Review

Cancer Research

FoxM1: A Master Regulator of Tumor Metastasis

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Abstract

The *FoxM1* transcription factor gene is overexpressed in cancer. Its expression is stimulated by oncogenic signaling pathways and reactive oxygen species. It is also a target of regulation by the tumor suppressor genes. The transcriptional activity of FoxM1 depends upon activation by cyclin and cyclin-dependent kinases as well as Plk1. FoxM1 stimulates expression of several genes involved in the cell cycle progression. Moreover, it supports proliferation of tumor cells by stimulating expression of the antioxidant genes and reducing oxidative stress. A new study provides evidence that FoxM1, in the absence of its inhibitor, the tumor suppressor Arf, drives metastasis of hepatocellular carcinoma (HCC). It induces an epithelial–mesenchymal–like transition phenotype in HCC cells, increases cell migration, and induces premetastatic niche at the distal organ of metastasis. FoxM1 directly activates genes involved in multiple steps of metastasis. In this review, we discuss the evidence for a master regulatory role of FoxM1 in tumor metastasis. *Cancer Res; 71(13); 4329–33. ©2011 AACR.*

Introduction

FoxM1 belongs to a large family of forkhead box (Fox) transcription factors. Unlike the other Fox-transcription factors, FoxM1 is associated with cell proliferation and is expressed only in proliferating cells (1, 2). In adult mammals, FoxM1 expression is detected mainly in the progenitor and regenerating tissues, and it is overexpressed in various human malignancies. For example, gene expression profiles in carcinomas, including prostate, breast, lung, ovary, colon, pancreas, stomach, bladder, liver, and kidney, revealed that FoxM1 is overexpressed in all carcinomas (3). Also, high expression of FoxM1 in glioblastoma correlates with the tumorigenicity of the glioma cells (4). Moreover, in breast cancer, overexpression of FoxM1 strongly correlates with poor prognosis (5). Overexpression of FoxM1 in various tumors indicates a strong dependence of the tumor cells on FoxM1, and that is explained partly by its role in cell proliferation.

FoxM1 plays important roles in cell cycle progression (1, 2). FoxM1 stimulates expression of Skp2 and Cks1, which are involved in the proteolysis of p27Kip1 and G_1–S progression (1). FoxM1 also stimulates expression of a number of genes that are critical for the G_2–M progression. Included are *Plk1*, *Aurora B*, *Cyclin B1*, *CDC25B*, *CENP-A*, and *Survivin* (1). Therefore, it is not surprising that FoxM1 expression is restricted to proliferating cells. Interestingly, FoxM1 itself is regulated during the cell cycle. The transcriptional activation function of FoxM1 depends upon phosphorylation by cyclin and cyclin-dependent kinases (cdk) and by the Plk1 kinase. FoxM1 is phosphorylated in the C-terminal activation domain by cyclin/cdks, which serves as priming phosphorylation for further phosphorylations by Plk1 (6, 7). Mutations of the cyclin/cdk or the Plk1 phosphorylation sites render FoxM1 transcriptionally inactive (6, 7). The transcriptionally active, phosphorylated FoxM1 accumulates as the cells progress through the cycle (6–8). At the end of M-phase, FoxM1 becomes dephosphorylated (6), and in early G_1-phase of the next cycle, it is polyubiquitinated by APC/C-Cdh1 for degradation by the proteasome (8). The degradation of FoxM1 in the early G_1-phase is important for regulated entry into S-phase (8). Thus, in proliferating cells, FoxM1 is synthesized and degraded in every cycle of cell division. Synthesis of FoxM1 in early G_1-phase, or during a transition from G_0 to G_1-phase, is stimulated by growth factors (8, 9).

