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EDITORIAL

Ectopic expression of the osteogenic master gene *RUNX2* in melanoma

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Abstract

The transcription factor *RUNX2* is the osteogenic master gene expressed in mesenchymal stem cells during osteogenic commitment as well as in pre-osteoblasts and early osteoblasts. However, *RUNX2* is also ectopically expressed in melanoma and other cancers. Malignant melanoma (MM) is a highly metastatic skin cancer. The incidence of MM has increased considerably in the past half-century. The expression levels and mutation rates of genes such as *BRAF*, *KIT*, *NRAS*, *PTEN*, *P53*, *TERT* and *MITF* are higher in melanoma than in other solid malignancies. Additionally, transcription factors can affect cellular processes and induce cellular transformation since they control gene expression. Recently, several studies have identified alterations in *RUNX2* expression. In particular, the regulation of *KIT* by *RUNX2* and the increased expression of *RUNX2* in melanoma specimens have been shown. Melanocytes, whose transformation results in melanoma, arise from the neural crest and therefore show "stemness" features. *RUNX2* plays an important role in the re-activation of the MAPK and PI-3K/AKT pathways, thus endowing melanoma cells with a high metastatic potential. In melanoma, the most frequent metastatic sites are the lung, liver, brain and lymph nodes. In addition, bone metastatic melanoma has been described. Notably, studies focusing on *RUNX2* may contribute to the identification of an appropriate oncotarget in melanoma.

Key words: *RUNX2*; Mesenchymal stem cells; Epitelial mesenchymal transition; Bone; Melanoma

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Core tip: In addition to its physiological expression in osteogenic cells, *RUNX2* ectopic expression is also reported in several cancers. Melanoma cells, which arise from the neural crest, are not typical epithelial cells and

exhibit "stemness" features. For this reason the epithelial mesenchymal transition process may be enhanced in melanoma cells. *RUNX2* expression in such context increases the migration and invasiveness of melanoma cells; it can therefore be considered a new oncotarget in melanoma.

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INTRODUCTION

In recent times, the incidence of malignant melanoma (MM) has increased. The increased number of MM patients may be ascribed to lifestyle and environmental changes. Unfortunately, the mortality rate of MM is very high, as MM is highly metastatic and genetically resistant to apoptosis. The surgical treatment of skin lesions before cell spreading is considered a successful therapeutic approach. However, after metastasis and dissemination of cells has occurred, the therapeutic tools are limited. Despite an initial positive response to treatment, melanoma cells become resistant to chemotherapy[1]. Many studies performed in animal models and in cell culture have identified the complex mechanism involved in the metastatic progression of melanoma. Mutations in master transcription regulators such as *BRAF, KIT, NRAS, PTEN, P53, TERT*, and *MITF* have been found frequently[2]. In particular, the microphthalmia-associated transcription factor (*MITF*) is an important oncogene, and it plays a critical role in melanoma transformation due to its role in melanocyte proliferation and differentiation[3]. However, transcription factors in general may affect cellular processes and thereby induce cellular transformation. Among them, *RUNX2*, the master gene of osteogenic differentiation, has been shown to be involved in the transformation and metastatic progression of melanoma[4-6]. *RUNX2*, together with *RUNX1* and *RUNX3*, belongs to the *RUNT*-related gene family[7]. These heterodimeric transcription factors have a DNA-binding "A" subunit and a non-DNA binding "B" subunit. The genomic and cDNA structures of the *RUNT* family members are evolutionarily conserved[8]. *RUNX2* is located on human chromosome 6; its coding sequence is organized in eight exons and controlled by two promoters. Isoforms may originate by the alternative use of promoters or by the alternative splicing of exons; however, the DNA-binding domain remains invariant[7]. *RUNX2* induces the commitment of mesenchymal stem cells to the osteogenic lineage by acting either as a monomer or as a heterodimeric complex, which shows a higher DNA binding activity[7]. Interestingly, differences in *RUNX2* expression are associated with the skeletal differences between modern humans and Neanderthals[9]. Otto *et al*[10] using an in vivo model, showed that the ossification process is lacking in *RUNX2* KO mice. *RUNX2* is expressed not only in mesenchymal stem cells to commit these cells to osteogenic differentiation but also in pre-osteoblasts and early osteoblasts. It is then downregulated, as its continuous expression would prevent osteoblast maturation. This aspect is important for bone remodelling. In acromegaly patients, who are characterized by an excessive production of GH and IGF-1, a high fracture risk occurs; we have demonstrated that RUNX2 gene overexpression induces bone loss and impairs bone remodelling in these patients[11].

