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Short survey

MicroRNA-driven deregulation of cytokine expression helps development of drug resistance in metastatic melanoma

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ABSTRACT

microRNAs are major components of the eukaryotic post-transcriptional machinery and are frequently deregulated during cancer development. Increasing evidence points to them also as key players in the establishment of drug resistance. In this review, we provide an updated overview of the role of miRNAs in melanoma development and drug resistance and postulate that they are able to drive these processes in concert with deregulation of inflammatory and angiogenic cytokine expression. Notably, we have identified by querying the Cancer Genome Atlas database, a defined set of miRNAs which mostly have an impact on the development of melanoma and have recognized the main downstream pathways controlled by them. Most importantly, these miRNAs, which are down-regulated in metastatic melanomas as compared to primary tumors, are also able to predict prognosis of BRAF-mutated melanoma patients. Finally, we discuss the possibility that a common miRNA signature characterizes not only acquired resistance to MAPKi but also innate resistance to anti-PD-1 immunotherapy, since these conditions are both associated with alterations of the same pro-angiogenetic and pro-inflammatory pathways.

1. Introduction

microRNAs (miRNAs) are short regulatory RNAs of 19–24 long nucleotides generated by a complex and tightly regulated biogenesis process, constituting the most expressed class of non-coding RNAs in eukaryotic cells, whose main function is the post-transcriptional modulation of gene expression [1,2]. miRNAs are able to affect mRNAs through a perfect or near-perfect binding to their 3′UTR, causing mRNA degradation or block of translation, respectively (Fig. 1A) [3]. In particular, the "seed region" of each miRNA, which is the portion on its 5′end (from position 2 to 8), is responsible for recognizing the target mRNAs [4]. The sequence of this specific region allows us to allocate mature miRNAs into the same family [4]. One of the most important features of miRNAs is their capability to potentially target dozens of mRNAs simultaneously, thereby affecting multiple cellular pathways (Fig. 1B, left) [5]. Conversely, a single intracellular pathway could be affected by multiple miRNAs, which are capable of binding different sequences in the 3′ UTR of the same targeted mRNAs (Fig. 1B, right). These features effectively explain why miRNAs are the most potent post-transcriptional regulators of gene expression and are the reason they are potentially involved in every biological function in both healthy and diseased states [6]. Most importantly, there are both conserved and non-conserved miRNAs binding sites virtually in every eukaryotic mRNA and it is for this reason they are supposed to be under miRNA control.

miRNA biogenesis is tightly regulated by transcription factors, which could be conversely targeted by miRNAs in feedback regulatory loops [4]. For example, the critical role of the MYC-miR-26a-EZH2 network has been described and associated with aggressive B-cell lymphoma progression [7]. miRNA sequences are mostly located in clusters within various genomic contexts and are classified as "intergenic" or "intronic" [8]. The first class is directly transcribed from own promoters, whereas the second is located within introns of noncoding or coding transcripts and regulated by their host gene promoters [8]. miRNAs are all transcribed by RNA polymerase II in a pri-miRNAs long primary transcript, which is processed in the nucleus by the Drosha/DGCR8

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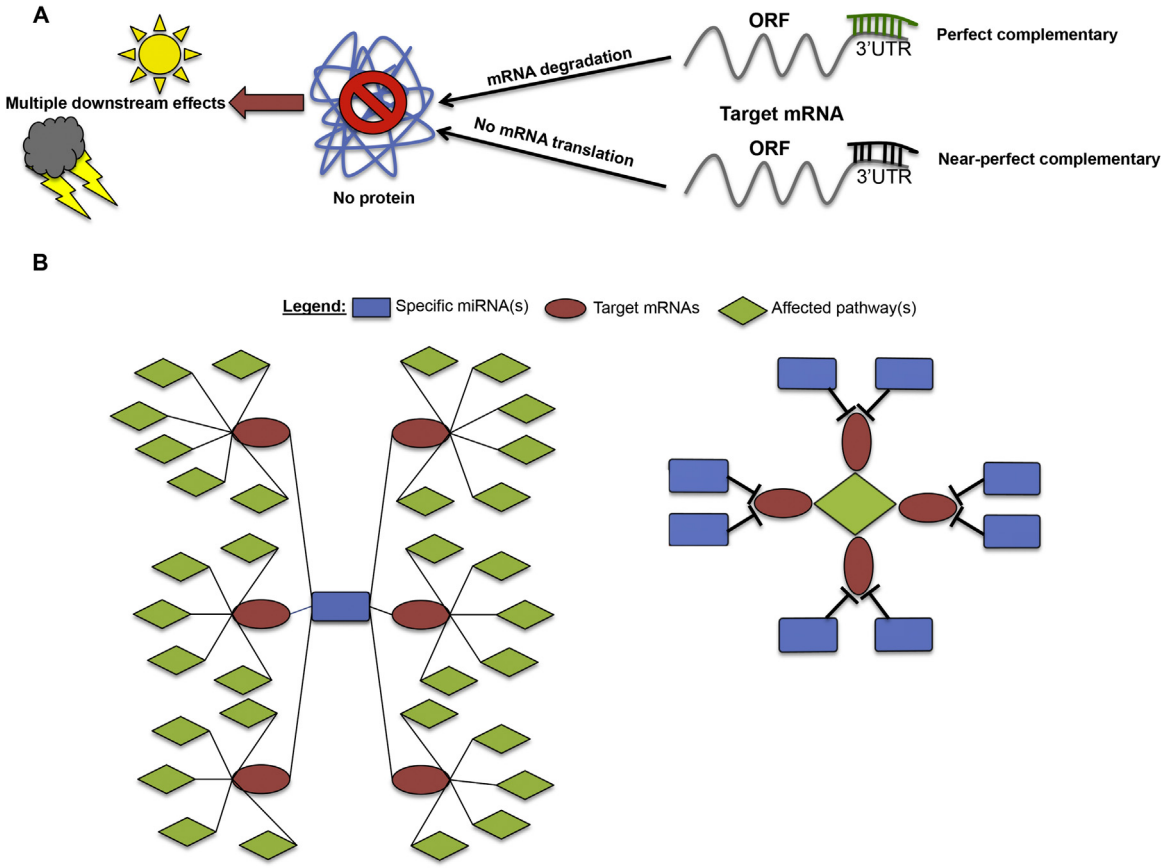

