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Developing a physiological map as a framework to study chemical-induced liver steatosis

Luiz Carlos Maia Ladeira[1], *Alessio Gamba*[1], *Raphaëlle Lesage*[2], *Anouk Verhoeven*[3], *Jian Jiang*[3], *Jonas van Ertvelde*[3], *Ramiro Jover*[4], *Tamara Vanhaecke*[3], *Vinken Mathieu*[3], *Liesbet Geris*[1 2 5], *Bernard Staumont*[1]

1 *University of Liège, Giga In Silico Medicine, Liège, Belgium*
2 *KU Leuven, Skeletal Biology and Engineering Research Center, Leuven, Belgium*
3 *Vrije Universiteit Brussel, Pharmaceutical and Pharmacological Sciences, Brussel, Belgium*
4 *University of Valencia, Departamento Bioquímica y Biología Molecular, Valencia, Spain*
5 *KU Leuven, Biomechanics Section, Department of Mechanical Engineering, Leuven, Belgium*
*lcladeira@uliege.be **liesbet.geris@uliege.be*

1. Introduction

Physiological maps (PMs) are conceptual constructs that integrate knowledge as mechanistic representations of biological processes [1]. They are indeed a type of pathway model [2], with the main goal of describing a physiological process. PMs can be used qualitatively as a mechanistic background in Adverse Outcome Pathways (AOP) creation and refinement, supporting model rationale, and quantitatively to develop computational models serving different purposes. Here, we developed a liver lipid metabolism PM (LLMPM) to serve as a framework to improve a steatosis AOP network and build an ontology [1] for the study of chemical-induced steatosis.

2. Materials and Methods

We adapted the workflow from the Disease Maps project [3] to construct the LLMPM. First, relevant physiological literature (mainly review papers and book chapters) was curated with the help of domain experts. Then, we listed the fundamental mechanisms to be mapped and screened online databases (e.g. [4]) for previously described pathways. Finally, we integrated pathways and data from literature using the CellDesigner software.

3. Results

Fig. 1 shows a part of the LLMPM we designed. The identified key mechanisms are: fatty acids uptake, fatty acids synthesis, triacylglycerol synthesis, cholesterol synthesis and glycolysis (as input); mitochondrial beta-oxidation, peroxisomal beta-oxidation, microsomal omega-oxidation, ketogenesis, and very-low-density lipoproteins (VLDL) secretion (as output); hormones and transcriptional factors (as regulators). The pathways are represented considering the human genome and proteome.

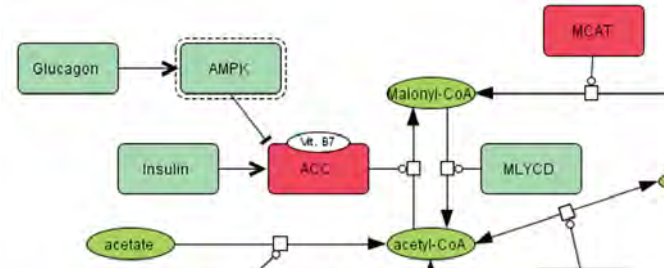

Fig. 1 – Part of the liver lipid metabolism PM, mapping the mechanisms described as pathways using the systems biology graphical notation.

4. Discussion and Conclusions

We built this network considering expert-curated literature and community-developed pathways previously available, focusing on physiological mechanisms. This network needs to be continuously updated if it is to be a dynamic tool serving the community in the aforementioned ways. However, we can already glimpse its usage potential in this early stage. This map is a multi-layered tool that will be developed further to integrate a pathological information represented by AOPs as well as quantitative kinetic and chemical information. In due course, every layer will be integrated to form a chemical-induced disease ontology [1]. Ultimately, such a tool might provide a broader understanding of liver pathways influenced by specific chemicals, with subsequent integration into more complex networks downstream to an initial molecular events, allowing future toxicity prediction and disease modeling.

5. References

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