RUNX2 OVEREXPRESSION IN CANCER

The *RUNX* family members are frequently deregulated in human cancer. Runx proteins are involved in critical cellular processes such DNA repair, apoptosis, hypoxia, the inflammatory response, EMT, stem cell functions, and oncogene-induced senescence, and they interact with different signalling pathways such as the RAS-ERK, WNT, TGFβ, BMP and Notch pathways[12]. In addition, *RUNX2* is involved in osteolytic diseases, neoangiogenic processes, and invasion and metastasis of solid tumours[4]. *RUNX2* can be associated with HDA6 and can thereby prevent the pro-apoptotic activity of P53 through its deacetylation[13]. *RUNX2* is ectopically expressed in several solid tumours such as breast cancer, pancreatic cancer, prostate cancer, lung cancer, and ovarian epithelial cancer; therefore, we have proposed *RUNX2* as a mesenchymal stem marker for cancer[14,15]. Interestingly, we observed higher levels of *RUNX2* expression in cancer patients with bone metastases compared to patients without bone metastases[15]. In thyroid cancer patients, we observed higher expression of *RUNX2* in cancer tissue as well as in circulating mRNA compared to those levels of *RUNX2* expression in controls[16]. In addition, *RUNX2* expression was higher in cancer patients with microcalcifications compared to patients without microcalcifications[16]. Finally, it has been reported that *RUNX2* induces its target genes SDF-1, CXCR7 and BSP, promoting bone homing[17].

RUNX2 IN MELANOMA

Ectopic expression of *RUNX2* in melanoma tissue and in melanoma cell lines has been shown to be associated with bone sialoprotein (BSP)[18]. BSP has been associated with tumour invasiveness[18]. *RUNX2* also regulates several matrix metalloproteinases that are involved in melanoma progression; therefore, *RUNX2* may be regarded as a common regulator of both BSP and metalloproteinases[19]. This finding could also explain the expression of other bone proteins, such as osteopontin and osteocalcin, in melanoma[20,21]. TGFβ, which induces metastasis formation in advanced melanoma stages[22], can upregulate the expression of *RUNX2* in melanoma

cell lines[23]. In contrast, the tumour suppressor p14ARF reduces *RUNX2* expression[24]. Loss-of-function *p14ARF* mutations lead to increased expression of *RUNX2* and melanoma progression[24]. Ectopic expression of *RUNX2* in melanoma has been associated with invasiveness; it has been demonstrated that *RUNX2* overexpression mediates the migration ability of melanoma cells[6]. Notably *RUNX2* stimulates *VEGF* gene expression[25] and the upregulation of angiogenesis, consequent to *RUNX2* overexpression, may represent a critical step for tumor metastasis.

Furthermore, *RUNX2* overexpression upregulates *SOX9, SNAI2* and *SMAD3*. These transcription factors are involved in EMT as well as in cytoskeletal remodelling and thus enhance the motility and invasive potential of cancer cells[17]. In melanoma, the overexpression of *EGF-R, PDGFRβ, AXL* and *IGF-1R* induces the reactivation of the MAPK and PI3K/AKT pathways, which are involved in migration and invasion processes[26]. The reactivation of these pathways is due to tyrosine kinase receptor-based autocrine loops, in which *RUNX2* plays a pivotal role[5]. The MAPK and AKT pathways regulate most physiological processes, such as proliferation, differentiation and cell survival. It has been suggested that the MAPK and AKT pathways are strongly associated with each other in melanoma; the link between the PI3K/AKT (AKT pathway) and MAPK/ERK1/2 (MAPK pathway) cascades is well known[27]. AKT enhances RUNX2 expression either directly or by inactivating RUNX2 regulators. Similarly, RUNX2 activates the PI3K/AKT pathway by regulating different components[4]. This reciprocal activation induces tumour progression and aggressiveness. In addition, RUNX2 promotes the crosstalk between MAPK and AKT through EGFR, as has been shown in human mammary epithelial cells[28] through the reduction of ERK-mediated inhibition of EGFR and the AKT pathway. The lung, liver, brain and lymph nodes are the most frequent metastatic sites for melanoma cells[29]. Since melanocytes arise from the neural crest, they are not typical epithelial cells; they show "stemness" features. This last finding could partially explain the high metastatic potential of melanoma[29]. Solid malignancies such as breast, prostate and lung cancers form metastases in bone. However, metastatic bone diseases from MM are under-investigated. The data in the literature report an incidence of skeletal metastases in MM patients that ranges from 0.85% to 18.6%[30]. Recently, Zekri *et al*[31], managing MM patients at two referral cancer centres in England, showed that bone metastases occur in 4.1% of patients at all stages of MM. In addition, another study showed that 17.2% of metastatic melanoma patients had metastases in bone tissue.

CONCLUSION

MM accounts for less than 5% of cutaneous malignancies. However, its incidence has been increasing considerably in the past half-century. Therefore, extensive research focusing on the genes involved in melanoma transformation and on the modulation of these genes is needed. Several studies have highlighted the involvement of RUNX2, the master gene of osteogenic differentiation, in melanoma. The invasiveness and metastatic features conferred by RUNX2 seem to be related to its ability to promote EMT. In addition, melanocytes are not typical epithelial cells, and their stemness features could explain melanoma invasiveness. Since metastatic melanoma has a poor prognosis, new and more effective therapeutic tools should be developed in order to implement current therapies. In this context, the exploitation of molecules actually involved in melanoma, such as RUNX2, represents an important frontier for the identification of new oncotargets. Transcription factors have been ignored thus far by the pharmaceutical industry; nonetheless, many studies have identified their central role in cellular transformation. We believe that future efforts directed towards unravelling the complex roles of RUNX2 may contribute to the identification of new therapeutic tools that improve the quality of life of melanoma patients.

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