Abstract Title

Exosomal delivery of miR-24-3p impedes T-cell proliferation and differentiation by repressing FGF11 and correlates with prognosis in nasopharyngeal carcinoma

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BACKGROUND: Tumor-derived exosomes (T-EXO) deliver a broad range of cargo, including proteins, microRNAs, mRNAs, and DNA fragments between cell interaction, to regulate the intercommunication between cancer cells and their microenvironments.

HYPOTHESIS: To investigate the role and its related mechanism of T-EXO carried miR-24-3p in the regulation of T-cell proliferation and differentiation.

METHODS: T-EXOs were isolated from NPC cell lines or patient sera. Exosomal and cellular miRNA expression were measured by microRNA chip array or quantitative reverse transcription PCR (qRT-PCR). T-cell proliferation and differentiation was performed in a co-culture system in the presence or absence of T-EXOs and analyzed by flow cytometry. Phosphorylation level of ERK and SATA proteins were determined by immune blotting. FGF11, CD4, CD8 and Foxp3 expression in NPC samples were detected by immunohistochemistry, a standard two-tailed Student's t-test and Pearson's chi-squared test were used for group comparison.

RESULTS: miR-24-3p was enriched in T-EXO from nasopharyngeal carcinoma (NPC) patient sera or NPC cells, which correlated with worse disease-free survival (DFS). The exosomes (miR-24-3p-sponge-EXO) released from miR-24-3p-sponge-TW03 cells in which miR-24-3p was knocked down by sponge failed to hinder T-cell proliferation and Th1 and Th17 differentiation or to induce Treg differentiation in vitro. Mechanism dissection revealed that miR-24-3p-sponge-EXO-treated T-cells up-regulated P-ERK, P-STAT1 and P-STAT3 but down-regulated P-STAT5 compared with NC-sponge -EXO-treated T-cells. FGF11 was identified as a directly target gene of miR-24-3p by in vivo and in vitro assessment. More importantly, T-EXO repressed the FGF11 expression in T-cells during proliferation and differentiation. Interestingly, once blockade of the FGF11 expression in T-cells by lenti-shFGF11, miR-24-3p-sponge-EXO did impede the shFGF11-T-cell proliferation, Th1 and Th17 differentiation but induce Treg differentiation. miR-24-3p-sponge-EXO-treated T-cells didn't up-regulate P-ERK, P-STAT1 and P-STAT3 or down-regulate P-STAT5 when FGF11 was knockdown in T-cells. Interestingly, the FGF11 expression in tumor-infiltrating lymphocytes (TILs) significantly positively correlated with the number of CD4+ and CD8+ TILs and predicted a favorable patient DFS ($p < 0.05$). In addition, the cellular and exosomal miR-24-3p was increased when NPC cells under hypoxia.

Conclusion: We unveil that the exosomal miR-24-3p takes an important role in T-EXO-mdiated T-cell suppression in NPC microenvironment via repressing FGF11 expression, leading to tumor progression and having a potential prognostic value.