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MIR-520E CAN REGULATE TRANSFORMING GROWTH FACTOR SIGNALING AND INHIBIT NSCLC INVASION

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Abstract. Transforming growth factor-β (TGF-β) pathway plays crucial roles during the carcinogenesis and metastasis. Transforming growth factor-β receptor 2 (TGFBR2) is a key molecule for the regulation of TGF-β pathway and frequently downregulated or lost in several cancer types including non-small cell lung cancer (NSCLC). However, little is known about the mechanism of miRNA-mediated TGFBR2 downregulation in NSCLC. Also, TGF-β pathway is often regulated by negative feedback mechanisms, which allow cancer cells to escape growth inhibition from TGF-β. Here, we found that the significance of mir-520e for TGFBR2 downregulation and the negative regulation of TGF-β signaling in NSCLC. We demonstrate that mir-520e is upregulated in metastatic tumor tissues compared to non-metastatic ones and its expression is inversely correlated with that of TGFBR2 in clinical samples. We further discovered that TGF-β decreased TGFBR2 expression and, treatments of the chemical inhibitors of histone deacetylase and DNA methyltransferase did not influence TGF-β-induced TGFBR2 downregulation. TGF-β dramatically increased the expression of mir-520e targeting TGFBR2. ChIP-PCR experiments showed that mir-520e is transcriptionally induced by SMAD2/3 in response to TGF-β. Our findings reveal a novel negative feedback mechanism in TGF-β signaling via mir-520e and that mir-520e overexpression could be a predictive factor for NSCLC metastasis.

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