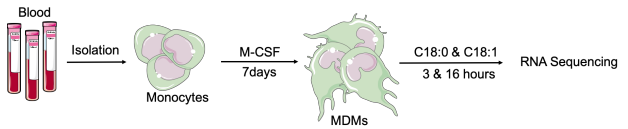
Metabolic reprogramming of human monocytes/macrophages in obesity ; implications in obesity-linked inflammation and cancers.

Margaud Iovino, Megan Colonval, Nicolas Paquot and Sylvie Legrand
Laboratory of Immunometabolism and Nutrition, GIGA-I3, University of Liege

INTRODUCTION

Obesity is an ongoing worldwide epidemic now recognized as a low-grade inflammatory disease, favoring the development of metabolic diseases and cancers. This systemic inflammation results mainly from an excessive accumulation of M1-polarized macrophages in adipose tissue. Chronic, low-grade inflammation has long been associated with cancer initiation, promotion and progression. Free fatty acids (FFAs) concentrations are strongly increased in adipose tissue and in the blood of obese patients. Since saturated fatty acids, unlike unsaturated ones, were shown to induce pro-inflammatory pathways, they are suspected of triggering this M1 macrophage polarization.

RNA sequencing (RNAseq) : stearate (C18 :0) is able to induce M1-like phenotype in human monocytes-derived macrophages (MDMs). **Hypoxia and glycolysis pathways are significantly upregulated** through Gene Set Enrichment Analysis (GSEA), suggesting that **stearate could trigger a glycolytic switch**.



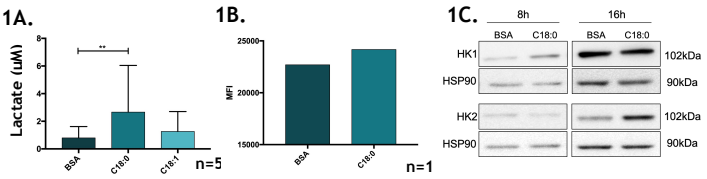
AIMS

The objectives of this project are (i) to investigate the metabolic reprogramming in saturated fatty acid-stimulated MDMs in vitro and (ii) to assess the metabolic status of circulating monocytes in obese versus lean patients.

RESULTS

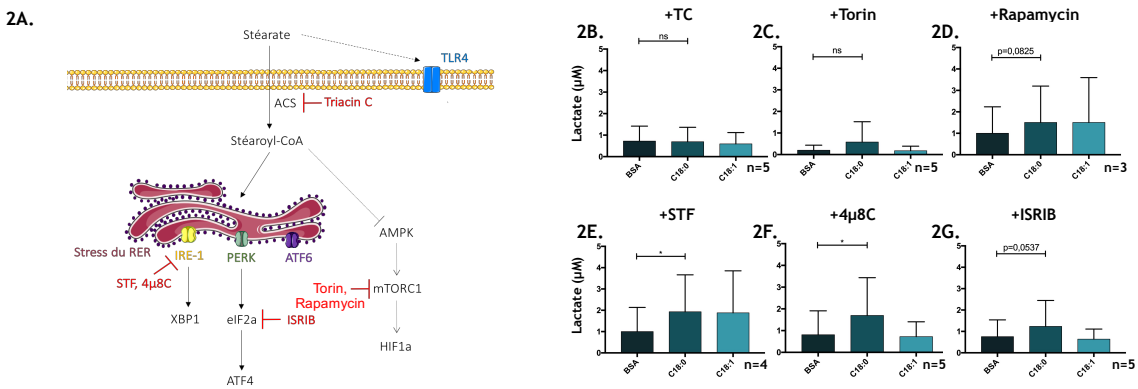
a. Validation of the glycolytic switch on MDMs treated with FFAs

- *Lactate secretion (figure 1A.)*
- *2-NBDG uptake (figure 1B.)*
- *Glycolytic enzyme expression (figure 1C.)*



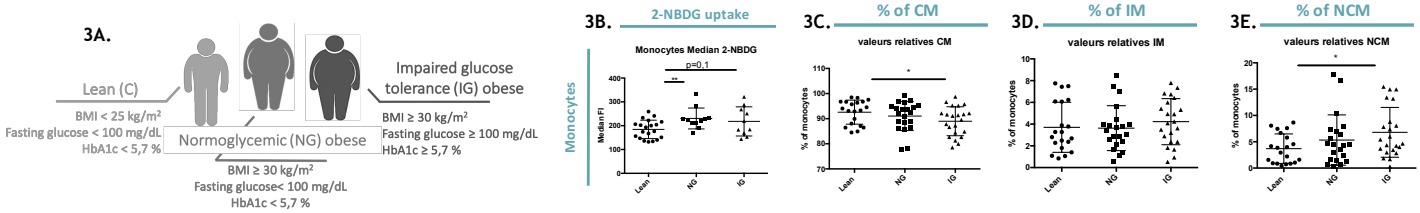
b. Study of molecular mechanisms underlying glycolytic switch

Effects of various inhibitors on C18:0-induced signalling pathways *(figure 2A.)*. Preliminary results suggest that C18:0 has to be activated by the acetyl CoA synthase (ACS) inside cells to be able to induce the glycolytic switch *(figure 2B.)*. Both ER stress and mTORC1 pathways were highlighted in the GSEA. While ER stress is not involved *(figure 2E-G.)*, the mTORC1 pathway seems to play a role *(figure 2C-D.)*.



c. Analyses on circulating monocytes from obese compared to lean patients (figure 3A.)

Significant increase in the 2-NBDG uptake by monocytes from obese compared to lean patients *(figure 3B.)*. Fluctuations of monocytes subpopulations, classical (CM), intermediate (IM) and non classical (NCM) *(figure 3C-E)*; the % of inflammatory NCM is significantly increased in glucose-intolerant obese versus lean patients *(figure 3E)*.



CONCLUSION

This project should bring a better understanding of the metabolic reprogramming that occurs in ATMs and circulating monocytes and fuels sterile inflammation in obesity. It could lead to new therapeutic strategies that would not directly target the pro-inflammatory signaling cascades but rather the metabolic pathways of human monocytes/macrophages.