M2 MACROPHAGE-DERIVED EXOSOMAL MICRORNA-21-3P PROMOTES COLORECTAL CANCER PROGRESSION VIA MEDIATING FAM46C

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Background In the tumor microenvironment, macrophages play critical roles in tumor suppression and progression, depending on their subtypes, M1 and M2 macrophages, respectively. Especially, macrophage-derived exosomes modulate the gene expression of cancer cells by delivering miRNAs to downregulate specific genes. FAM46C, also known as terminal nucleotidyltransferase 5C (TENT5C), is initially recognized as a non-canonical polyadenylate ribonucleic acid polymerase and has been identified as a tumor suppressor in multiple myeloma. However, the function of FAM46C in other cancers is still unclear.

Methods M2 macrophages was cocultured with cancer cells and the conditioned media was collected to purify exosomes and identify miRNAs in it. Target genes of miRNAs were predicted using the public open database, miRDB - MicroRNA Target Prediction Database. The 3'UTR of miR-21-3p was cloned into psiCHECK™-2 Vector (Promega, Madison, WI, USA) for the luciferase activity assay. RT-qPCR assay with gene-specific primers was performed on an ABI 7500 system (Applied Biosystems, Foster City, CA, USA). The comparison analysis of the mRNA expression levels in tumor and paired normal tissues using the TCGA database was performed to confirm the expression of miRn-21 and FAM46C in colorectal cancers.

Results In this study, we identified that M2 macrophage-derived exosomal miR-21-3p downregulates FAM46C, thereby promoting colorectal cancer progression. First, we showed that M2 macrophages secrete exosomal miR-21-3p in the co-culture system with cancer cells. Then, we predicted FAM46C as a target of miR-21-3p using the public open database. To demonstrate the interaction between miR-21-3p and FAM46C, we showed that miR-21-3p directly targets and inhibited the expression of FAM46C using the 3'UTR reporter assay. Also, we found an increase of miR-21-3p and a notable decrease in the expression of FAM46C in colorectal cancers by comparison analysis of the mRNA expression levels in tumor and paired normal tissues using the TCGA database. Finally, we revealed FAM46C inhibits proliferation and migration in the colorectal cancer cells due to changes of the lipid metabolism in the tumor microenvironment.

Conclusions Taken together, we demonstrated that M2 macrophages enhances aggressiveness of colorectal cancers via exosomal miR-21-3p directly targeting FAM46C in the cancer cells. By unraveling the mechanisms underlying the regulation of FAM46C expression in tumor microenvironment, we can expect to shed light on novel therapeutic avenues that could effectively counteract cancer progression in colorectal cancer patients.

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