FoxM1 expression is also induced by oncogenes (Fig. 1; ref. 9). For example, activated RAS increases expression of FoxM1, and the increase in FoxM1 expression is critical for RAS-induced transformation. RAS increases expression of FoxM1 by inducing the cellular levels of the reactive oxygen species (ROS; ref. 9). In fact, ROS alone were shown to activate expression of FoxM1 (9). Following induction by ROS, FoxM1 functions in a negative feedback loop to attenuate the levels of ROS by stimulating expression of the antioxidant genes Superoxide Dismutase (*MnSOD*), *Catalase*, and Peroxiredoxin 3 (*PRDX3*; ref. 9). This ROS-regulatory function of FoxM1 protects proliferating normal or tumor cells from oxidative stress and promotes survival (Fig. 1). Consistent with that notion, tumor cells expressing ROS-inducing oncogenes (such as *RAS* or *Akt*) are addicted to FoxM1 for their survival (9). Moreover, the tumor cells overexpressing FoxM1 are resistant to apoptosis or premature senescence induced by oxidative stress, which has strong implications in resistance to chemotherapy. In that

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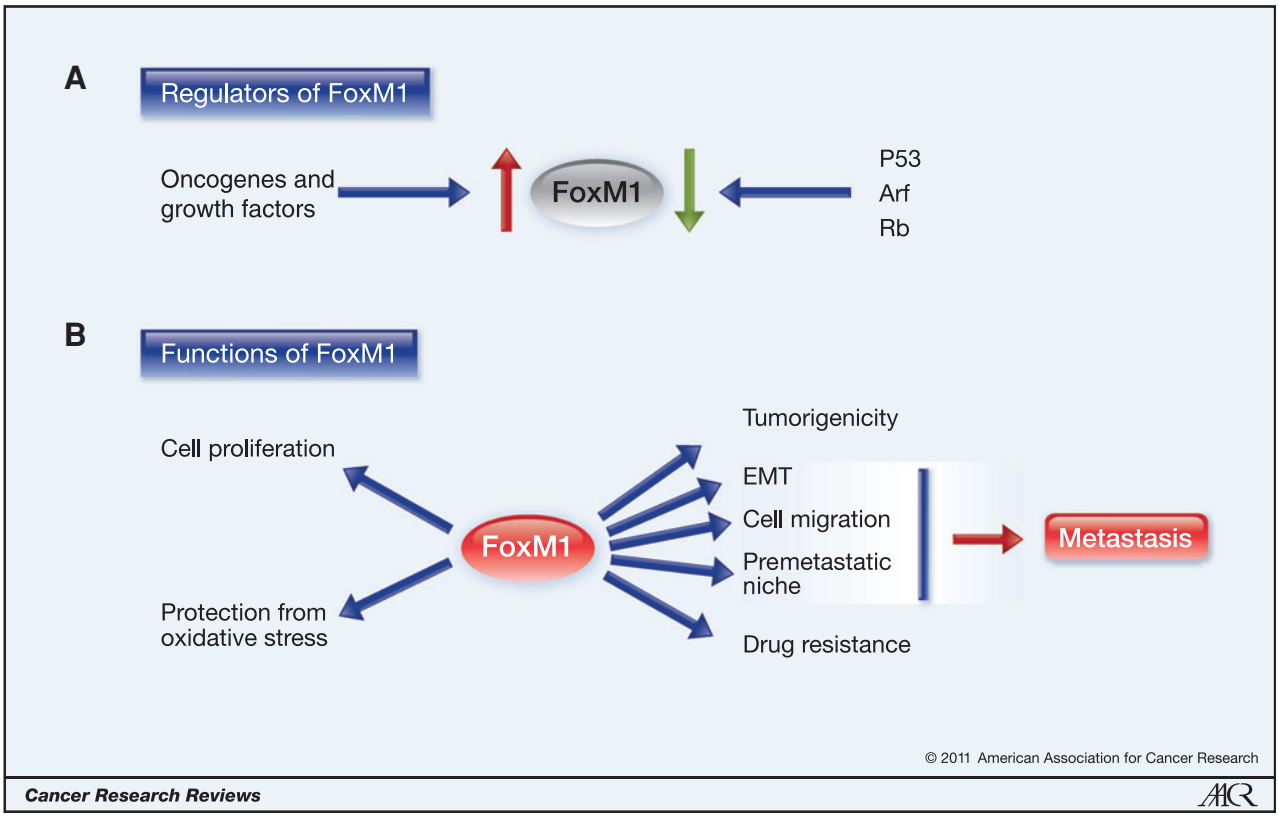

