miR-193a AS NEW POTENTIAL THERAPEUTIC AGENT AND BIOMARKER IN CUTANEOUS MELANOMA

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Introduction: MicroRNAs (miRNAs) are promising diagnostic biomarkers and potential therapeutic targets or drug themselves in cancer. Their presence in blood and other physiological fluids may be a source of information useful for disease diagnosis, prognosis and treatment. Many miRNAs are involved in cancer development and progression. MiR-193a acts as potential tumour suppressor in malignant pleural mesothelioma, gastric and non-small-cell lung cancer and it regulates drug and chemoradiation resistance in bladder and oesophageal cancer, respectively. As regards melanoma, actually a study evaluating the expression of miR-193a in cutaneous melanoma tissues and cell lines and a pilot investigation from our laboratory on its levels in plasma of melanoma patients compared to healthy controls have been realized. Nevertheless, no data are reported on the role of miR-193a on the control of melanoma cell proliferation and metastasis. In the present study, the tumour suppressor effect of miR-193a ectopic expression was investigated in vitro and *in vivo* melanoma model. Parallely, its expression in plasma exosomes derived from stage IV melanoma patients was analysed in order to confirm its role as diagnostic biomarker.

Materials and methods: In order to evaluate the tumour suppressor role of miR-193a in melanoma cells, we studied its influence on intracellular pathways regulating survival, proliferation, apoptosis and migration, such as MAPK/ERK, and PI3K/Akt, and on markers involved in epithelial-mesenchymal transition (EMT). The *in vivo* miR-193a anti-cancer effects were evaluated in the murine B16.OVA melanoma model by using a viral (Modified Vaccinia Ankara, MVA) platform. Exosomes were isolated from plasma samples of melanoma patients and healthy donors, and their miR-193a levels were determined via quantitative real-time PCR.

Results: In vitro experiments showed a significant decrease of melanoma cell viability and migration and an increase of apoptosis in transfected cells. Furthermore, a significant decrease in B-Raf protein levels and in phosphorylation of Akt and Erk proteins was observed, suggesting the miR-193a ability to interfere with cell proliferation and survival. Vimentin and E-Cadherin transcriptional and protein levels were significantly modulated, indicating the potential of this miRNA to contrast EMT. A significant decrease of the miR-193a target PD-L1in the *in vivo* murine melanoma model, suggests an efficient delivery of the functional miR by the viral platform. Finally, a statistically significant decrease in the miR-193a levels was observed in exosome-derived plasma of metastatic melanoma patients compared to healthy donors.

Discussion and conclusion: Our data suggest that miR193a represents a potential therapeutic agent reducing melanoma progression and confirm its diagnostic biomarker role in this cancer type. Experiments aimed at deepened its anti-melanoma potential in the *in vivo* model are ongoing.