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Review

Tumor suppressor microRNAs: A novel non-coding alliance against cancer

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ABSTRACT

Tumor initiation and progression are the outcomes of a stepwise accumulation of genetic alterations. Among these, gene amplification and aberrant expression of oncogenic proteins, as well as deletion or inactivation of tumor suppressor genes, represent hallmark steps. Mounting evidence collected over the last few years has identified different populations of non-coding RNAs as major players in tumor suppression in almost all cancer types. Elucidating the diverse molecular mechanisms underlying the roles of non-coding RNAs in tumor progression might provide illuminating insights, potentially able to assist improved diagnosis, better staging and effective treatments of human cancers. Here we focus on several groups of tumor suppressor microRNAs, whose downregulation exerts a profound oncologic impact and might be harnessed for the benefit of cancer patients.

1. Introduction

In most epithelial tissues, cancer develops through separate and interrelated steps of clonal expansion, genetic diversification, and clonal selection. During cancer development, cancer cells acquire diverse biological capabilities that are conferred by numerous genetic and epigenetic modifications [1]. In recent years, different high-throughput platforms have been used for the genomic, transcriptomic, proteomic, and epigenetic analyses to search for new biomarkers involved in cancer and to bring new insights into the several aspects of cancer pathophysiology [1]. In addition to the classical transcriptional cell regulators involved in cancer development, a class of non-coding RNAs, termed microRNAs (miRNAs) has emerged as critical regulators of gene expression acting predominantly at the post-transcriptional level. MiRNAs were first identified through their ability to regulate developmental processes, such as developmental timing and cell fate transitions [2]. Subsequently, miRNAs have been studied in relation to cancer development. A large number of miRNAs that map to specific regions of the human genome have been shown to be frequently deleted or amplified in cancer [3]. Several lines of evidence indicate that miRNAs might be differentially expressed in cancer cells, in which they form unique expression patterns or signatures [4]. Sevignani and colleagues reported a significant association between the chromosomal location of miRNAs and those of mouse susceptibility loci that influence the development of solid tumors [5]. Dysregulation of miRNAs in cancer can occur through both epigenetic changes, including aberrant DNA methylation and histone modification [6], and genetic alterations. These two biological mechanisms can affect the production of the primary RNAs, their processing to the mature miRNA forms, and/or interactions with mRNA targets [7].

More recent studies indicate that mutations affecting proteins involved in the processing and maturation of miRNA, such as TARBP2, DICER1 and XPO5, can also lead to overall reductions in miRNA expression [8–10]. Consistent with these observations, miRNAs are thought to act mainly as tumor suppressor genes, and their deregulation is currently recognized as a common feature of human cancers. Later on, additional data indicated that the expression of miRNAs is mainly downregulated in tumor tissues, as compared to corresponding healthy tissues, which supported the role of miRNAs as primarily tumor suppressors [4,8,9,11,12]. In the same vein, there is evidence that an extensive downregulation of miRNAs is one of the first outcomes of the stimulation of signaling cascades downstream to specific growth factor receptors

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implicated in a number of human cancers, including breast cancer [13]. For example, EGF signaling rapidly and simultaneously induces an extensive downregulation of multiple miRNAs, reflecting coordinated regulation at the level of miRNA synthesis, processing or degradation [13].

Along with the dominance of tumor suppressor microRNAs, several well-characterized oncogenic miRNAs have been reported in tumors. An interplay between RNA-binding proteins and oncogenic miRNAs, which drive expression of proto-oncogenes or maintenance of stem cell phenotypes, contributes to human cancer [14]. One example relates to oncogenic receptors for growth factors, such as the EGF-receptor (EGFR/ErbB) family of receptor tyrosine kinases, the expression of which is regulated by several miRNAs [15]. In the same vein, signaling pathways are ideal candidates for miRNA-mediated regulation, owing to the sharp dose-sensitive nature of their effects. For instance, EGFR activation induces miR-7 expression through a RAS-MYC pathway. In support of this, MYC binds to and activates the miR-7 promoter and ectopic miR-7 promotes cell growth and tumor formation in lung cancer cells [16]. Thus, in addition to the EGFR/ErbB family, oncogenic miRNAs (onco-miRs) affect the responsiveness of cells to signaling molecules, such as transforming growth factor-beta, WNT and Notch [17]. miRNAs control not only cellular proliferation and programmed cell death, but also dissemination of tumor cells and colonization of distant organs (metastasis). Indeed, some miRNAs are associated with the invasive and metastatic phenotype of breast and other cancer cell lines or metastatic tumor tissues [18,19].

MiRNAs are also deregulated upon exposure to both metabolic cancer risk factors and exposures to carcinogenic substances [20,21]. Thus, miRNAs may represent at the same time both predictors and players of cancer development. A number of life-style factors (e.g., diet rich in fats and refined carbohydrates) and pathological conditions (e.g., obesity), often related to inflammation and cancer, result in deregulation of specific miRNAs [22–25]. In addition, there is evidence of an altered expression of miRNAs in relation to the exposure to well-known carcinogenic substances such as asbestos, formaldehyde and cigarette smoke in lung and hepatic tissue [26,27]. In regard to this evidence, one study examined the expression of 484 miRNAs in the lungs of rats exposed to environmental cigarette smoke for 4 weeks. It was found that 126 miRNAs were down-regulated at least 2-fold and 24 miRNAs were downregulated more than 3-fold [28].