Fig. 1. miRNAs are able to affect multiple mRNAs thus controlling multiple molecular pathways. miRNAs bind the 3′UTR of mRNAs with a perfect or near-perfect binding thus provoking their degradation or reduced translation, respectively (A). miRNAs are able to affect the expression levels of dozens of mRNAs thus controlling multiple molecular pathways (B).

complex [6]. This complex cuts the pri-miRNAs in order to generate a 70 bp long pre-miRNA [6]. This intermediate miRNA is exported into the cytoplasm where it is processed by the endonuclease RNAse III Dicer, consequently giving rise to the mature miRNA duplex [6]. The mature miRNA, together with the Argonaute2 and the transactivation-responsive RNA-binding proteins, is assembled into the RISC complex (RNA-induced silencing complex) [6]. This complex is responsible for the removal of the complementary strand and for the generation of the fully functional miRNA [6].

As previously mentioned, miRNA clusters are generally co-expressed, but interestingly each individual mature miRNA may also be regulated at the post-transcriptional level through various mechanisms, such as the addition of a non-templated nucleotide at the 3′ end, a process called RNA "tailing" or through RNA methylation or regulation of RNA stability by several specific nucleases [4]. Finally, miRNA expression can also be regulated by epigenetic mechanisms such as DNA methylation and histone modifications [4].

miRNAs dysregulation is involved in various human diseases, especially in cancer. Indeed it is possible to distinguish between healthy and cancer tissues thanks to specific miRNA signatures, which could represent a specific footprint potentially different in each type of human tumor. In 2002, Calin and colleagues first described miRNA deregulation in human cancer and identified miR-15a/16-1 cluster deletion in chronic lymphocytic leukemia [9]. This event directly causes anti-apoptotic B-cell lymphoma 2 (BCL2)-overexpression because it was demonstrated that this oncogene is a molecular target of both these tumor suppressor miRNAs [9]. In addition, the same investigators were able to show that many known miRNAs are located in genomic regions frequently altered in human cancers [10]. Starting from these findings, in the last fifteen years miRNAs have been the object of many intensive studies and the focus of thousands of scientific publications where several cancer-associated miRNAs have been described. Nowadays, more than 2500 human miRNAs have been developed and have now been classified as oncosuppressor miRNAs, such as miR-15/16, let-7, miR-200, miR-34, miR-107 and miR-126, or oncomiRs, for example miR-221/222, miR-21 and miR-10b [5,6].

Here, we review the role of miRNAs in melanoma development and drug resistance with particular emphasis on their correlation with inflammatory and angiogenic cytokine deregulation.

2. Malignant melanoma and resistance to targeted therapies

Melanoma is the most aggressive and lethal type of skin cancer that arises from melanocytes [11]. Metastatic disease has a highly unfavorable prognosis and is poorly influenced by standard chemotherapy. Up until about 10 years ago, chemotherapy for melanoma was based on two FDA-approved drugs, fotemustine and dacarbazine, and on immunotherapy with IL-2, which provided only a modest benefit in survival [12]. In recent years, the introduction of novel agents based on immunotherapy and on targeted therapies has dramatically improved clinical outcome owing to their ability to significantly enhance the proportion and duration of objective responses of patients as well as to improve progression free and overall survival. The first approach is based on immune checkpoint inhibitors targeting CTLA4 and PD-1/PD-L1 interaction, whereas the second involves the use of MAPK pathway inhibitors (KIs) [13]. These molecules have been developed