Title (200 characters max): **The exosomal microRNA miR-503: a key modulator of resistance to chemotherapy in breast cancer cells**

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Abstract (400 words max):

The communication between cancer cells and their microenvironment is an essential aspect of cancerology. Therefore, understanding how the environment could affect tumor cells behavior is critical for the development of new anti-cancer therapies. In this study, we focus on the communication between the endothelium and breast cancer cells by extracellular vesicles (EVs), small vesicles released by cells implicated in cell-cell communication. More precisely we wondered if chemotherapeutic treatment could affect the communication via EVs. Previously, we identified a microRNA, miR-503 which exhibited upregulated levels in endothelial exosomes released by endothelial cells (ECs) upon epirubicin treatment. Moreover, this endothelial EVs loaded with this miRNA affected the proliferative and invasive capacity of tumor cells. In this study, we highlighted an exosome-dependent transfer of microRNAs from endothelial to tumor cells. This suggests that there might be a specific mechanism that sorts miR-503 into EVs.

Understanding how cells specifically export some microRNA in EV is currently an important challenge that we would like to tackle in this project. We thus decided to identify the proteins involved in the export of miR-503 and to determine their role in tumorigenicity.

Using a mass spectrometry approach, we identified proteins bound to miR-503that we called miR-EXO proteins. Five miR-EXO proteins, were identified: ANXA2, hnRNPA2B1, VIM, TSP-1 and FN1. To determine if those proteins are involved in the export of miR-503 in EVs we transfected ECs with siRNAs targeting those proteins, produced exosomes and quantified the levels of miR-503. We found that hnRNPA2B1 silencing increased miR-503 sorting into EVs.

Then we wanted to know if the miR-EXO proteins could impact tumor cells behavior. For that purpose, we knock-downed the miR-EXO proteins in breast cancer cells and we observed that hnRNPA2B1 silencing decreased their proliferation, migration and invasion. Finally, we wanted to determine if our *in vitro* observations are relevant in human patients. Indeed, we found that the level of miR-503 is elevated in patients

undergoing neoadjuvent therapy for breast cancer. Computational analysis showed that miR-503 level in breast cancer tissue is correlated with poor survival and negatively correlated with HNRNPA2B1 level. All together, our results showed that hnRNPA2B1 acts as an inhibitor of miR-503 export and suggest its implication in breast cancer progression via EV communication. Interestingly, we observed that miR-503 level is lower in epirubicin-resistant cancer cells. For further studies we would like to determine if this mechanism is involved in response to chemotherapy.

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