

Amadori rearrangement products as potential biomarkers for inborn errors of amino-acid metabolism

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Identification of accumulating metabolites in the body fluids of patients with inborn errors of metabolism plays a crucial role in developing diagnostic strategies for these diseases and understanding their pathophysiology. The inborn error of metabolism phenylketonuria (PKU) is well-known to result in the accumulation of toxic amounts of phenylalanine in body fluids, however its levels often fail to directly explain the variability in outcomes observed among treated patients. This presents a need for biomarkers that better represent clinical status. Untargeted metabolic profiling using liquid chromatography-mass spectrometry (LC-MS) is due to its high sensitivity the method of choice for finding new biomarkers in body fluid samples but a fundamental limitation of this approach remains the identification of the detected signals. There are often multiple isobaric candidate structures that are difficult to distinguish on the basis of mass spectrometry alone.

In this talk I will show how a novel approach combining infrared ion spectroscopy and NMR spectroscopy lead to the identification of a Phe-glucose Amadori rearrangement product as a novel biomarker for PKU. We show that analogous amino acid-glucose metabolites are formed in the body fluids of patients with other accumulating amino acids, unravelling a previously overlooked group of biomarkers for a whole group of inborn errors. Amadori rearrangement products are well-known intermediates in the formation of advanced glycation end-products and have been associated with the pathophysiology of diabetes mellitus and with ageing, but are now shown to also form under conditions of aminoacidemia which may provide new insights in disease pathophysiology.