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From Physiological Map to Ontology Unravelling Kidney Toxicity

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1. Introduction

In the emerging field of computational toxicology, many predictive tools are available today, covering different toxicological endpoints and providing high accuracy predictions [1]. However, two main issues affect these in silico models. First, models are mainly based on animal-test data, raising ethical concerns and lacking a good correlation when applied to human toxicity. Second, models often cannot explain the biological mechanisms of toxicity, since they are developed solely on the structures of toxic/non-toxic chemicals. To overcome current limitations, we developed a new systems biology approach to build a Physiological Map (PM) based on human data and represented in an online interactive interface.

2. Materials and Methods

The semi-automated method described here is useful to retrieve data in order to build the initial PM, as well as for its validation. An initial manual literature review, with the support of domain experts, is supplemented by computational interrogation of ontologies (e.g. Gene Ontology) creating a network of genes, proteins, molecules, and phenotypes [2]. Then, this automatically generated network can be converted into pathways to add manually to the PM. Ultimately, the PM is represented using the graphical layout of CellDesigner and can be visualized on the web using the MINERVA platform, allowing field experts to review it.

3. Results

We developed several PMs in the frame of the European project ONTOX. The project aims to improve risk assessment in the liver, kidney, and developing brain, avoiding the use of animal tests [3]. We present here the kidney PM, organized in its main compartments: tubular lumen, blood, glomerulus, proximal tubule, the loop of Henle, distal tubule, and collecting duct. We display all the processes involved in filtration, reabsorption and secretion for urine production. The PM shows the normal physiology but it is aimed to study two pathological conditions: kidney cristallopathy and tubular necrosis.

4. Discussion and Conclusions

The method proposed here guides the user through the construction of PM even starting from limited information. The PMs are initially developed as a qualitative and static representation of physiological processes. However, they can be useful for the parallel or subsequent development of adverse outcome pathways. The next step is to add kinetic parameters and transform our PMs into dynamic and quantitative models able to describe different cellular conditions. At the end, all the collected data can be organized in a dictionary of related elements, a structure called ontology in ONTOX project. This represents an exceptional opportunity to improve toxicological predictions and investigate human toxicities from a new perspective.

5. References

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