学位論文内容の要約

Dissertation Summary

学位論文題目

Functional analysis of miR-199a-3p in tumor endothelial cells
（腫瘍内皮細胞における miR-199a-3p の機能解析）

博士の専攻分野の名称:博士（歯学）　　氏名:Hong Yuying

Tumor angiogenesis, the formation of new blood vessels within tumors, is essential for tumor growth and metastasis. Tumor blood vessels differ from normal vasculature both physiologically and morphologically, exhibiting characteristics such as reduced pericyte coverage and increased vascular permeability. These abnormalities contribute to a tumor microenvironment that facilitates cancer progression. Tumor endothelial cells (TECs), which line tumor-associated blood vessels, display distinct phenotypic and functional features compared with normal endothelial cells (NECs), including chromosomal abnormalities and resistance to anticancer drugs.

MicroRNAs (miRNAs) are small non-coding RNAs approximately 20 nucleotides in length that regulate gene expression post-transcriptionally by binding to target mRNAs, resulting in mRNA degradation or translational repression. Although miRNAs play important roles in tumor progression, their specific functions in TECs remain incompletely understood.

In this study, NECs and TECs were isolated from non-tumor and tumor regions of human renal cancer tissues. Comprehensive miRNA array analysis was performed to compare miRNA expression profiles between NECs and TECs, revealing that miR-199a-3p was the most upregulated miRNA in TECs. Functional analyses demonstrated that overexpression of miR-199a-3p in NECs significantly enhanced cell proliferation, migration, and invasion, whereas inhibition of miR-199a-3p in TECs suppressed these cellular functions. These findings indicate that miR-199a-3p contributes to the pro-angiogenic phenotype of TECs.

Target gene prediction using four independent databases identified CD151 as a potential target of miR-199a-3p, and subsequent experiments confirmed that miR-199a-3p directly represses CD151 expression. Gene knockdown studies further demonstrated that silencing CD151 promoted endothelial cell proliferation, migration, and invasion, thereby phenocopying the effects of miR-199a-3p overexpression. Additionally, both miR-199a-3p overexpression and CD151 knockdown reduced adhesion to collagen IV, a major extracellular matrix component, resulting in enhanced migratory capacity. Loss of CD151 was shown to activate ERK signaling in TECs, leading to a significant increase in endothelial cell migration and invasion, key processes in angiogenesis. Furthermore, both miR-199a-3p overexpression and CD151 silencing markedly upregulated MMP2 expression in TECs, suggesting that this signaling axis promotes extracellular matrix degradation as well as cellular motility.

To our knowledge, this is the first study to demonstrate that miR-199a-3p–dependent suppression of CD151 leads to ERK activation in endothelial cells, revealing a novel role for miR-199a-3p in coordinating extracellular matrix interactions and intracellular signaling during tumor angiogenesis. These findings indicate that upregulation of miR-199a-3p enhances the pro-angiogenic phenotype of TECs and suggest that the miR-199a-3p–CD151–ERK signaling pathway represents a promising target for further investigation in tumor angiogenesis.

In conclusion, our results suggest that miR-199a-3p regulates tumor angiogenesis through suppression of CD151 and subsequent activation of ERK signaling in TECs. This study provides important mechanistic insights into the regulation of tumor angiogenesis and indicates that components of the miR-199a-3p–CD151–ERK axis may serve as promising molecular targets for anti-angiogenic cancer therapy. Further in vivo validation and clinical studies will be required to clarify the broader biological significance and therapeutic potential of this pathway.