HORIZON 2020

Polymers in the Liver: Metabolism and Regulation

Results in Brief

Personalised models yield insights into metabolic diseases

Benefiting from systems medicine – uniting clinical, experimental and computational expertise – PoLiMeR's personalised models of inherited metabolic diseases could contribute to better treatment monitoring.

HEALTH

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Inherited metabolic diseases IEMs are genetic diseases where the body cannot process nutrients properly, potentially leading to metabolite deficiencies or the accumulation of toxic metabolites. There are over 1 900 such diseases.

Most treatments involve dietary adjustments, nutrient supplements or removing toxic nutrients from the diet, which according to Barbara Bakker, coordinator of the PoLiMer project, "is often not so simple and can have a significant impact on patients and families."

PoLiMeR focused on medium chain acyl-CoA dehydrogenase deficiency (MCADD) and glycogen storage disease (GSD) – diseases where patients can't properly process fat or carbohydrates respectively – so risk potentially lethal low blood glucose levels during sleep or strenuous exercise.

PoLiMeR's computer models, designed to better predict disease progression in individual patients, could one day help clinicians identify those likely to incur severe

symptoms or to respond well to treatment.

As a Marie Skłodowska-Curie Actions supported project, PoLiMeR trained 15 early-stage researchers (ESRs) under the clinical, experimental and computational pillars of systems medicine.

Learning from patient-specific disease models

PoLiMer concentrated on liver-related diseases.

“The liver is a hub for the body’s metabolic regulation, processing and storing nutrients, and detoxifying detrimental metabolites, so liver dysfunction profoundly affects a person’s health,” explains Bakker, from the University Medical Center Groningen (website in Dutch).

PoLiMeR’s computer models represented different levels of complexity and were designed to replicate the underlying molecular processes involved in metabolic diseases. They were informed by: patient data, patient-derived organoids (miniature liver-on-chip with multiple cell types and vasculature), thin patient-derived organ slices and animal studies.

A detailed model was made of a glycogen molecule to better understand how it grows, forms branches and is broken down to release glucose.

“By including specific genetic mutations that encode the enzymes involved, we could better predict how certain diseases affect the glycogen structure and the regulation of blood glucose levels,” notes Bakker.

Regarding the metabolic pathway, fat oxidation in cells was modelled whereby inclusion of patient-specific enzyme levels helped explain why some patients get severe symptoms, while others get mild or no symptoms.

“This model highlighted the impact of individual differences in ability to maintain sufficiently high coenzyme A (a vitamin B5 derivative) levels. MCADD patients risk severe coenzyme A deficiency which may exacerbate symptoms, particularly during stress conditions, such as cold,” says Bakker.

The team also built a whole cell level model, encompassing all known liver reactions and reflecting how metabolic processes are rerouted by the body in the case of a metabolic disease.

“This model suggested that altered vitamin metabolism may also play an important role in GSD,” adds Bakker.

For analysis, the team used mass spectrometry to quantify protein concentrations in the cells that catalyse metabolic processes (enzymes), metabolite concentrations themselves, or, by incorporating stable isotopes, the rates of these processes.

Bringing systems medicine closer to the clinic

In support of the EU's healthcare aims for more personalised medicine, the researchers now hope to bring systems medicine closer to the clinic, where their approach could be applied to a range of treatments, as well as other diseases, such as diabetes.

"While gene therapies could one day reduce the risks from metabolic diseases, we will still need tools to optimise and assess these treatments by monitoring glucose production, for example, which we are already trialling in patients," says Terry Derks, metabolic paediatrician and PoLiMeR researcher.

Additionally, as part of a new consortium, a deeper dive will also be undertaken into the metabolism of vitamins and cofactors.

"Vitamin supplements could prove to be a very affordable and accessible way for IEM patients to manage their symptoms," concludes Bakker.

Keywords

PoLiMeR, metabolic disease, liver, fat, carbohydrates, glycogen, metabolites, glucose, coenzyme A, model

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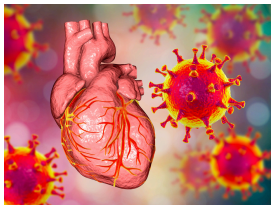

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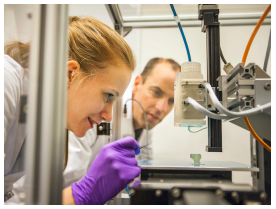

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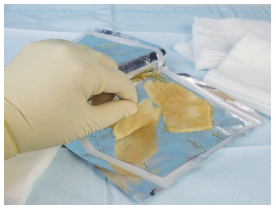

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Project Information

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