Universität Basel

Research Project

Impact of the NADPH Pool in the Endoplasmic Reticulum on Metabolic and Hormonal Regulation

Third-party funded project

Project title Impact of the NADPH Pool in the Endoplasmic Reticulum on Metabolic and Hormonal Regulation
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An impaired redox control in the endoplasmic reticulum (ER) with unfolded-protein response (UPR) and ER-stress has been associated with major diseases such as cancer, cardio-metabolic disorders, and chronic inflammatory diseases. Thus, it is crucial to elucidate the mechanisms underlying ER-redox control and identify involved modulators and biological reactions. The NAD(P)H/NAD(P)$^+$ redox couple is essential for many biological functions and, in contrast to the cytoplasm, its regulation in the ER and the relevance of luminal NADPH for physiological functions such as intracellular calcium signaling, UPR control, and the metabolism of glucose, fatty acids, oxysterols, and glucocorticoids is insufficiently understood.

The discovery of hexose-6-phosphate dehydrogenase (H6PDH) revealed a mechanism for luminal NADPH generation and provided a link between energy status and glucocorticoid signaling. To date, 11b-hydroxysteroid dehydrogenase 1 (11b-HSD1) is still the only well characterized NADPH-dependent luminal enzyme. Besides its well-known role in glucocorticoid activation and involvement in metabolic and inflammatory diseases, increasing evidence revealed a role of 11b-HSD1 in oxysterol and bile acid metabolism, warranting further studies. Moreover, there must be other NADPH-dependent enzymes because 11b-HSD1 cannot account for the myopathy and increased susceptibility of hepatocytes toward toxicants observed in situations of H6PDH-deficiency.

Based on previous results, we hypothesize that **1)** the ratios of certain bile acids serve as potential prognostic markers for decreased 11b-HSD1 activity in rodents and human, **2)** 11b-HSD1 is involved in the formation of dihydroxylated oxysterols that modulate the activities of nuclear receptors (ROR, ERβ, LXRβ) and the G-coupled receptor EBI2, **3)** H6PDH delivers NADPH for fatty acid elongation in the ER, which is needed for rapid cell proliferation, **4)** loss of H6PDH affects UPR and renders cells susceptible to substances causing ER-stress, and **5)** other enzymes generating and utilizing NADPH in the ER exist and need to be identified and characterized.

To study the consequences of ER NADPH depletion on hormonal and metabolic functions, and to identify and characterize novel modulators of luminal NADPH, we propose to:

- evaluate whether ratios of certain 7oxo to 7β-hydroxy bile acids in plasma/serum can serve as markers for reduced 11b-HSD1 activity in human,
- further explore the role of 11b-HSD1 in oxysterol and bile acid metabolism and the modulation of cognate receptors,
- study other enzymes generating or utilizing NADPH in the ER,

– study the impact of H6PDH on fatty acid synthesis/metabolism,
– investigate the impact of H6PDH on breast cancer cell properties,
– study the susceptibility of H6PDH-deficient primary liver and kidney cells to ER-stress, and
– explore the use of IP-MS and BioID to investigate protein-protein interactions in the ER.

Steroids and other lipophilic compounds in different matrices will be quantified using LC-MS/MS. The role of luminal NADPH and consequences of its depletion on metabolic and hormonal responses will be studied using enzyme preparations, cell-based models upon modulating the corresponding enzyme(s) by overexpression, downregulation by siRNA or pharmacological inhibition. Further, studies in transgenic mice and mice treated with inhibitors and in primary cells will be performed. Also, protein interaction methods will be employed, attempting to identify novel players in ER NADPH regulation.

The proposed research should significantly enhance our current knowledge on the role of NADPH in the ER. The expected findings are relevant to understand the coupling between cellular energy state, hormonal regulation, ER redox regulation, and oxidative stress-induced damage. Disturbed functions of the enzymes studied are associated with impaired inflammatory responses, cardio-metabolic disorders and cancer, and the results of the proposed project should support the future development of therapeutic interventions.

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