Figure 1. A, FoxM1 expression is stimulated by oncogenes and growth factors and inhibited by p53. Rb and p19Arf inhibit activity of FoxM1. B, FoxM1 stimulates expression of genes involved in cell division, attenuation of oxidative stress, tumorigenicity, and drug resistance. A new study (20) showed that FoxM1 could stimulate expression of genes involved in various steps of tumor metastasis, including epithelial–mesenchymal transition (EMT), cell migration, and premetastatic niche formation.

regard, it is noteworthy that FoxM1 overexpression in breast cancer cells was shown to confer resistance to cisplatin, trastuzumab, and paclitaxel (10, 11). Interestingly, those studies indicated additional pathways through which FoxM1 overexpression confers drug resistance.

The functions of FoxM1 in expression of the cell division genes, and in attenuation of oxidative stress, are significant for cancer development and progression. Consistent with that, expression and the transcriptional activity of FoxM1 are regulated by the tumor suppressor genes (Fig. 1). For example, expression of FoxM1 is regulated by p53 (12, 13). It was suggested that the G_2–M checkpoint function of p53 relies on inhibition of FoxM1 expression (12). FoxM1 is regulated by p19Arf. P19Arf binds to FoxM1 and relocalizes FoxM1 to the nucleolus, thereby inhibiting expression of the FoxM1-activated genes (14). The regulation of FoxM1 by p19Arf is significant because there is new genetic evidence, discussed below, that p19Arf inhibits tumor metastasis induced by FoxM1.

FOXM1 Drives Metastasis

Metastasis of tumor involves a series of interrelated events (see ref. 15 for a comprehensive review). Briefly, the initial steps involve vascularization of the primary tumor for aggressive growth through secretion of angiogenic factors, increased motility and invasion of the tissue stroma through secretion of the matrix metalloproteinases, and other changes in the tumor cells, such as the epithelial–mesenchymal–like transition (EMT-like). The invasive tumor cells penetrate the blood vessels (intravasation) to enter the circulation or migrate through the lymphatic channels. The tumor cells also associate with bone marrow–derived cells, endothelial cells, stromal cells, and others, which provide a supportive microenvironment for the tumor cells. The circulating tumor cells extravasate into the parenchyma of a distal organ, where they undergo metastatic growth. Interestingly, several *in vitro* studies on FoxM1 implicated its involvement in the early steps of metastasis. For example, FoxM1 was shown to stimulate invasion and angiogenesis of pancreatic cancer cells through induction of matrix metalloproteinase genes *MMP-2* and *MMP-9*, as well as *VEGF* (16). Similar functions of FoxM1 in stimulating expression of the *MMP* genes were also described in glioma (17). Moreover, overexpression of FoxM1 coincides with metastasis of prostate cancer (18). However, direct *in vivo* evidence for a role of FoxM1 in tumor metastasis was lacking. That evidence came from *in vivo* studies of FoxM1 in hepatocellular carcinomas (HCC).