In this review, we highlight the contribution of miRNA modulation, in particular prevalent downregulation of specific miRNAs, to cancer development. Due to space consideration, this review concentrates on a selected group of tumor suppressor microRNAs. Table 1 lists some additional molecules within this category, which we do not discuss in the main text. They include miR-34, a p53 target gene [29,30], miR-31, an inhibitor of metastasis [31], as well as miR-205 [32], miR-375 [33], miR-203 [34–36], as well as miR-15a [37–39]. Because many downregulated miRNAs function as tumor suppressors, better understanding of the biological mechanisms underlying their modulation will likely enable new strategies for prevention, early detection and therapy of cancer.

1.1. MiR-10b3p: the early arm of the miR-10b locus

The so-called miRNA-10b locus is located on chromosome 2, within the cluster of the HOXD genes, in an intergenic region between HOXD4 and HOXD8 [40]. Processing by Drosha and Dicer transforms the RNA product of the miRNA-10b locus into a 22-nucleotide RNA duplex that contains two distinct 5′ phosphorylated strands with 3′ overhangs (Fig. 1). The functional strand of the duplex, referred to as the guide strand, is miR-10b5p while the other, passenger strand generates miR-10b3p. MiR-10b5p was originally identified as a molecules down-regulated in primary breast tumors, compared to normal breast tissues [41]. Similarly, downregulation of miR-10b5p by promoter hyper-methylation has been reported in gastric tumors [42]. The Weinberg's group later reported that miR-10b5p acts as a metastasis-supporting miRNA, due to its ability to favor migration and invasion of breast cancer cells [43,44]. In line with this, miR-10b5p targets the HOXD10 gene, a repressor of several modulators of cell migration [44]. The expression of miR-10b5p is tightly controlled by the transcription factor Twist, a well-established regulator of epithelial-to-mesenchymal transition (EMT). Increased expression of miR-10b5p was detected in the vasculature of breast IDC (invasive ductal carcinoma) grade III tumors, compared to lower expression in DCIS (ductal carcinoma in situ) [45]. The pleiotropic activity of miR-10b5p could also rely on its ability to target the expression of diverse tumor suppressors, including TP53, HODX10, PAX6, NOTCH1 and FOXO3 (see Table 2) [46].

Biagioni et al. originally reported that the expression of miR-10b3p was down-regulated in breast tumors, relative to matched peri-tumoral tissues [12]. This downregulation occurred, at least in part, through the methylation of CpG islands located within the regulatory regions of the miR-10b locus [12]. Ectopic expression of miR-10b3p inhibited proliferation of breast cancer cell lines and reduced the size of xenografted breast tumors. Three pivotal proteins involved in the control of cell proliferation, namely BUB1, PLK1, and CCNA2, were shown to serve as targets of miR-10b3p. Accordingly, intratumoral injection of a mimic of miR-10b3p reduced the expression of BUB1, PLK1 and CCNA2 proteins [12]. The prognostic role of miR-10b3p and of its target was evaluated in the MEATBRIC dataset. This analysis included 1286 breast cancers from 5 different subtypes: HER2+ (127 patients), basal-like (209 patients), luminal A (479 patients), luminal B (312 patients), and normal-like (151 patients), for which both mRNA and miRNA data were available [12]. mRNAs and miRNAs were measured for each tumoral and normal samples of the METABRIC dataset. Kaplan-Meyer analysis revealed a significant association between low expression levels of miR-10b3p and poor disease-specific survival [12]. This association was not evidenced for the augmented expression of miR-10b5p. The combined application of the COSMIC algorithm [47] and miRanda predictions uncovered 15 target mRNAs of miR-10b3p [12]. Among those targets three, BUB1, PLK1 and CCNA2 were confirmed, and additional cell cycle related targets were also identified. Increased expression of BUB1, PLK1 and CCNA2 was associated with poor survival (Table 2) [12] .

These findings have several implications to the roles played by miR-10b in breast tumorigenesis. Presumably, the expression of miR-10b3p is altered in the early stages of mammary cell transformation. This could lead to aberrant cell proliferation, mediated by increased expression of the cell cycle related targets of miR-10b3p. In line with early alterations, downregulation of miR-10b3p expression appears to occur independently from the subtype of breast cancer, suggesting that it might represent an event preceding specification of breast cancer subtypes. Interestingly, the regulation of the expression of the two strands derived from the miR-10b locus is controlled by the combination of epigenetic and transcriptional events. While downregulation of miR10b-3p occurs through methylation of CpG islands, the transcription factor TWIST up-regulates the expression of miR-10b5p [44]. This might underlie mechanistically the dual and opposite roles of the miR-10b locus: Early in breast tumorigenesis miR-10b3p downregulation leads to aberrant cell proliferation, while TWIST-mediated transcriptional induction of miR-10b5p contributes, as a late step, to shape a metastatic phenotype.

Unlike downregulation of miR-10b3p, which occurs independently from the breast cancer subtype, up-regulation of miR-10b5p might be specifically selected in highly metastatic breast tumors. Thus, waves of miR-10b3p and 5p targets might

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