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Review Article

MiR-218 Mediates tumorigenesis and metastasis: Perspectives and implications

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ABSTRACT

MicroRNAs (miRNAs) are a class of small non-coding RNAs that negatively regulate gene expression at the post-transcriptional level. As a highly conserved miRNA across a variety of species, microRNA-218 (miR-218) was found to play pivotal roles in tumorigenesis and progression. A group of evidence has demonstrated that miR-218 acts as a tumor suppressor by targeting many oncogenes related to proliferation, apoptosis and invasion. In this review, we provide a complex overview of miR-218, including its regulatory mechanisms, known functions in cancer and future challenges as a potential therapeutic target in human cancers.

Contents

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Introduction

MicroRNAs (miRNAs) are a class of small non-coding RNAs that regulate gene expression by binding to partially complementary sequences of target mRNAs [1]. At present, more than 700 miRNAs have so far been identified and over 800 more are predicted to exist in humans [2]. Considering that a single miRNA potentially targets up to hundreds of genes, miRNAs are involved in all sorts of functions in physiology, ranging from cell differentiation, proliferation, apoptosis and migration to regulation of the endocrine system, hematopoiesis, fat metabolism, limb morphogenesis [3].

Due to their abundant presence and far-reaching potential, miRNAs have a revolutionary impact on cancer research over the course of the past two decades, playing significant roles in tumorigenesis and metastasis. Attributed to the increasing evidence revealing the involvement of miRNAs in human malignancies, as well as the rapid discovery of miRNA targets and related pathways, a number of miRNA-based therapeutics for cancer have been developed.

MiR-218 is a vertebrate-specific intronic miRNA coexpressed with its host genes, tumor suppressor gene SLIT2/3. The mature form of miR-218 is generated from two separate loci, miR-218-1 and miR-218-2, which are located on chromosomes 4p15.31 and 5q35.1 within the introns of SLIT2 and SLIT3, respectively [4]. Accumulating evidence suggests that miR-218 is frequently downregulated in various cancers and acts as a tumor suppressor, such as those reported in colorectal cancer [5], breast cancer [6], clear cell renal cell carcinoma [7], being correlated with clinical staging, prognosis and metastasis. Therefore, in recent years, miR-218 is becoming the focus of attention for many scientists due to its aberrant expression in multiple cancer types.

Expression profiles of miR-218 in cancer

Decreased miR-218 expression in cancer cell

MiR-218 was initially reported to inhibit Hela cell proliferation and induce apoptosis in 2005 [8]. Subsequently, the comprehensive analyses of miRNA microarray showed that miR-218 was significantly repressed in several kinds of cancer tissues, including gastric, colon, prostate and pancreatic cancers [9,10]. Since then, a host of research studies have illustrated that miR-218 acts as a tumor suppressor in multiple cancers. As summarized in Fig. 1, miR-218 expression is constantly reduced in tumors, including those reported in bladder [4], prostate [11], pancreatic [12], colorectal [13], cervical [14], thyroid [15] and gastric cancers [16], as well as in nasopharyngeal carcinoma (NPC) [17], glioma [18], medulloblastoma [19], osteosarcoma [20], esophageal squamous cell carcinoma (ESCC) [21] and lung squamous cell carcinoma (SCC) [22]. Furthermore, it was found to be reduced even in circulating system of cervical cancer [23] and gastric cancer patients [24], being intimately correlated with poor prognosis and reduced overall survival.

In addition, miR-218 depression is associated with multiple drug resistance. A 7.79-fold decrease of miR-218 expression was observed in etoposide-resistant breast cancer cells compared with etoposide-sensitive cells [25]. Reduced miR-218 levels also confer resistance to chemotherapy in glioblastoma multiforme [26]. On

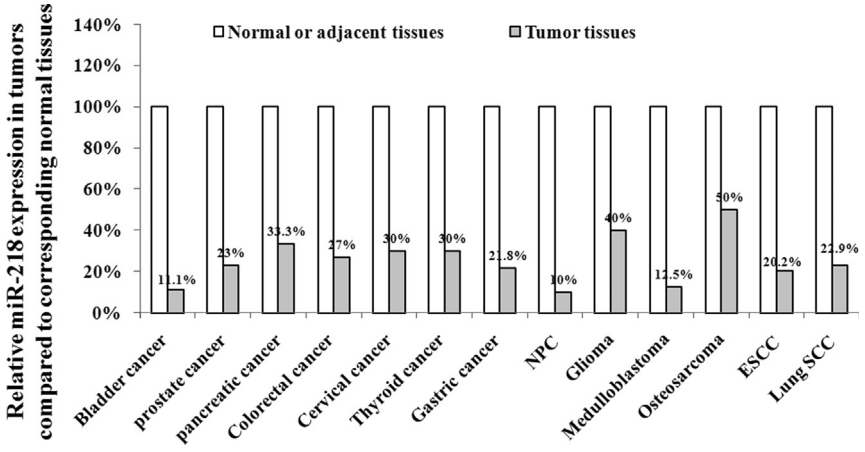

Fig. 1 – MiR-218 expression in multiple cancers compared with their normal tissues. The expression levels of miR-218 are remarkably decreased in cancer specimens compared with their corresponding normal tissues, respectively.

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