The role of FoxM1 in HCC development was studied using a mouse strain (*FoxM1* fl/fl), in which the *FoxM1* alleles were floxed. The *FoxM1* alleles were specifically deleted in the adult

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liver by mating the mice with a transgenic strain that expresses Cre recombinase under the control of albumin promoter (14). Interestingly, deletion of *FoxM1* had very little effect on the survival of the mice, indicating that FoxM1 function is not critical for the normal hepatocytes (14). However, when the mice were subjected to the diethylnitrosamine (DEN)/phenobarbital (PB) liver carcinogenesis protocol, a well-established carcinogenesis protocol for liver cancer in which mice develop liver cancer (HCC) by 9 to 12 months with high penetrance, the mice harboring deletion of the *FoxM1* alleles in the liver did not develop HCC. The observations showed an essential role of FoxM1 in HCC development (14). Moreover, when *FoxM1* was deleted after development of HCC, there were significant decreases in the sizes of HCC, suggesting that FoxM1 is a potential molecular target for HCC therapy. Gusarova and colleagues (19) extended the observations further by using a cell-penetrating form of a peptide derived from p19Arf that was previously shown to inhibit FoxM1 (14). Residues between 26 and 44 of p19Arf, when injected in mice bearing HCC, induced apoptosis of the HCC cells without having a significant effect on the neighboring normal hepatocytes.

Although FoxM1 is essential for HCC development, overexpression of FoxM1 alone did not have significant effect on HCC development (ref. 20 and references therein). Therefore, Park and colleagues (20) decided to study the effect of FoxM1 overexpression in the absence of p19Arf, a potent inhibitor of FoxM1. These authors generated a bi-transgenic strain (*FoxM1bTg:Arf* $^{-/-}$), in which FoxM1 was expressed from the Rosa26 promoter in *Arf* $^{-/-}$ background. When that strain was subjected to the DEN/PB liver carcinogenesis protocol, the mice developed very aggressive HCC. More interestingly, the HCC in the *FoxM1bTg:Arf* $^{-/-}$ background, unlike the single transgenics, were highly metastatic. More than 70% of the HCC in *FoxM1bTg:Arf* $^{-/-}$ mice exhibited metastasis to the lung. The extent of metastasis was reduced significantly when one copy of Arf was present (*FoxM1bTg:Arf* $^{+/-}$ mice), indicating that p19Arf inhibits FoxM1-induced metastasis. The authors also showed that ectopic expression of FoxM1 in *Arf* $^{-/-}$ HCC cells, which were nonmetastatic, induced metastatic ability in experimental metastasis assays (20).

The mechanistic studies by Park and colleagues suggested that FoxM1 could function as a master activator of metastasis, as it induced various steps of metastasis (Fig. 1; ref. 20). For example, FoxM1-induced metastasis of HCC involved EMT of the HCC cells. Also, ectopic expression of FoxM1 in cells expressing lower levels of Arf could induce EMT-like changes (20). There was a loss of E-cadherin expression, and that was accompanied by an increase in the level of Snail, a repressor of E-cadherin expression. The EMT-like changes could be related to increased activation of the Akt-signaling pathway in HCC because the Akt pathway has been shown to stabilize Snail (ref. 20 and references therein). A recent study using *E-cadherin* promoter-luciferase construct indicated that expression of FoxM1 could activate transcription driven by the E-cadherin promoter (21). To explain the apparent discrepancy with the observation by Park and colleagues (20), the authors of that study suggested that the Snail-mediated repression of *E-cadherin* and other mechanisms might be dominant in tumor cells, as they studied the *E-cadherin* promoter activity in normal kidney cells. Also, the level of Arf could be a factor. Clearly, further analyses on the endogenous promoter will be required to resolve the basis of the discrepancy. Nevertheless, in addition to EMT-like changes, expression of FoxM1 increased cell migration. Interestingly, FoxM1 was shown to transcriptionally activate Stathmin, which increases cell motility by destabilizing microtubules. In the HCC cells, FoxM1 increased expression of VEGF, an activator of angiogenesis (20). In addition to activating the mechanisms that allow HCC cells to escape the primary tumor sites, FoxM1 stimulated pathways that are involved in premetastatic niche formation (ref. 20 and references therein). It was shown that FoxM1 could bind to the promoters of lysyl oxidase (*LOX*) and lysyl oxidase-like 2 (LOXL2) and could stimulate their expression. LOX and LOXL2 were shown to be involved in generating premetastatic niche at the distal organ of metastasis (22). Park and colleagues showed the presence of premetastatic niche in the lung sections of their *FoxM1bTg:Arf* $^{-/-}$ mice harboring HCC. The nontumorous lung sections contained $Cd11b^+$ and $c\text{-}kit^+$ cells and exhibited evidence for collagen deposition. Moreover, using mouse xenograft models, Park and colleagues showed that the *Arf* $^{-/-}$ HCC cells, upon overexpression of FoxM1, became highly tumorigenic, as mice injected s.c. developed tumors. Those tumors secreted LOX and LOXL2 to induce premetastatic niche in the lung (20). Interestingly, inhibition of LOX or LOXL2 inhibited premetastatic niche and metastasis without affecting the increase in tumorigenicity by FoxM1.

