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Metabolomics of inborn errors of metabolism: A strategy to inform on genetically predisposed allostasis

Carolus Reinecke

Manager of the National Metabolomics Platform, South Africa

Abstract

Metabolite profiles relate to the interaction of the genotype with the environment and therefore provide a molecular reflection of the phenotype. Phenotyping is crucial to find biomarkers and obtain biological insights into health and disease in humans. There is a growing recognition that insights into phenotype dynamics, like on homeostasis and allostasis, deepen these insights. Both these phenomena relates to the ability to adapt and cope with a stress challenge. It is furthermore increasingly recognized that cell-intrinsic alterations in nutrient and energy metabolism underlie multiple disease states like cancer, diabetes, and neurological disorders. Using a metabolomics approach, we have recently shown that this also holds true for some inborn errors of metabolism. Here we present a strategy for the analysis of the metabolite profile of patients with the same homozygous c.367 G>A nucleotide change in exon 4 of the isovaleryl-dehydrogenase gene, causing isovalericacidemia (IVA). Using a pipeline of case and data reduction, we observed that the metabolite profile and clinical symptoms in symptomatically treated infant IVA patients indicated that their energy demand for maintaining homeostasis exceeds the energy they can generate obtain from the diet. In the neonatal period the shift from aerobic to anaerobic energy production in skeletal muscle (Warburg effect) and a reverse Warburg effect in the liver seems to dominate.

Based on these and related observations we developed a conceptual model of early neonatal allostasis in IVA patients, indicating a genetic predisposition for this systemic condition. We propose that (1) mTORC1, a key regulator of autophagy which is exquisitely sensitive to cellular growth conditions, is inhibited by 3-hydroxy-isovaleric acid. (2) This results in a switch from autophagy to a SIRT1 stimulated growth requirement, partially contributing to allostasis in these patients. (3) Isovaleryl-CoA cause prenatal acylation of SIRT3 regulated mitochondrial enzymes, which furthermore aggravate allostasis, with the potential of development of the fatal consequences of an allosatic load.

We are convinced that understanding the dynamics of systemic changes (maintenance of homeostasis, development of allostasisand of an allostatic load) will become crucial in personalized medicine to inform on the underlying biological and pathophysiological processes that characterize several inborn errors of metabolism as well as in other multiple metabolic conditions.

Biography

Carolus Reinecke studiedat the Potchefstroom University for Christian HigherEducation in South Africa, majored in Chemistry, Physics and Physiology, and obtained an MSc-degree in Physical Chemistry. His PhD in Biochemistry was done at the University of Leiden in The Netherlands, and wasthen appointed at his *alma mater* to start a Department of Biochemistry.Their field of research was on inherited metabolic diseases, and their findings are published in several journals of repute, including the Journal for Inborn Errors of Metabolism, of which he was a member of the editorial board.He became Professor of Biochemistry in 1972. Several of his students became professors in South Africa and abroad.

He was elected as Vice-President for Academic and Student Affairs in 1984 and became President of the Potchefstroom University in 1989 till his retirement at the age of 60 in 2001. He served as Chairman of the Committee of University Principals and an honorary doctorate was conferred to him by Kosin University, South Korea, for his promotion of Christian Scholarship.

Email: **Carools.Reinecke@nwu.ac.za**