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REVIEW

MiR-506: A Multitasker in Suppression of the Epithelial-to-Mesenchymal Transition

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MiRNAs emerge as important regulators of epithelial-to-mesenchymal transition (EMT). The Best known EMT regulatory miRNAs are targeting the transcriptional repressors of E-cadherin (E-cad). We identified miR-506 as a key EMT inhibitor through directly targeting the E-cad transcriptional repressor, SNAI2. Our recent studies showed that miR-506 simultaneously suppresses vimentin and N-cad. Thus, miR-506 possesses a multitasking property in the suppression of EMT and metastasis and thus may represent a promising tool in cancer therapeutics.

Keywords: miR-506; epithelial-to-mesenchymal transition; vimentin; N-cadherin; epithelial ovarian cancer; nanoparticle

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Introduction

Epithelial ovarian cancer (EOC) is the most lethal gynecological malignancy [1]. It has been well documented that epithelial-to-mesenchymal transition (EMT) is a critical process that is underlying the metastasis process [2]. Therefore, extensive research has been devoted to interrogate EMT regulatory network in EOC. The molecular hallmarks of EMT include down-regulation of E-cadherin (E-cad) and up-regulation of mesenchymal proteins, such as vimentin and N-cadherin (N-cad). Downregulation of E-cad has been considered a driver for this process [3-7]. The functional role of vimentin and N-cad is not well understood.

In recent years, it has become evident that the small non-coding RNAs, miRNAs, are important regulators of EMT. The let-7 and miR-200 miRNA families have shown to target E-cad transcriptional repressors [8, 9]. MiR-30a and miR-138 were shown to directly target VIM [10, 11]. Few miRNAs have been reported to regulate both E-cad and mesenchymal proteins.

Our recent investigation of the EMT regulatory network in the serous subtype of EOC characterized miR-506 as a robust EMT inhibitor through directly targeting E-cad repressor SNAI2 [12]. MiR-506 has also been shown to suppress EMT in breast cancer [13]. When we examined 7publicly available miRNA target gene databases, we found that *VIM* and *CDH2* had 1 predicted binding site of miR-506[14]. We next performed two sets of functional validation using reporter gene assays. We found that miR-506 suppressed the reporter activity linked to the 3'-UTR from *VIM* or *CDH2* that contain the predicted binding site. Control miRNA or removal of the binding site did not exhibit the regulation by miR-506 [14]. These results showed that miR-506 suppresses EMT through three key molecules that are intimately linked

to the two spectrums of this cell lineage transition.

We sought to understand how important the regulation of the vimentin is to the EMT process. Vimentin is an intermediate cell filament protein that is commonly considered as a mesenchymal marker. Whether vimentin plays a more active role in the EMT process is not well understood. Using siRNAs to directly target Vimentin, we found that Vimentin actually plays an active role in this process [14]. Attenuation of vimentin led to acquisition of epithelial phenotype. The treatment of cells with siRNA for vimentin led to inhibition of cell migration in both transient and stable transfection conditions [14]. In contrast, siRNA treatment for N-cad did not lead to marked changes in cell migration and invasion. Because N-cad is known to mediate cellular interaction with extracellular matrix [15], the current experimental setting may not mean N-cad does not play an active role in EMT. Rather, the role of N-cad in EMT may manifest itself in experimental setting when extracellular matrix components are considered. Future experiments will shed light on this unresolved question. Future experiments may include multiple cellular components (e.g., tumor cells and fibroblast co-cultures) to better determine the role of N-cad. Communication between tumor cells and their microenvironment is currently a hotly pursued area of investigation in cancer cell biology.

In summary, our recent investigations have revealed that miR-506 has a multitasking role in the suppression of EMT through the direct regulation of not only E-cad through SNAI2 but also of 2 recognized mesenchymal proteins, vimentin and N-cad. Therefore, miR-506 has emerged as a key network gatekeeper for epithelial and mesenchymal lineage switches by simultaneously regulating multiple nodes in the sophisticated regulatory network. We believe this is a clinical relevant finding given that our studies have shown that miR-506, when delivered through a nanoparticle vehicle, effectively reduced the tumor burden and inhibited invasive growth and metastasis in EOC orthotopic mouse models. It is our hope that miR-506 will become a promising new therapeutic agent to suppress tumor EMT and cancer progression.

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