Extracellular vesicles as novel biomarkers of effects for endocrine disruptors in non-alcoholic fatty liver diseases (NAFLD)

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Working hypothesis and aims (approximately 8 lines):
EDs include several hundred compounds defined by their ability to interfere at any level with the action of hormones; among them, some are able to increase the susceptibility to metabolic disorders (NAFLD, diabetes, obesity). In a similar context, our team has already shown that exposure to certain xenobiotics (hydrocarbon / alcohol or phthalate / alcohol) promotes the transition from steatosis to steatohepatitis. However, it remains essential to assess more precisely the impact of EDs in NAFLD, but also to better understand the molecular and cellular mechanisms involved in the deleterious effects of these molecules. In this context, the main objectives of this thesis are: 1) the development and validation of in vitro approaches to evaluate the effects of EDs on NAFLD in the HepaRG model; 2) to evaluate the effects of these EDs on the production of EVs by HepaRG; 3) to test the influence of EVs from HepaRG treated with EDs on the inflammatory phenotype of macrophages.

Main milestones of the thesis (approximately 12 lines):
This thesis project mainly aims at evaluating the impact of EDs in NAFLD and to determine their mechanisms of action while seeking to develop in vitro tests for screening the effects of metabolic disturbances of EDs on the liver using culture of human hepatocytes HepaRG. To respond to this challenge, this work will consist of 3 stages. The first step will be to evaluate the potential of EDs to induce steatosis by measuring lipid metabolism in HepaRGs (Seahorse / palmitic acid, triglyceride assay, Nile Red, EROD) and to compare the effects of EDs with fatty acids or amiodarone supplementation (known inducers of steatosis in HepaRG). In the second step, we will study the effects of these EDs on the production of EVs by HepaRG in conditions of steatosis or not (ultrastructure by electron microscopy, size and quantity by NTA (nanoparticle tracking analysis), protein content by Western blotting and cytometry, lipid content by cholesterol assay). As inflammation has a central role in the progression of NAFLD, in the third step, we will expose macrophages to EVs produced by steatotic HepaRG to study the functions of these macrophages, more specifically phagocytosis (kit using fluorescent bacteria) and production of inflammatory markers (ELISA, qPCR).

Scientific and technical skills required by the candidate (2 lines):
The candidate must have a Master 2 in the field of Biology & Health (or equivalent), and preferably have serious experience in the field of toxicology. He should have a good general level in cell biology (lipid metabolism, intracellular trafficking, inflammation) and good skills in cell culture. He must have a high sense of organization, a strong aptitude for teamwork (interaction, coordination, proposal, dynamism) while being able to work independently, good capacities to synthesize and present scientific results (communication) and good skills in English.

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

National and international collaborations:
- Department of Cytokinetics, Institute of Biophysics of the Czech Academy of Sciences, Brno, République Tchèque – Jan Vondracek (Oberon European consortium)
- RECETOX. Faculty of Science, MasarykUniversity, Kamencie, Brno, République Tchèque – Pavel Babica (Oberon european consortium)
- Instituto de Investigación, Desarrollo e Innovación en Biotecnología Sanitaria de Elche (IDIBE), Universitas Miguel Hernández, Elche, Espagne – Alonso-Magdalena Paloma (Oberon european consortium)
- STLO – Agrocampus INRAE (Université de Rennes 1) - Dr E Guédon (NTA, extracellular vesicles)
- UMR CNRS 6226 Institut des Sciences Chimiques de Rennes- Dr F Gauffre (NTA, extracellular vesicles)
- IRSET Inserm U1085 (Université de Rennes 1) – équipe 5'Dynamique du microenvironnement et cancer'– Dr Sophie Langouet (Oberon european consortium)
- Inserm UMR S-1124 "T3S, Environmental Toxicology, Therapeutic Targets, Cellular Signaling and Biomarkers", Paris – Dr Xavier Coumoul et Dr Karine Audouze (Oberon european consortium)