UNIVERSITÉ FRANÇOIS - RABELAIS TOURS

n2c Nutrition Croissance Cancer
INSERM UMR 1069
TOURS

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

Role of the *SCN4B* gene and its expression product, Navβ4, in the prevention of metastatic invasion, Induction of its expression, and inhibition of cancer progression by dietary fatty acids

The high mortality of carcinomas is mainly the cause of the development of metastases for which no specific markers or treatments exist. The formation of metastases relies on a series of complex and multistep mechanisms leading to the escape of cancer cells from the primary tumour after the acquisition of migration and invasion properties. Recently, we have identified the *SCN4B* gene, encoding for the Navβ4 auxiliary subunit of voltage-gated sodium channels (Na_V), as a critical protagonist in the progression of breast cancer, independently of Na_V subunit (Bon et al., *Nat Commun* 2016). The *SCN4B* gene is highly expressed in epithelial cells of normal breast, but its expression is reduced in cancer tissues, and most particularly in invasive tumours, to be almost absent in high-grade tumours and metastases. At the cellular level, the loss of *SCN4B* expression potentiates cancer cell invasiveness by increasing the activity of the RhoA GTPase, leading to a very aggressive mesenchymal-amoeboid hybrid phenotype. The experimental overexpression of SCN4B in cancer cells reduces their invasiveness and the development of metastases. We propose that *SCN4B* could represent a metastasis-suppressor gene. Sustaining or inducing *SCN4B* gene expression in cancer cells could open new strategies to prevent metastasis development. Some polyunsaturated fatty acids (PUFAs), have been identified as dietary factors that could have anticancer properties (Bougnoux et al., *Prog. Lipid. Res.* 2010). Our preliminary results indicate that the expression of *SCN4B* is strongly induced by specific PUFA supplementations, which in turn inhibit cancer cell invasiveness (Bon et al., preliminary results). The objectives of the PhD project are the following:

i) to study the mechanisms by which *SCN4B* controls cancer cell invasiveness both *in vitro* and *in vivo*.
ii) to study the regulation of *SCN4B* expression by fatty acids, and the level of *SCN4B* expression in the tumours of patients in relation with the fatty acids composition of their peritumoral adipose tissue, and
iii) to identify the anti-invasive and anti-metastasic activity of PUFA supplementation through the modulation of *SCN4B* expression.

Techniques available for the PhD project:

- Cell and tissue cultures (among which cell migration and invasion assays)
- Molecular and cellular biology (mRNA extraction, RT-qPCR, reporer gene assays, protein extraction, western blotting, co-immunoprecipitation, pull-down assays)
- Cell electrophysiology (patch clamp)
- Lipid biochemistry (analysis of fatty acids from triglycerids and phospholipids) by thin layer chromatography and gaz chromatography

- Fluorescence microscopy (immuno-cytofluorescence, time-lapse microscopy, confocal microscopy)
- Immunohistochemistry
- In vivo experiments

5 significant publications :

[1] BRISSON L., GILLET L., CALAGHAN S., BESSON P., LE GUENNEC J.-Y., **ROGER S.#*** & GORE J.* NaV1.5 enhances breast cancer cell invasiveness by increasing NHE1-dependent H^+ efflux in caveolae. **Oncogene**, 2011 Apr 28;30(17):2070-6.

[2] BRISSON L., DRIFFORT V., BENOIST L., POET M., COUNILLON L., ANTELMI E., RUBINO R., BESSON P., LABBAL F., CHEVALIER S., RESHKIN S.J., GORE J. & **ROGER S#**. $Na_V1.5$ sodium channels allosterically regulate the NHE-1 exchanger and promote breast cancer cell invadopodial activity. **J. Cell Science**. 2013 Nov 1;126(Pt 21):4835-42.

[3] DRIFFORT V., GILLET L., BON E., MARIONNEAU-LAMBOT S., OULLIER T., JOULIN V., COLLIN C., PAGÈS J.-C., JOURDAN M.-L., CHEVALIER S., BOUGNOUX P., LE GUENNEC J.-Y., BESSON P. & **ROGER S.#**. Ranolazine inhibits $Na_V1.5$-mediated breast cancer cell invasiveness and lung colonization. **Molecular Cancer** 2014, 13:264

[4] WANNOUS R., BON E., GILLET L., CHAMOUTON J., WEBER G., BRISSON L., GORÉ J., BOUGNOUX P., BESSON P., **ROGER S.**, CHEVALIER S. Suppression of PPARβ, and DHA treatment, inhibit $Na_V1.5$ and NHE-1 pro-invasive activities. **Pflugers Arch - Eur J Physiol** (2015) 467:1249–1259

[5] BON E., DRIFFORT V., GRADEK F., MARTINEZ-CACERES C., ANCHELIN M., PELEGRIN P., CAYUELA M.-L., MARIONNEAU-LAMBOT S., OULLIER T., GUIBON R. , FROMONT G., GUTIERREZ-PAJARES J. L., DOMINGO I., PIVER E., MOREAU A., BURLAUD-GAILLARD J., FRANK P.G., CHEVALIER S., BESSON P. & **ROGER S.#** SCN4B acts as a metastasis-suppressor gene preventing hyperactivation of cell migration in breast cancer. **Nature Communications.** 2016; 7: 13648.

Contact:

Unité Inserm UMR1069 Nutrition, Croissance et Cancer (www.n2c.univ-tours.fr)
Université François-Rabelais de Tours
PhD Supervisor : Sébastien ROGER
Email : sebastien.roger@univ-tours.fr
Phone : 0033 2 47 36 61 30

PhD Starting : 01st October 2017
Funding : Ministry of Research

Deadline for applications: **10 April 2017**