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

Yan Sun 1, Delia Mezzanzanica 2, Wei Zhang 3

1Departments of Pathology, Tianjin Medical University Cancer Institute and Hospital, Tianjin 300060, China
2Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
3Departments of Pathology, The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

Correspondence: Wei Zhang
E-mail: wzhang@mdanderson.org
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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 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

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, 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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