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The enrichment of miR-23b-3p, miR-126-3p and GAS5 in extracellular vesicles from breast cancer cells treated with sorafenib inhibited the tumor growth of xenografts in zebrafish model

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Extracellular vesicles (EVs) are secreted by all cell types for intercellular communication and transport nucleic acids, peptides, lipids and metabolites to recipient cells.
We previously demonstrated that the treatment of breast cancer cells with the multikinase inhibitor sorafenib, determined the dysregulation of the tumor-suppressor transcripts miR-23b-3p, miR-126-3p and GAS5. Here, we collected the EVs released by breast cancer cells (HCC-1937, MDA-MB-231, MCF-7 and MDA-MB-453) treated with sorafenib. We quantified the levels of the 3 ncRNAs encapsulated in the EVs by ddPCR and we found the increase of these ncRNAs. The EVs used as vehicles of miR-23b-3p, miR-126-3p and GAS5 in breast cancer cells, determined an increased expression levels of the 3 ncRNAs up to 7.5 times ($p < 0.01$) and the inhibition of cellular proliferation in vitro (up to 19%; $p < 0.01$). To establish the role of the EVs as carriers of ncRNAs in vivo, at 48 hpf we injected the MDA-MB-231 cells in zebrafish embryos and we treated the xenografts with the EVs rich of miR-23b-3p, miR-126-3p and GAS5 secreted by MDA-MB-453 cells. We found the reduction of the xenograft tumor area (84%; $p < 0.0001$, 24 h post-treatment), the inhibition of the angiogenesis and the reduction of the number of micrometastasis in the tails.
Our findings indicate a new way to enrich EVs with tumor-suppressor ncRNAs by treating the cells with an anti-cancer drug; the role of EVs as vehicles of ncRNAs; the combined effect of miR-23b-3p, miR-126-3p and GAS5 in limiting the aggressive properties of breast cancer in vitro and in vivo.