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REVIEW ARTICLE

MicroRNA signatures landscape in renal cell carcinoma - related epithelial to mesenchymal transition

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Summary

Epithelial malignancies demonstrate aggressive phenotypes (increased metastatic potential) due to mechanisms including the epithelial-to-mesenchymal transition (EMT). Novel micro-epigenetic markers –the micro-RNAs (miRs) - are under investigation in solid malignancies for diagnostic, prognostic or specific targeted therapy purposes. miRs are considered very promising and significant genetic markers for categorizing patients by their molecular characteristics, extending also their complicated genetic signatures. miRs are short, non-coding RNAs consisting of 20-25 nucleotides located at intra- or inter-gene regions. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. Their deregulation in cancer cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumour suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations leads to a loss of miRs-mediated repression of target mRNA. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been confirmed. In some of them, their upregulation correlates with an increased ongogenic activity, whereas in others the same miR type acts as a suppressor agent. In the current special molecular review we describe specific miRs in EMT development and progression in renal cell carcinoma (RCC).

Key words: *gene, renal cell carcinoma, microRNAs, epithelial-to-mesenchymal transition*

Introduction

Cell malignant transformation is mediated by an aberrant gene expression, including predominantly oncogenes upregulation combined with suppressor genes downregulation that lead to cell cycle deregulation [1]. In fact, cancer genome consists of all genetic alterations that modify the normal DNA/m RNA sequences triggering a cataract of molecular reactions inside and outside the nucleus micro-environment [2]. Point mutations, polymorphisms, abnormal gene copy number (amplification, deletion), or structural chromosomal rearrangements (translocations) and epigenetic modifications detectable by different molecular techniques provide critical information to oncologists for handling those patients in a rational therapeutic way regarding their isolated molecular

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landscape [3]. Quite recently, micro-RNAs (miRs) are considered novel significant markers for categorizing patients based on their molecular characteristics extending their genetic signatures. In the current molecular review, we explored the role and described specific miRs implicated in epithelial-to-mesenchymal transition (EMT) development and progression in renal cell carcinoma (RCC).

miRs: structure and function

MiRs demonstrate an increasing interest for understanding their role in cancer and also in handling patients via targeted therapeutic agents [4]. miRs are short, non-coding RNA molecules consisting of 20-25 nucleotides located at intra- or inter-gene regions [5]. RNA polymerase II is responsible for their transcription. Initially, pri-miRNAs are reformed to pre- miRs followed by a maturation process. In the nucleus, the RNase III enzyme Drosha complex provides release of the pre-miRs to the cytoplasm where the final single-stranded mature miR is produced [6]. Functional miRs mediate a positive regulation of posttranscriptional gene silencing. MiRNA deregulation in cancer cells due to genetic (mutations, translocations), epigenetic (DNA hypermethylation of tumour suppressor genes, extensive genomic DNA hypomethylation, aberrant histone modification patterns) and transcriptional alterations leads to a loss of miR-mediated repression of target mRNA [7-9]. Interestingly, a biphasic role of miRs in cancers of different histogenetic origin has been detected. In some of them, their upregulation seems to correlate with increased ongogenic activity, whereas in others the same miRNA type acts as a suppressor agent (miRNA 29 in hepatocellular carcinoma and lung cancer, miRNA 26a in lung and breast lung cancer, respectively) [10,11]. Mirs deregulation has been detected to be implicated in a variety of carcinomas including thyroid, esophageal, Epstein-Barr-related nasopharyngeal carcinoma, or hepatocellular [12-15]. Understanding biogenesis, maturation and functional aspects of miRNAs we realize that their transcriptional-expression profile should be a useful molecular tool for typing and classifying subgroups of patients with the same histopathological cancer, as well as targeting specific genes and modifying the corresponding response rates to specific inhibition molecules [16].

Epithelial-to-mesenchymal transition (EMT) phenomenon

Carcinogenesis is a multi-step procedure comprising a broad spectrum of genetic (chromosome and gene structural/numerical aberrations) and epigenetic (DNA methylation, histone modifications, and specific micro-genetic non-coding markers deregulation) alterations. Additionally, epithelial malignancies demonstrate aggressive phenotypes (increased metastatic potential) due to mechanisms including the EMT). EMT phenomenon is based on a combination of intra-extra-cellular modifications that enhance cell adhesion disruption, and also focal cell/tissue transformation to a mesenchymal phenotype [17]. EMT is implicated in metastatic process by releasing cancer cell migration/invasion, and also by inducing proliferation and suppressing apoptotic mechanisms. Concerning epithelial malignancies- including RCC-E cadherin/catenin complex -involved also in EMT- releases tumor metastasis mechanisms increasing also the stage of disease. Based on these alterations, specific agents such as calcitriol (vitamin D3, an active form of vitamin D) seems to suppress E-cadherin downregulation in RCCs [18]. For these reasons it is involved in elevated rates of malignant tumor relapse and decreased responses to targeted or chemotherapeutic strategies.

