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Metal ion dyshomeostasis as a driver of coagulatory complications in Diabetes

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Diabetes is a group of conditions that impact upon the body's ability to control blood glucose concentration. In Type 1 Diabetes (T1DM) is largely due to insulin insufficiency. Type 2 Diabetes (T2DM) is associated with defective insulin signaling. Both T1DM and T2DM have wide-ranging consequences for the body as glucose levels are associated with many physiological processes. Individuals with diabetes have an increased risk of cardiovascular disease and coagulatory defects are observed in individuals with T1DM and T2DM. Our work has revealed that metal ion homeostasis is differentially affected in T1DM and T2DM. For example, HbA1c, a marker for elevated blood glucose, correlates with plasma concentrations of magnesium (negatively) in T1DM and copper (positively) in T2DM. Notably, in ex vivo experiments, the reduced plasma $Mg2+$ in T1DM was found to be associated with abnormal fibrinolysis. In addition, we have shown that T2DM is associated with defective plasma $Zn2+$ handling, caused by increased Non-Esterified Fatty Acid (NEFA) binding to Human Serum Albumin (HSA) – an interaction which allosterically regulates the ability of the protein to bind and buffer $Zn2+$. Using isothermal titration calorimetry, we reveal that pathophysiological concentrations of NEFAs reduce $Zn2+$ binding to HSA. Addition of myristate and $Zn2+$ increase thrombin-induced platelet aggregation in platelet-rich plasma and increase fibrin clot density and clot time in a purified protein system. The concentrations of key saturated and monounsaturated NEFAs positively correlate with fibrin clot density in individuals with T2DM and controls. Collectively, this work increases our understanding of the roles $Mg2+$ and $Zn2+$ play in the development of thrombotic complications T1DM and T2DM and will have future implications for the management of diabetes.

Recent Publications

1. Hierons, S.J., Abbas, K., Sobczak, A.I.S. et al. Changes in plasma free fatty acids in obese patients before and after bariatric surgery highlight alterations in lipid metabolism. Sci Rep 12, 15337 (2022).

2. Regan-Smith S, Fritzen R, Hierons SJ, Ajjan RA, Blindauer CA, Stewart AJ. Strategies for Therapeutic Amelioration of Aberrant Plasma Zn2+ Handling in Thrombotic Disease: Targeting Fatty Acid/Serum Albumin-Mediated Effects. International Journal of Molecular Sciences. 2022; 23(18):10302.

3. Czub, M. P., Stewart, A. J., Shabalin, I. G. & Minor, W. (2022). Organism specific differences in binding of ketoprofen to serum albumin. IUCrJ 9, 551-561.

Biography

Alan Stewart graduated from the university of Edinburgh with a BSc (Hons) degree in Biochemistry in 1999 and a PhD in 2003. In 2009 After postdoctoral positions in Edinburgh at the Roslin institute and MRC human reproductive sciences unit he moved to the university of St Andrews to establish his own research group. His research focusses on metal ions in disease. To date his work has attracted grant funding from UK research councils, British heart foundation, fight for sight and the Leverhulme trust. He has published over 85 research papers, many of which are in world class and field-leading journals. He has sat on several UK Research and innovation grant panels, is a member of the Narodowe Centrum Nauki (NCN) - National Science center of Poland funding panel and sits on the editorial boards of the journals, scientific reports, nutrients and BioMetals. He has an H-index of 35 (Google Scholar).

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