HCC is one of the deadliest malignancies, mainly because the current therapeutic approaches are ineffective. For eligible patients, a curative surgery is the preferred method of therapy. However, a unique feature of HCC is intrahepatic metastasis, which makes surgical intervention largely ineffective, and 5-year survival following surgery remains very low (23). Therefore, understanding the mechanisms of metastasis of HCC will be important. Intrahepatic metastasis of HCC is associated with loss in the expression of E-cadherin (24). Moreover, increased expression of snail, a regulator of E-cadherin, has been correlated with poor prognosis of HCC (25). In addition, overexpression of Stathmin correlates with the aggressiveness of HCC (26). Interestingly, as described above, these changes in E-cadherin, Snail, and Stathmin expression were observed also in the HCC of the *FoxM1bTg:Arf* $^{-/-}$ mice. Moreover, the development of HCC in the bi-transgenic mouse model of Park and colleagues was associated with fibrosis of the liver, which also is observed during development of HCC in humans. Thus, the bi-transgenic mouse model developed by Park and colleagues has many features of human HCC and, therefore, offers an excellent model to investigate the basis of poor prognosis of HCC and the mechanisms involved in the intrahepatic metastasis of HCC.

Metastasis of HCC was not observed in the *Arf* $^{+/+}$ background (20). Moreover, in the *Arf* $^{+/-}$ background, the FoxM1-driven metastasis was significantly lower compared with that in the *Arf* $^{-/-}$ background. Clearly, Arf is a potent inhibitor of

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FoxM1-induced metastasis. It is noteworthy that FoxM1 overexpression and silencing of Arf are common events in cancer. Although FoxM1 is overexpressed in HCC, the extent to which *Arf* is mutated or silenced in HCC is not clear. One study with 117 HCC samples provided evidence for loss of Arf expression by hypermethylation in about 42% of the samples and loss of heterozygosity in 27% of the samples (27). Also, it is possible that high-level expression of FoxM1 is able to overcome the Arf regulation and induce development of aggressive HCC. Arf is known to regulate numerous pathways, including activation of p53 (see ref. 28 for a review). Therefore, at this point, it is unclear exactly how Arf inhibits metastasis. Interestingly, a cell-penetrating form of a peptide corresponding to residues between 26 and 44 was shown to inhibit expression of *LOX*, *LOXL2*, and *Stathmin*, which are activated by FoxM1. Moreover, the peptide was able to efficiently inhibit FoxM1-driven metastasis in an experimental metastasis assay (20). Therefore, it is likely that FoxM1 is the major target of Arf regulation that leads to inhibition of metastasis. However, further studies on the FoxM1/Arf interaction will be important in determining how Arf inhibits FoxM1-induced metastasis. It is possible that detailed studies on the FoxM1/Arf interaction will lead to the development of new therapeutic approaches against aggressive HCCs.

