O12 Tumor-secreted exosomal miR-424: impact on prostate tumorigenesis in mouse models and patients

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Introduction & Objectives: Recent data highlight the relevance of tumor-secreted exosomes for cancer progression. Exosomes are extracellular micro-vesicles secreted in body fluids and have strong potential as liquid biopsy biomarkers for diagnostic, prognostic and therapeutic purposes. Our data indicate that miR-424 is secreted in exosomes and promotes cancer stem cell phenotypes and tumor development by autocrine/paracrine mechanisms. The goal of this study was to evaluate secretion of miR-424 in plasma exosomes from primary and advanced prostate tumors and assess the functional impact of exosomal miR-424 in vitro and in vivo.

Materials & Methods: Exosomes were isolated from cell culture medium, tumor xenografts, and plasma from patients using commercial kits or ultracentrifugation. Cell-free plasma samples from patients with organ-confined, metastatic and castration-resistant prostate tumors were collected with Ethical committee approval. Quality of isolated exosomes was verified by western blotting for specific protein markers, transmission electron microscopy and confocal microscopy. miR-424 was measured by qRT-PCR. Phenotypic changes in recipient cells were assessed by in vitro tumor-sphere assays and in vivo tumor growth. Systemic administration of isolated exosomes was done by tail vein injection and tissue distribution monitored using the IVIS Spectrum system.

Results: miR-424 expressing prostate cancer cells and tumor xenografts secrete miR-424 into exosomes. To determine the clinical relevance of these findings, we examined the level of miR-424 in exosome preparation from cell-free plasma obtained from patients with localized, metastatic and castration-resistant prostate cancer. While weak positivity was found in a limited number of patients with organ-confined disease, about 40% of patients with metastatic and castration-resistant prostate tumors were positive for exosomal miR-424, suggesting a relation between disease progression and exosomal miR-424 secretion. To assess the functional implications of miR-424 secretion in exosomes, we performed in vitro and in vivo experiments. Exosomal miR-424 was efficiently transferred to normal and tumor cells and promoted stem-like and tumorigenic phenotypes in recipient cells. Moreover, systemic supplementation of miR-424 containing exosomes by tail vein injection in mice bearing subcutaneous xenografts led to the exosome localization at the tumor site and promoted tumor growth in vivo.

Conclusions: Our data demonstrate that miR-424 is secreted in exosomes in cell cultures and tumor xenografts. Exosomal miR-424 is more frequent in plasma from patients with advanced-stage disease compared to organ-confined prostate cancer. Our data indicate that miR-424 released in exosomes can affect tumor progression and metastatic spread in prostate cancer patients. These findings can be exploited to design innovative diagnostic and therapeutic strategies for prostate cancer.