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Glycation sites of serum proteins as potential diabetes type 2 biomarkers

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Abstract

Non-enzymatic glycosylation or glycation is a common posttranslational modification produced by a chemical reaction between amino groups in proteins and sugars (aldoses or ketoses). The resulting Amadori- and Hynes-products can degrade to advanced glycation end-products (AGEs), known as markers of several metabolic diseases including diabetes. Diabetic conditions favour glucose-derived Amadori products, which is already used to measure the long-term blood glucose level by glycated haemoglobin (HbA1c). To establish middle-term diabetes markers, we have developed and optimized chromatographic and mass spectrometry techniques to identify glycation sites in proteins even if present only at low levels.

Plasma samples from diabetes type 2 patients and age-matched controls were digested with trypsin and the glycated peptides were enriched by boronic acid affinity chromatography. Thus more than 40 glycation sites in 14 proteins were identified by data-dependent acquisition using nanoRPC-ESI-LTQ-Orbitrap-MS/MS. Several positions in these proteins were found to be differentially glycated in diabetic patients and healthy individuals using label free quantification. Surprisingly, not all glycated peptides demonstrated significantly different abundance in diabetic plasma digests in comparison to controls. Thus, peptides resembling fourteen differentially modified sites in human serum albumin (HSA) were quantified as prospective markers by a MRM-method. Quantification relied on authentic and internal (stable isotope-labelled) synthetic peptide standards. Furthermore, enrichment by affinity chromatography and solid phase extraction were optimized for recovery and precision. Finally, we could show that several sites in HSA are glycated at significantly higher level in diabetes patients (p<0.05) indicating that they might represent promising type 2 diabetes biomarkers.

Biography

Ralf Hoffmann studied chemistry and was awarded a Ph.D. from Saarland University, before he continued his career at the Wistar Institute (Philadelphia, U.S.A.) as research associate and head of the “Analytical Laboratory” at the Biological and Medical Research Center (Dusseldorf, Germany). Since 2002 he is a full professor (C4 level) at Universitat Leipzig. His research focuses on protein analytics to study posttranslational modifications in the context of Alzheimer’s disease, cellular aging, oxidative stress, and diabetes as well as the design of peptide drug candidates and compound vaccines. He is the author of more than 130 peer-reviewed scientific publications, co-inventor on eight patent applications, and serves as regional editor for “Protein and Peptide Letters” and three editorial boards.