Recommendations for Future Research

The observations on the role of FoxM1 role in metastasis of HCC have strong implications on metastasis of other tumors, as overexpression of FoxM1 is a common event in cancer. For example, the correlation between FoxM1 overexpression and metastasis of prostate cancer (18) should be investigated further to establish a causal link. Also, FoxM1 overexpression in breast cancer is considered to be a biomarker for poor prognosis (5). On the basis of the observations by Park and colleagues (20), it is tempting to speculate on the existence of a causal link between FoxM1 overexpression and metastasis of breast cancers. The study by Park and colleagues has linked FoxM1 to only a limited number of genes that have been implicated in metastasis. It is unclear how FoxM1 overcomes the inhibitory effects of the metastasis suppressor genes. Studies on metastasis suppression have identified a large number of genes (see ref. 29 for a review) that affect metastasis without having effects on the growth of the primary tumors. Also, several microRNA genes called metastamir have been characterized that have pro- or antimetastatic activity (reviewed in ref. 30). Future studies on the connections between FoxM1 overexpression and inactivation of the metastasis suppressor genes, as well as those with metastamir, will provide valuable insights into the mechanisms of FoxM1, which seems to be a master regulator of metastasis.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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References

1. Wang IC, Chen YJ, Hughes D, Petrovic V, Major ML, Park HJ, et al. Forkhead box M1 regulates the transcriptional network of genes essential for mitotic progression and genes encoding the SCF (Skp2-Cks1) ubiquitin ligase. Mol Cell Biol 2005;25:10875–94.
2. Laoukili J, Kooistra MR, Brás A, Kauw J, Kerkhoven RM, Morrison A, et al. FoxM1 is required for execution of the mitotic programme and chromosome stability. Nat Cell Biol 2005;7:126–36.
3. Pilarsky C, Wenzig M, Specht T, Saeger HD, Grützmann R. Identification and validation of commonly overexpressed genes in solid tumors by comparison of microarray data. Neoplasia 2004;6:744–50.
4. Liu M, Dai B, Kang SH, Ban K, Huang FJ, Lang FF, et al. FoxM1B is overexpressed in human glioblastomas and critically regulates the tumorigenicity of glioma cells. Cancer Res 2006;66:3593–602.
5. Bektas N, Haaf A, Veeck J, Wild PJ, Lüscher-Firzlaff J, Hartmann A, et al. Tight correlation between expression of the Forkhead transcription factor FOXM1 and HER2 in human breast cancer. BMC Cancer 2008;8:42–50.
6. Chen YJ, Dominguez-Brauer C, Wang Z, Asara JM, Costa RH, Tyner AL, et al. A conserved phosphorylation site within the forkhead domain of FoxM1B is required for its activation by cyclin-CDK1. J Biol Chem 2009;284:30695–707.
7. Fu Z, Malureanu L, Huang J, Wang W, Li H, van Deursen JM, et al. Plk1-dependent phosphorylation of FoxM1 regulates a transcriptional programme required for mitotic progression. Nat Cell Biol 2008;10:1076–82.
8. Park HJ, Costa RH, Lau LF, Tyner AL, Raychaudhuri P. Anaphase-promoting complex/cyclosome–Cdh1-mediated proteolysis of the forkhead box transcription factor is critical for regulated entry into S phase. Mol Cell Biol 2008;28:5162–71.
9. Park HJ, Carr JR, Wang Z, Nogueira V, Hay N, Tyner AL, et al. FoxM1, a critical regulator of oxidative stress during oncogenesis. EMBO J 2009;28:2908–18.
10. Kwok JM, Peck B, Monteiro LJ, Schwenen HD, Millour J, Coombes RC, et al. FOXM1 confers acquired cisplatin resistance in breast cancer cells. Mol Cancer Res 2010;8:24–34.
11. Carr JR, Park HJ, Wang Z, Kiefer MM, Raychaudhuri P. FoxM1 mediates resistance to herceptin and paclitaxel. Cancer Res 2010;70:5054–63.
12. Barsotti AM, Prives C. Pro-proliferative FoxM1 is a target of p53-mediated repression. Oncogene 2009;28:4295–305.
13. Pandit B, Halasi M, Gartel AL. p53 negatively regulates expression of FoxM1. Cell Cycle 2009;8:3425–7.
14. Kalinichenko VV, Major ML, Wang X, Petrovic V, Kuechle J, Yoder HM, et al. Foxm1b transcription factor is essential for development of hepatocellular carcinomas and is negatively regulated by the p19ARF tumor suppressor. Genes Dev 2004;18:830–50.
15. Talmadge JE, Fidler IJ. AACR centennial series: the biology of cancer metastasis: historical perspective. Cancer Res 2010;70:5649–69.
16. Wang Z, Banerjee S, Kong D, Li Y, Sarkar FH. Down-regulation of Forkhead Box M1 transcription factor leads to the inhibition of inva-

