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Project: METACT - METabolic interplay between peroxisome-endoplasmic reticulum contACT sites and mitochondria-endoplasmic reticulum contact sites during metabolic dysfunction-associated fatty liver disease

Metabolic dysfunction-associated fatty liver disease (MAFLD) is the liver manifestation of metabolic syndrome, consisting in a hepatic accumulation of lipids. While MAFLD is predicted to concern near 50% of the global adult population in 2040, no medication has been developed to counter its progression. Recent studies have identified a novel interorganelle communication in the liver, that consists in the endoplasmic reticulum engaging contact sites with both mitochondria and peroxisome, hence termed as peroxisome-endoplasmic reticulum-mitochondria (PEWM) complex.
Individually, mitochondria-endoplasmic reticulum contact sites (MERCS) and peroxisome-endoplasmic reticulum contact sites (PERCS) have been described to regulate mitochondria function and peroxisome biogenesis, respectively. Although the formation of a tri-organellar complex suggests an interplay between MERCS and PERCS, this has not been evaluated yet. Recent report have shown that lipid metabolism regulation affects PEWM complexes formation. Additionally, MERCS abundance correlates with the progression of MAFLD, further suggesting a role of PEWM complexes in MAFLD pathogenesis. We will develop innovative PERCS- and MERCS-specific imaging probes to evaluate how changes in energy substrates availability affect simultaneously the formation of MERCS and PERCS. Our second objective is to deepen the understanding of PEWM complex as a regulatory hub, by questioning whether and how the modulation of MERCS and PERCS alters the function of peroxisome and mitochondria, respectively. Furthermore, we will identify the components of MERCS and PERCS that impart their metabolic sensitivity. Finally, we will evaluate in vivo how integrity of PEWM complexes is regulated throughout the progression of MAFLD. We will study animal models of PERCS deficiency to assess their interplay with MERCS and their role in MAFLD pathogenesis. This could lead to the discovery of a novel therapeutical target for treating MAFLD.

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