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Cancer Science & Pediatrics 2019: How to reconcile the microRNA-200 family with different tumour sites? - Mohammed Y Almaghrabi - King Abdullah Medical City, Saudi Arabia

Mohammed Y Almaghrabi

King Abdullah Medical City, Saudi Arabia

The microRNA-200 family is a small molecule which can play a potential role in cancer diagnosis and treatment. The miR-200 family includes 5 members (miR-200a, -200b, -200c, -141, -429). The steady decrease of miR- 200 family expression correlated with the increasing number of lymph node metastasis in breast cancer. The miR-200 family is down regulated in gastric cancer. Expression of miRNA-200 family members and ZEB2 associated with brain metastases of gastric adenocarcinoma. miR200 family can inhibit ovarian cancer cell invasiveness and metastasis. Downregulation of both miR-200c and miR-141 independently predicted disease-free survival in hepatocellular carcinoma. It is still challenging to use miR-200 family in daily practice since most of the published studies at a preclinical phase. Redoubling the efforts and another manner should be created to accelerate the implementation.

The landmark study of lin-4 in Caenorhabditis elegans identified a novel class of molecules called microRNA (miR), which are small non-coding RNAs consisting of 18–25 nucleotide base pairs. These small nucleic acids regulate gene expression by binding to the 3′ untranslated region (3′-UTR) of mRNA, resulting in translational repression or transcript degradation. Over 2,500 miRs have been identified in the human genome since their discovery in 1993 and it has been determined that 30–50% of genes that code for proteins are controlled by miR in humans.

Thus, miRs have emerged as integral components of various biological processes, including cell proliferation, migration, differentiation, apoptosis and angiogenesis. It has been demonstrated that the altered expression of miR is associated with tumorigenesis and the progression of different types of cancer. By regulating multiple potential target genes, miR expression may lead to pathological changes in cells, ultimately contributing to the development of cancer.

One family of miR, the miR-200 family, has been identified to be crucial in tumorigenesis. Members of the miR-200 family are downregulated in aggressive human tumors and target different signaling pathways including the Notch, Wnt and transforming growth factor β (TGF-β) pathways, thus inhibiting migration, tumor cell adhesion, epithelial-to-mesenchymal transition (EMT) and angiogenesis. The present review will focus on summarizing the roles of the miR-200 family as putative tumor suppressors in tumor progression and propose that the restoration of miR-200 expression may have therapeutic implications for the clinical treatment of metastatic and drug-resistant tumors. The primary step and important characteristics of tumor metastasis are the disassembly of tight junctions and loss of apical-basal polarity among cancer cells. The loss of epithelial markers and the gain of mesenchymal morphological features in cancer cells contributes to the suppression of the transmembrane adhesion receptor E-cadherin and a gain in the expression of mesenchymal markers, including vimentin, collagen, fibronectin, and the E-cadherin transcriptional repressors ZEB1 and ZEB2 (also known as SMAD-interacting protein.

These vital molecules cause the extracellular matrix-induced stimulation of the integrin signal pathway, resulting in focal adhesion formation, which facilitates cancer cell migration, invasion and metastasis. The transcriptional factors ZEB1 and ZEB2 induce EMT by repressing the expression of E-cadherin and promoting cancer cell migration, invasion and metastasis. TGF-β also serves an important role in the EMT in epithelial cells as it commands cell proliferation and differentiation during the process of embryonic development or cancer progression.

It is widely accepted that angiogenesis, the formation of new blood vessels from pre-existing ones, is a fundamental process required for cancer development and growth. Without angiogenesis, cancer cells inside the tumor undergo apoptosis. The angiogenesis switch depends on the balance of angiogenesis activators and inhibitors. The activation of angiogenesis is initiated when pre-existing vessels become permeable in response to stimulating factors, including vascular endothelial growth factor (VEGF), placental growth factor and angiopoietin VEGF is the most well-known fundamental factor and modulator of angiogenesis.

VEGF combined with its receptors fms-like tyrosine kinase (flt1) or VEGF receptor (VEGFR)-1 and kinase-insert domain containing receptor (KDR) or VEGFR-2, stimulates endothelial cell migration, proliferation and survival. As angiogenesis is essential for tumor growth, inhibiting VEGF signaling using strategies such as small interfering RNA, small molecule inhibitors, antibodies and VEGF-traps is a promising therapeutic approach for cancer treatment. Furthermore, research has demonstrated that miR-200 family members are involved in the regulation of vascular development and angiogenesis by downregulating VEGF signaling.

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