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EXTRACELLULAR VESICLES: ACTORS AND MARKERS OF THYROID CANCERS

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Background: Papillary thyroid carcinoma (PTC) carrying $BRAF^{V600E}$ mutation is the most frequent subtype of thyroid cancers. Despite very good prognosis in most cases, postsurgery recurrences and metastases occur in 5-15% of patients. Moreover, differential diagnosis between benign and malignant nodules is still challenging. Knowledge about extracellular vesicles (EVs) in PTC could rise a double interest: a better understanding of the biology of PTC and its clinical behavior, and an improvement of differential diagnosis between thyroid cancer subtypes.

Aims: The goals of this project are to (i) identify miRNAs actors and markers, released via EVs by the tumor, (ii) decipher the mechanisms by which they impact thyroid cancer and its microenvironment, and (iii) evaluate the diagnostic value of circulating miRNAs.

Methods and results: Using a mouse model in which $BRAF^{V600E}$ is selectively expressed in thyrocytes upon doxycycline injections, we isolated control and PTC-EVs from dissociated tissue by differential ultracentrifugations. Vesicles in the high-speed pellet displayed a size and some specific markers that were consistent with exosomal characteristics. Sequencing was performed to identify miRNAs with a differential abundance in EVs isolated from control- and $BRAF^{V600E}$ PTC-tissues.

To study the role of those EV-miRNAs, we focused on upregulated candidates, as those are the first deregulated and the most susceptible to be involved in intercellular communications within the tumour microenvironment. *In silico* analysis revealed an enrichment of upregulated EV-miRNAs in immune-related pathways. Considering the massive recruitment of macrophages in our model, we asked if PTC-EVs could affect macrophage phenotype. We treated primary bone marrow-derived macrophages with control and PTC-EVs and showed that PTC-EVs promote an anti-inflammatory gene signature in macrophages.

On another hand, EVs were isolated from plasma of patients with thyroid diseases before and after thyroidectomy. Upregulated miRNAs were measured in tissue, in plasma and in plasma-derived EVs in order to assess their diagnostic value. Whereas the upregulation of our candidates was confirmed in human PTC compared to benign diseases, no solid correlation could be demonstrated with miRNA level in plasma or plasma-EVs.

Conclusions: We provided a gradual tissue- and EV-miRNAs profiling during $BRAF^{V600E}$-driven PTC development and thyrocytes dedifferentiation. Even if deregulated in human PTC, selected candidates did not give convincing results as new non-invasive biomarker. However, we highlighted a role of EV-miRNAs in promoting an anti-inflammatory phenotype in macrophages supporting the establishment of a permissive microenvironment for tumor development.