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sion and angiogenesis of pancreatic cancer cells. Cancer Res 2007; 67:8293–300.
17. Dai B, Kang SH, Gong W, Liu M, Aldape KD, Sawaya R, et al. Aberrant FoxM1B expression increases matrix metalloproteinase-2 transcription and enhances the invasion of glioma cells. Oncogene 2007;26: 6212–9.
18. Chandran UR, Ma C, Dhir R, Bisceglia M, Lyons-Weiler M, Liang W, et al. Gene expression profiles of prostate cancer reveal involvement of multiple molecular pathways in the metastatic process. BMC Cancer 2007;7:64–85.
19. Gusarova GA, Wang IC, Major ML, Kalinichenko VV, Ackerson T, Petrovic V, et al. A cell-penetrating ARF peptide inhibitor of FoxM1 in mouse hepatocellular carcinoma treatment. J Clin Invest 2007;117:99–111.
20. Park HJ, Gusarova G, Wang Z, Carr JR, Li J, Kim KH, et al. Deregulation of FoxM1b leads to tumour metastasis. EMBO Mol Med 2011;3:21–34.
21. Wierstra I. The transcription factor FOXM1c binds to and transactivates the promoter of the tumor suppressor gene E-cadherin. Cell Cycle 2011;10:760–6.
22. Erler JT, Bennewith KL, Cox TR, Lang G, Bird D, Koong A, et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. Cancer Cell 2009; 15:35–44.
23. Masuda T, Beppu T, Ishiko T, Horino K, Baba Y, Mizumoto T, et al. Intrahepatic dissemination of hepatocellular carcinoma after local ablation therapy. J Hepatobiliary Pancreat Surg 2008;15: 589–95.
24. Inayoshi J, Ichida T, Sugitani S, Tsuboi Y, Genda T, Honma N, et al. Gross appearance of hepatocellular carcinoma reflects E-cadherin expression and risk of early recurrence after surgical treatment. J Gastroenterol Hepatol 2003;18:673–7.
25. Miyoshi A, Kitajima Y, Kido S, Shimonishi T, Matsuyama S, Kitahara K, et al. Snail accelerates cancer invasion by upregulating MMP expression and is associated with poor prognosis of hepatocellular carcinoma. Br J Cancer 2005;92:252–8.
26. Hsieh SY, Huang SF, Yu MC, Yeh TS, Chen TC, Lin YJ, et al. Stathmin1 overexpression associated with polyploidy, tumor-cell invasion, early recurrence, and poor prognosis in human hepatoma. Mol Carcinog 2010;49:476–87.
27. Anzola M, Cuevas N, López-Martínez M, Saiz A, Burgos JJ, Martínez de Pancorboa M. P14ARF gene alterations in human hepatocellular carcinoma. Eur J Gastroenterol Hepatol 2004;16:19–26.
28. Sherr CJ. Divorcing ARF and p53: an unsettled case. Nat Rev Cancer 2006;6:663–73.
29. Hurst DR, Welch DR. Metastasis suppressor genes at the interface between the environment and tumor cell growth. Int Rev Cell Mol Biol 2011;286:107–80.
30. Hurst DR, Edmonds MD, Welch DR. Metastamir: the field of metastasis-regulatory microRNA is spreading. Cancer Res 2009; 69:7495–8.

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