC	H1	Yes
Cui et al. (2005)	30	IHC	NS	No

^{a}N, number of patients in the cohort.
^{b}IHC, immunohistochemistry; ISH, *in situ* hybridization; NB, Northern blot; RT-PCR, reverse transcribed polymerase chain reaction; WB, Western blot
^{c}H1, NM23-H1; H2, NM23-H2; NS, non-specific antibodies or antibody specificity not given.

results, it appears that the selective detection of the Nm23-H1 protein using specific anti-Nm23-H1 antibodies may help increase the accuracy in predicting recurrence of HCC.

Concerning NM23-H2, its expression was not associated with metastatic potential (Yamaguchi et al., 1994; Iizuka et al., 1995, 2003), suggesting that the Nm23-H1 isoform may correlate better with metastasis suppression of HCC than the Nm23-H2 isoform and that the biological function of Nm23-H2 is distinct from that of Nm23-H1.

Interestingly, many studies also reported a higher level of Nm23-H1/H2 in neoplastic lesions as compared to the uninvolved surrounding liver. Indeed, Nakayama et al. (1992) reported overexpression in more than half of the HCC. Also, in 83% of HCC examined by Lin et al. (1998), the NM23-H1 mRNA level was higher in tumor tissues compared with the adjacent non-tumor tissues. Shimada et al. (1998) and Cui et al. (2005) also observed that the neoplastic tissue overexpressed Nm23 proteins as compared to non-tumor tissue. Taken together, these data indicate that NM23 expression increases during formation of the primary tumor and then decreases when the tumor becomes metastatic. However, no correlation between the intensity of Nm23 expression in HCC and tumor size or number of lesions in the liver could be observed (Nakayama et al., 1992; Yamaguchi et al., 1994; Liu et al., 2005). We have also noted in recent microarray analyses an increase in NM23-H2 in HCC (Shirota et al., 2001) and in active cirrhosis associated with HCC (Zindy et al., 2005). Proteomic analysis of sera identified autoantibodies against Nm23-H1 from 14% of patients with HCC but not in sera from healthy individuals or from patients with chronic hepatitis, perhaps relevant to the overexpression of Nm23 in HCC (Le Naour et al., 2002).

It should be mentioned that three studies (Lin et al., 1998; Shimada et al., 1998; Cui et al., 2005), reported no correlation between the level of NM23 expression and the metastatic potential of HCC. The study by Lin et al. (1998) evaluated the NM23-H1 transcript by RT-PCR while Shimada et al. (1998) and Cui et al. (2005) used immunohistochemistry to evaluate the Nm23 proteins. For the latter studies, the specificity of the antibodies was not indicated and cross-reactivity with Nm23-H2 could not be excluded.

Very little data is available about the mechanisms responsible for the change in NM23-H1 expression in HCC, which could be due to LOH, changes at the transcriptional and/or translational level, or alteration in protein stability. Some authors examined mRNA and protein levels in parallel to the genomic alterations of the NM23-H1 locus in HCC (Fujimoto et al., 1998; Liu et al., 2005). In particular, in the report of Fujimoto et al. (1998) there was no reduction in the mRNA level despite a marked reduction in the protein level in two out of five human HCC examined, indicating that regulation of Nm23-H1 expression may also occur at the post-transcriptional level in HCC. Neither allelic deletion nor point mutation in the coding region of the NM23-H1 gene was observed in any HCC sample of this study and in study of Lin et al. (1998). Indeed, LOH in the region of the NM23-H1 gene (17q21) is a rare event in HCC although gain of this chromosome arm is observed in about 40% of liver cancers (Thorgeirsson and Grisham, 2002). This could suggest that the overexpression observed in primary tumors could, at least partly, result from gene amplification while the decrease concomitant with metastatic spread could result from post-transcriptional events.

Hepatoma cell lines

Confirming clinical studies, several *in vitro* studies reported an inverse association between NM23 expression and the

Table 2 NM23 in various hapatoma cell lines

Refs.	Cell lines	Method.	Isoform	Comments
(A) NM23 expression and correlation with the metastatic potential				
Lin et al. (1995)	SK-Hep-1, Mahlavu, J5, J7, J3-28, Hep3B, HepG2, PLC/PRF/5	NB	H1	Inverse association
Jiang et al. (1996)	H22-16A3-F, H22-A2-P (murine hepatoma)	NB	M1	Inverse association
Fujimoto et al. (1998)	HepG2, HuH-1, HuH-2, HLF	NB	H1	Association with poor differentiation
Tian et al. (1999)	MHCC97	RT-PCR	H1	mRNA detected
Seki et al. (1999)	OCUH-16, Nuk-1, Huh-7, PCL/PRF/5	WB	H1	No clear association
Liu et al. (2000)	7721	NB	H1	↑ due to ATRA ↓ due to EGF
Li et al. (2002)	MHCC97	IHC	H1	Highly invasive No protein detected
Lin et al. (2000)	HepG2 (TRα1)	NB, WB	H1	T3 ↓ NM23 and ↑ metastasis
Ding (2004)	MHCC97-L MHCC97-H	Proteomic	H1	↓ in the higly invasive cell line
Huang (2005)	SK-Hep-1	RT-PCR, WB	H1	Lycopene ↑ NM23 and ↓ invasion
(B) Effect of NM23 transfection on the metastatic potential				
Guo et al. (2000)	7721		H1	↓ in invasion and GnT-V
Liu (2002)	7721		H1	↓ in invasion and SLeX
Duan (2005)	7721		H1	↓ in invasion and transferases

