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Subcellular transport of the catalytic subunit of glucose-6-phosphatase in physiological and pathological states

Laboratory :
UMR_S 1213, Nutrition, Diabetes and the Brain (NUDICE)
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Research project:
Metabolic pathologies induced by an excessively caloric diet, which used to affect mainly Western industrialized countries, now represent a global epidemic, with, for example, a projected 134% increase in the number of Africans suffering from diabetes, and 13% of Europeans, by 2045 (International Diabetes Federation 2021). Type 2 diabetes is a progressive pathology that is characterized by an imbalance between endogenous glucose production and glucose utilisation. Understanding how glucose production is controlled and proposing ways of reducing it are therefore interesting strategies in the management of this pathology.

Glucose-6-phosphatase, and more specifically its catalytic unit G6PC1, is the enzyme required for endogenous glucose production. Its expression is restricted to three organs: the liver, kidneys and intestine. While hepatic glucose production promotes the development of diabetes, intestinal glucose production protects against it, by inducing a nervous message to the hypothalamus.

In the laboratory, we have identified a new mechanism for regulating hepatic glucose production. G6PC1 is able to migrate to the plasma membrane and release glucose from the hepatocyte. Specific inactivation of this pathway reduces hepatic glucose production and protects against the development of diabetes in mice.

The objectives of the internship will be 1/ to study which hormonal and nutritional mechanisms control the ability of G6PC1 to migrate to the plasma membrane and 2/ to determine whether these mechanisms are altered during diabetes. Depending on the progress of the project, the cellular determinants involved in G6PC1 transport to the plasma membrane will then be analyzed.

Methods :

- Cell biology (hepatoma cell lines, primary hepatocytes, stable and transient transfections of fluorescent constructs).
- Biochemistry (membrane extraction, western-blot, enzymatic analyses).
- Immunofluorescence on mouse tissues.
- Imaging (TIRF and confocal microscopies, live-cell imaging).
- Image analyses

No animal experiments are required for this internship, as the tissues to be used are available.

References related to this project:

1. **Gautier-Stein A**, Chilloux J, Soty M, Thorens B, Place C, et al. A caveolin-1 dependent glucose-6-phosphatase trafficking contributes to hepatic glucose production. 2023. **Mol. Metab**. 70:101700
2. Soty M, Chilloux J, Delalande F, Zitoun C, Bertile F, Mithieux G, **Gautier-Stein A.** Post-Translational Regulation of the Glucose-6-Phosphatase Complex by Cyclic Adenosine Monophosphate Is a Crucial Determinant of Endogenous Glucose Production and Is Controlled by the Glucose-6-Phosphate Transporter. **J Proteome Res.** 2016 Apr 1;15(4):1342-9.
3. M. Soty , J. Chilloux , S. Casteras , A. Grichine, G. Mithieux and **A. Gautier-Stein**. New insights into the structure and organisation of the two subunits of Glucose-6-phosphatase. **Biochimie** 2012 Mar;94(3):695-703.