Deciphering the macro and microvascular effects of extracellular vesicles-borne inflammasome components in metabolic syndrome and hypertension

Thesis title: 

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Socio-economic and scientific context (approximately 10 lines): 

Metabolic syndrome (MetS), affecting close to 20% of French population, is characterized by the cluster of interrelated risk factors for cardiovascular diseases, including hypertension. Components of MetS, such as hyperglycemia, hypercholesterolemia, hypertension and obesity, lead to an increased risk of atherosclerotic development through endothelial dysfunction, smooth muscle cell hyperplasia and monocyte/macrophage infiltration. We have described that circulating extracellular vesicles (EVs), including microvesicles (MVs) and exosomes (Exos), small vesicles released from activated or apoptotic cells, are increased in patients from MetS including pro-coagulant and pro-inflammatory EVs, and mainly those from platelets, leukocytes and erythrocytes. Moreover, EVs from MetS patients induce vascular dysfunction associated with inflammation and oxidative stress through the activation of unfolded protein response. Thus, EVs from MetS patients, in addition to represent predictive factors, may account for specific vascular complications and inflammation described in MetS. Inappropriate activation of the NLRP3-inflammasome can contribute to the onset and progression of various diseases, particularly age- and metabolism-related diseases such as MetS. However the link between NLRP3-inflammasome and atherosclerosis development with respect to EVs are not known inasmuch EV-containing such cargo could alleviate inflammasome content of the cellular source especially vascular cells.

Working hypothesis and aims (approximately 8 lines): 

Since MetS and hypertension increase the risk of developing atherosclerosis, prediction of macro and micro-vascular complications associated with endothelial cells (ECs) and vascular smooth muscle cells (VSMCs) alterations and macrophage-evoked inflammation in MetS patients, even before to manifest symptoms, remains a key element. In this respect, EVs could represent a potential tool that allows estimating these problems. Our preliminary results indicate that the inflammasome complex, NLRP3, ASC and procaspase-1, is highly expressed in EVs from MetS patients, and they induce inflammation in VSMCs. We hypothesize that NLRP3 carried by EVs from MetS patients may be responsible, at least in part, to the enhanced vascular remodeling in MetS-associated impairment of organ perfusion, maintenance and repair, altering endothelial cell-crosstalk with neighboring cells such as VSMCs and macrophages. Thus, NLRP3 carried by EVs may represent both potential biomarkers and target for novel therapeutic strategies of cardiovascular diseases associated with MetS.

Main milestones of the thesis (approximately 12 lines): 

- EV isolation by series of centrifugation of plasma from non-MetS and MetS patients will be conducted for MVs and Exos. The size and the concentration of EVs from each patient will be analyzed by transmission electronic microscopy, Western blot, Nanoparticle tracking Analysis (NTA) and flow cytometry.
- Validation of the molecular implication of EVs expressing NLRP3 (EVsNLRP3+) in the alterations of the function of vascular cells and macrophages in the course of atherosclerosis in MetS. Determination whether NLRP3-inflammasome is the molecular link between MetS and enhanced EC, VSMC proliferation and migration, macrophage polarization and development of atherosclerosis process observed in these patients. Gain- and loss-of-function studies will include targeting the canonical and the non-canonical inflammasome.
- Validation of the pathophysiological relevance of EVsNLRP3+ in the course of atherosclerosis and hypertension-induced micro and macrovascular damage. Verification of NLRP3 involvement in the effects of EVs on endothelial VSMC and/or macrophages from different mouse strains fed with normal or high-fat diet in order to simulate metabolic and vascular alterations described in MetS patients. Also, atherosclerosis progression will be evaluated in these mice. For this, three mouse strains and their corresponding littermates will be used (NLRP3+/−, ApoE−/− and NLRP3/ApoE double knock out mice).

Scientific and technical skills required by the candidate (2 lines): 

- Cellular Biology, Molecular biology, Imaging and Functional studies of vascular function in mice.

3 publications from the team related to the topic (last 5 years): 


National and international collaborations: 

- Dr. M. Delibegovic, PTP1B et fonction vasculaire, Aberdeen, UK.
- Pr. M Lopez, central regulation of obesity, Santiago de Compostela, Spain
- Pr. I. Laher, obesity Vancouver, Canada.