MiRs landscape in RCC - related EMT

RCC is an aggressive malignancy with increased frequency worldwide. Exposed metastatic potential at the time of diagnosis leads the corresponding patients to poor prognosis and survival rates [19]. RCC comprises a variety of pathological entities that arise from the corresponding epithelia. Clear cell RCC covers 60-70% of all RCCs, whereas papillary and chromophobe histopathological subtypes are referred to the rest of them [20]. Among epigenetic mechanisms that seem to interfere with EMT development and progression in RCC, deregulation of miRs has a central role. Concerning the impact of specific miRs' deregulation in RCC, molecular analyses have revealed a landscape of these markers that enhance EMT progression and metastasis. MiR-155-5p represents a significant micro-genetic marker that is involved in epithelial malignant transformation and immune response rates [21]. Overexpression of miR-155-5p is correlated to apoptosis-inducing factor downregulation suppressing the apoptotic process. This alteration induces progression and recurrence of the malignancy in the corresponding patients [22]. In conjunction to the previous referred miR-155-5p - mediated activity, its overactivation was associated with decreased E-cadherin expression providing the eligible substrate for EMT progression in renal cancer cells *in vitro* and *in vivo*. The crucial role of miR-155-5p in RCC

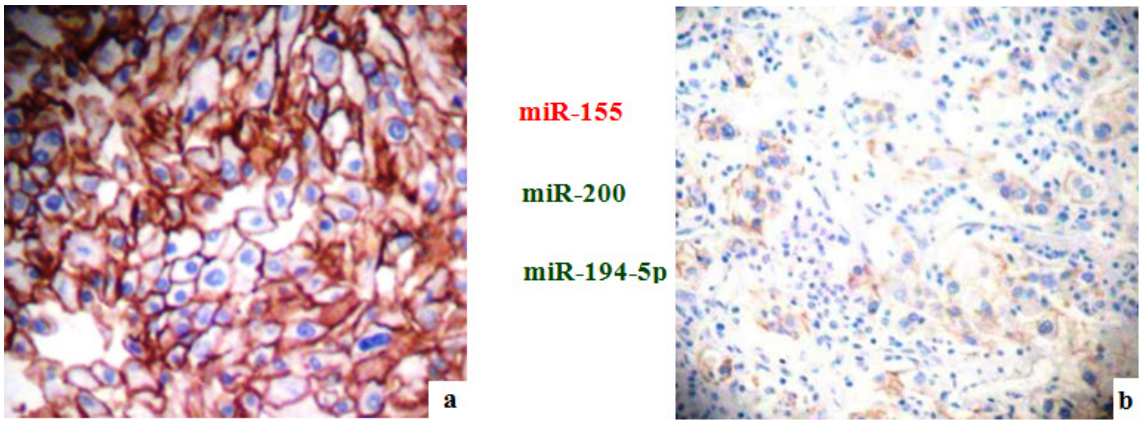

Figure 1. miRs that affect E-cadherin expression patterns in RCC (clear cell histotype). The molecule combined with N-cadherin, vimentin is critically involved in EMT progression. **a:** E-cadherin overexpression. **b:** Low expression of the molecule (DAB-based brown membranous staining pattern, original magnification 100x). MiR-155-5p (red) is frequently overexpressed in RCCs, whereas other miRs such as miR-200-a/b and miR-194-5p (green) -acting as suppressor factors - lose their expression and activity in RCC the first and in nephroblastoma the second, respectively (RCC: renal cell carcinoma, EMT: epithelial-to-mesenchymal transition, DAB: diaminobenzidine-tetrahydrocloride.

aggressive phenotypes is under investigation. Almost recently, a molecular study showed the existence of a unique pathway involved in EMT development and progression in these malignancies. Interaction between miR-155-5p and lncTCL6 is responsible for EMT progression and the corresponding lncTCL6-miR-155-Src/Akt pathway is overactivated in RCCs [23].

In conclusion, the previously referred and other similar molecular analyses suggest that miRs should be considered potentially reliable biomarkers for discriminating RCC patients at the basis of micro-genetic signatures, explaining in part differences in biological behaviour and response rates to specific targeted regimens. Involvement of deregulated miRs in RCC development and progression is a very promising topic of research especially for this role in modifying expression of EMT- related molecules [24,25] (Figure 1).

Conflict of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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