Note. Unless already mentioned in the legend to Table 1, abbreviations are: ATRA, all-trans retinoic acid; GnT-V, *N*-acetylglucosaminyltransferase V; SLeX, sialyl Lewis X antigens; TRα1, thyroid hormone receptor α1; T3, triiodo-thyronine hormone.

metastatic potential of hepatoma cell lines defined by the differentiation status, E-cadherin status, invasion and migration capacity of the cell line (Table 2). Indeed, Lin et al. observed a correlation between a low Nm23 protein level and a high *in vitro* invasive capacity when analyzing eight human liver cancer derived cell lines, SK-Hep-1, Mahlavu, J5, J7, J3-28, Hep3B, HepG2 and PLC/PRF/5 (Lin et al., 1995). Fujimoto et al. (1998) reported that the Nm23-H1 protein level was markedly decreased in the poorly differentiated HCC cell line, HLF, compared with the two moderately differentiated HCC cell lines, HuH-1 and HuH-2 and the hepatoblastoma cell line, HepG2. Jiang et al. (1996) observed similarly a lower level of NM23-M1 mRNA in a metastatic murine ascite hepatoma cell line as compared to its non-metastatic counterpart. Seki et al. (1999) have established a human HCC cell line from metastatic cells in lymph node (Nuk-1), which presented low Nm23-H1 expression and a high metastatic potential but no clear correlation was found with the three other cell lines that they have studied (Seki et al., 1999). HCC cell lines with high and low spontaneous metastasis potentials, MHCC97-H and MHCC97-L, have been established recently from a parental cell line obtained from a subcutaneous xenograft of a human HCC in nude mice (Tian et al., 1999). The parental cell line (MHCC97) which formed metastases in the lung after orthotopic inoculation into nude mice presented positive expression of NM23-M1 mRNA (Tian et al., 1999) but a low level of Nm23-H1 protein (Li et al., 2002). Interestingly, the recent proteomic analysis of the two derived cell lines, the metastatic one and its

less metastatic counterpart, showed a marked decrease in the Nm23-H1 protein level in aggressive cells (Ding et al., 2004).

Several studies have shown a correlation between an inhibitory action of different factors on the invasive properties of hepatoma cell lines with their ability to modulate NM23 expression. Lin et al. (2000) reported negative regulation of the NM23-H1 gene by thyroid hormone receptors in HepG2 cells. One consequence of thyroid hormone treatment of HepG2 cells overexpressing the thyroid hormone receptor subtype α1 (TRα1) was an increase in the invasive properties of HepG2 cells correlated with an inhibition of NM23-H1 (mRNA and protein) expression. Along the same line, the level of NM23-H1 mRNA was upregulated by all-*trans* retinoic acid (ATRA) in the human 7721 hepatocarcinoma cell line (Liu et al., 2000). Moreover, some alterations of the metastasis-associated biological phenotypes, such as cell motility and invasion, induced by ATRA, were similar to those induced by the transfection of the NM23-H1 cDNA suggesting that the decrease in motility and invasion by ATRA treatment could be at least partially mediated by the upregulation of Nm23-H1 expression. Chen et al. (2003) reported an association between expression of the wild type p53 and NM23-H1 and this would deserve further studies given the high incidence of p53 deregulated pathways in HCC. Very recently, Huang et al. (2005) demonstrated that the carotenoid lycopene inhibits cell migration and invasion of a highly invasive hepatoma cell line, SK-Hep-1, and that this effect is accompanied by an

induction of NM23-H1 expression at both the protein and mRNA levels.

As compared to other types of cancer, few studies have reported the inhibitory effect of NM23 enforced expression on the aggressive parameters of HCC derived cell lines. They mainly concern the 7721 cell line and the synthesis of glycans which might participate in the metastatic process. Indeed, after transfection of NM23-H1 cDNA into 7721 human hepatocarcinoma cells, the activity of N-acetylglucosaminyltransferase V (GnT-V), a key enzyme for the synthesis of glycans and glycoproteins, was decreased (Guo et al., 2000). The transfected 7721 cells also displayed changes in metastasis-related phenotypes, including decreases in cell migration and invasion through matrigel, which are similar to the phenotype of cells transfected with an antisense GnT-V cDNA. Along the same line, stable transfection of NM23-H1 cDNA into 7721 human hepatocarcinoma cells inhibited the expression of sialyl Lewis X antigens (Liu et al., 2002) and transferases involved in the synthesis of Lewis antigens (Duan et al., 2005) together with inhibition of cell migration and invasion, without any decrease in the growth rate. Lewis antigens such as SLeX have been reported to be involved in the metastatic process and to mediate the adhesion of malignant cells to vascular endothelium, which is a key step for intravasation and extravasation processes. Together, these findings suggest that the downregulation of transferases and its products could be one of the mechanisms to explain the suppressive effect of the NM23-H1 gene on metastasis.

