Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: Biosciences and Biotechnology Institute of Grenoble. Biology of Cancer and Infection laboratory. Team 3 "Invasion Mechanisms in Angiogenesis and Cancer".

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Research project title:
Defining the functional role of exosomal microRNAs in adrenocortical cancer cell aggressiveness

5 Keywords to describe the project: microRNA, exosomes, cancer cell/stromal cell communication, tumor microenvironment, post-transcriptional gene expression

Description of the project (aims, experimental techniques, recommended background): 10 to 15 lines:

Context:

Adrenocortical carcinoma (ACC) is an aggressive tumor with poor prognosis and limited therapeutic options. The molecular events that control aggressiveness and chemo-resistance of ACC are still poorly defined. We have recently reported that tumor and serum microRNA (miRNA) levels are dysregulated in patients with adrenocortical carcinoma as compared to patients with benign tumors or healthy subjects (Chabre et al, 2013). Importantly, two circulating miRNAs were identified as predictive biomarkers of recurrence and aggressiveness.

Preliminary Results:

In light of the emerging role of circulating miRNAs in shaping the tumor microenvironment (endothelial cells, fibroblasts, and immune cells) we focused our attention on our diagnostic/prognostic miRNAs biomarker candidates and observed that they were secreted by adrenocortical cancer cells in microvesicles called exosomes. Our preliminary data indicate that GFP-CD63 labeled exosomes derived from adrenocortical cancer cells are internalized by vascular endothelial cells (EC) and that specific exosomal miRNAs promote EC migration and organization into capillary structures.

Objectives and approaches:

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The present project aims at defining the contribution of extracellular dysregulated miRNAs to the aggressive phenotype of adrenocortical cancer along two axes:

(1) The characterization of adrenocortical cancer cells-derived exosomes and determination of their miRNA content using molecular and biochemical analyses, and (2) The study of the functional role of exosomal miRNA in cell-to-cell communication using *in vitro* 2D and 3D cell co-cultures (cancer cells in the presence of endothelial cells, macrophages, or fibroblasts).

Recommended background: Dynamic and motivated student, competent both in molecular and cellular biology techniques

Justification that the internship's subject fits with the general theme of GRAL (3 lines):
The studies proposed here are emerging aspects in oncology research. It is expected from the results to better understand how specific extracellular miRNAs can promote cancer cell aggressiveness by changing the phenotype of neighboring non-cancerous cells.

Relevant publications of the team:

1. Agosta C, Chabre O, Feige JJ, et al, **Cherradi N**.
   MiR-483-5p and miR-139-5p promote aggressiveness by targeting N-Myc Downstream-Regulated Gene family members in adrenocortical cancer. 2018 *International Journal of Cancer*, Minor revision.
2. **Cherradi N.** MicroRNAs as potential biomarkers in adrenocortical cancer: progress and challenges. *Frontiers in Endocrinology,* 2016 Jan 20; 6:195, 1-15. doi: 10.3389/fendo.2015.00195. /978-2-8178-0466-8_17.
3. Chabre O., Libé R., Assié G., Barreau O., Bertherat J., Bertagna X., Feige JJ, **Cherradi N**.
   Serum miR-195 and miR-483-5p are predictive of recurrence risk in adrenocortical cancer patients. *Endocr. Relat. Cancer*, 2013, 20, 579-594.

4. Singh P, Soon Patsy SH, Feige JJ, Chabre O, Zhao JT, **Cherradi N**, Lalli E, Sidhu SB. Dysregulation of microRNAs in adrenocortical tumors. *Mol Cell Endocrinol*, 2012, 351(1):118-28.