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## The mechanisms of asparaginase induced pancreatitis

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Asparaginase is an essential element in the successful treatment of Acute Lymphoblastic Leukemia, the most common type of cancer affecting children. However, in about 5–10% of cases this treatment causes Acute Pancreatitis (AP) as a side-effect. In AP, a potentially fatal human disease, the inactive pancreatic pro-enzymes become active enzymes inside the pancreatic acinar cells, digesting the pancreas and its surroundings. Under physiological conditions intracellular calcium signaling and Mg-ATP level are the key elements needed for stimulant-evoked exocytotic enzyme secretion from pancreatic acinar cells. Physiological $Ca^2$+ signals stimulate ATP production, whereas sustained global cytosolic $Ca^2$+ elevations decrease ATP levels and cause necrosis leading to AP. Alcohol and gallstones are the major causes of the disease. We have investigated the mechanism by which L-Asparaginase evokes AP. For the first time, we have shown that like other pancreatitis-inducing agents, Asparaginase evoked excessive intracellular Ca2+ release followed by $Ca^2$+ entry, decreased the intracellular ATP levels and reduced $Ca^2$+ extrusion. The toxic $Ca^2$+ signals induced by Asparaginase caused extensive cell necrosis. Our data indicate that the Asparaginase-induced pathology depends on protease activated receptor 2 and its inhibition prevented the toxic $Ca^2$+ signals and necrosis. Inhibition of $Ca^2$+ entry with GSK-7975A markedly reduced Asparaginase-induced cellular pathology. We have demonstrated a reduction in the intensity of Ca2+ extrusion due to the reduction in the intracellular ATP level limiting the energy supply to the Ca2+ ATPase in the plasma membrane. Supplementation of the medium with sodium pyruvate provided a similar degree of protection against pancreatic necrosis as PAR2 inhibition or GSK-7579A. $Ca^2$+ and ATP play key roles in Asparaginase-pancreatic pathology and therapeutic strategies must take both into account. We suggest that combined pharmacological control of intracellular calcium and ATP levels will prevent or alleviate AP and improve childhood cancer treatments..

### Biography

Julia V Gerasimenko has completed her PhD in 1996 from Bogomoletz Institute of Physiology, Kiev, Ukraine. She is a Senior Lecturer in Cardiff School of Biosciences, Cardiff University, UK. She has published 33 papers in reputed journals and has been serving as an Editorial Board Member of repute. She is a Member of Faculty of 1000 (Gastro-intestinal Physiology), The Physiological Society (UK), British Society for Cell Biology, European Calcium Society. She was an invited speaker for many scientific conferences in the UK and abroad.

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