NM23 invalidation in HCC mouse models

Several mouse models of HCC are available that present most of the molecular abnormalities found in human HCC and permit the sequential analysis of tumor development, which is not feasible in humans (Lee et al., 2005). In addition, transgenic NM23-M1 null mice constitute a powerful tool for investigating NM23 function in normal and pathological conditions (Arnaud-Dabernat et al., 2003). We have used these transgenic mice in two HCC mouse models, one chemically induced by diethylnitrosamine injection and the other obtained by crossing these mice with mice expressing in the liver the large T antigen of SV40, to delineate the role of NM23-M1 in metastatic spread. We found that the lack of NM23-M1 markedly promoted metastases in the SV40 model of liver carcinogenesis (Boissan et al., 2005b). NM23-M1 invalidation had absolutely no effect on primary tumor growth, in both the chemically induced and the SV40 models.

We have also followed the expression of the Nm23 isoforms during liver tumor progression by Western blotting, RT-PCR and immunohistochemistry. Some observations could be extrapolated to human HCC and help understand some of the data reported on NM23 expression in this cancer. Indeed, a differential pattern of expression between Nm23 isoforms and the type of carcinogenesis was observed. In the chemically induced hepatocarcinogenesis, Nm23-M1 (and to a lesser extent Nm23-M2) expression was highly increased in the neoplastic tissues as compared to pre-neoplastic and non-neoplastic tissues in the wild-type mice. In the NM23-M1 null mice, a compensatory increase in Nm23-M2 was observed in the tumors. In the SV40 model, no change in Nm23-M1 was observed but a high increase in Nm23-M2 was already detected in the pre-neoplastic stages. Thus, in the two mouse models, tumor formation was accompanied by a marked increase in Nm23 isoform expression, as often reported for human tumors. Only the SV40 model presented true metastases as shown by labeling with a hepatocyte marker. Interestingly, metastatic spread was not only favoured by the absence of NM23-M1 but also correlated with a decrease in Nm23-M1 expression in the metastases and in the primary tumors of the wild-type mice. Indeed, the primary tumors presented highly heterogeneous labeling as also reported for human tumors suggesting that the loss of NM23-H1/M1 in the primary tumor could favor metastasis. Furthermore, NM23 appears to have a role on the intrinsic properties of the tumoral cell. The dual expression pattern and the presence of the two closely related isoforms could explain the conflicting data reported in the literature. Selective anti Nm23-H1 antibodies could be a promising marker in HCC and other cancers.

Conclusions

The mechanisms by which NM23 may influence metastasis are largely unknown. Like enzymes involved in triphosphate nucleoside synthesis, NDPK isoforms could play a role in proliferation and signal transduction (for reviews: de Otero, 2000; Kimura et al., 2003; Steeg, 2003). They are found in complexes with proteins involved in endocytosis (for review: Narayanan and Ramaswami, 2003), motility (Otsuki et al., 2001) and cell adhesion (Fournier et al., 2003). Nm23-H1 also interacts with the kinase suppressor of Ras (KSR), a scaffold protein of the extracellular signal-regulated kinase (ERK)/mitogen-activated protein kinase (MAPK) pathway, which is involved in tumor invasion (Hartsough et al., 2002; Salerno et al., 2005). Nm23-H1 has also been reported to interact with DNA and to regulate gene expression (Postel, 2003). Nm23-H1 binds to promoters in the matrix metalloproteinase 2 gene (MMP-2; Cheng et al., 2002) and the platelet-derived growth factor A gene (PDGF-A; Ma et al., 2002). In addition, Nm23-H2 is the transcription factor PuF, which controls transcription of the *c-myc* gene (Postel et al., 1993).

This review clearly supports the hypothesis that the Nm23-H1 isoform acts as a suppressor of solid tumor

metastasis, in particular HCC. It is not known whether other Nm23 isoforms could be involved in metastatic spread. Microarrays analyses have shown upregulation of NM23-H4 in HCC developed in non-cirrhotic tissues (Delpuech et al., 2002). We cannot exclude the possibility that fine-tuning of the other(s) NM23 gene(s), could also be important in this process. Further comparative analyzes of their expression would undoubtedly help in clarifying their role. With the nearly constant association of an Nm23 defect with metastatic dissemination, at least in some cancers such as HCC, we can expect that elucidating the molecular consequences of a Nm23 deficiency could lead to a better understanding of the processes of metastatic spread. However, this process is too complicated to expect that the modification in the expression of a single gene will suppress the metastatic process. We could hope that progresses in the NM23 field combined with advances in other areas of oncology will lead to the discovery of new prognostic tools or therapeutic targets that will help to slow down metastasis and to improve cancer care.

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