Universität Basel

Research Project

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

Project funded by own resources

Project title Impact of the NADPH Pool in the Endoplasmic Reticulum on Metabolic and Hormonal Regulation
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Organisation / Research unit
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The role of the $NAD(P)^+$/NAD(P)H redox couple in the ER and the relevance of luminal NADPH for essential biological functions is insufficiently studied.

The discovery of hexose-6-phosphate dehydrogenase (H6PDH) revealed a mechanism for NADPH generation in the ER and provided a link between energy status and glucocorticoid signaling. The glucocorticoid activating 11b-hydroxysteroid dehydrogenase 1 (11b-HSD1) is, so far, the only well characterized NADPH-dependent luminal enzyme. However, the impact of H6PDH on macrophage function and inflammatory mediators and its effect on corticosteroid signaling remain unknown. Also, there must be other NADPH-dependent enzymes because 11b-HSD1 cannot account for the myopathy and the increased susceptibility of hepatocytes observed in situations of H6PDH-deficiency.

We hypothesize that **1)** NADPH-dependent 11b-HSD1 function (glucocorticoid-dependent and -independent) essentially modulates macrophage polarization and activity, and inhibition of 11b-HSD1 exerts anti-inflammatory and anti-infective effects, **2)** inhibition of 11b-HSD1 has glucocorticoid-independent metabolic effects by modulating oxysterol and bile acid homeostasis, and **3)** ER-luminal short-chain dehydrogenase/reductase (SDR) enzymes other than 11b-HSD1 are responsible for effects in macrophage, adipocytes, adrenal cells, hepatocytes and myocytes in situations of H6PDH-deficiency.

We propose to:

- investigate the role of luminal NADPH supply on macrophage polarization and function; distinguish between 11b-HSD1-dependent and -independent effects
- assess a role of 11b-HSD1 in the metabolism of EBI-2 ligands
- elucidate the impact of luminal NADPH supply and 11b-HSD1 on the metabolism of 7-ketocholesterol (7KC) and on bile acid homeostasis
- establish a method using redox-sensitive green-fluorescent proteins (roGFP) to determine the topology of ER membrane proteins in living cells; attempt to identify ER luminal enzymes other than 11b-HSD1
- characterize the NADPH-dependence of identified luminal enzymes
- develop a strategy to identify novel substrates of SDR enzymes

The role of ER luminal NADPH on metabolic and hormonal responses will be studied in transfected cells using recombinant enzymes, in cell lines with endogenous expression of the relevant enzymes and treated with siRNA, in primary cells from wild-type and H6PDH knockout mice, and in vivo in wild-type and transgenic mice. Structural modeling will be applied to search for SDR substrates and study experimentally verified target-ligand interactions.

The expected findings are relevant regarding the understanding of the coupling between cellular energy state, hormonal regulation, ER redox regulation, and oxidative stress-induced damage. Disturbed functions of the enzymes investigated are associated with impaired inflammatory responses and with cardio-metabolic disorders. The results should support the future development of therapeutic interventions.

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ID	Kreditinhaber	Kooperationspartner	Institution	Laufzeit - von	Laufzeit - bis
3707760	Odermatt, Alex	Lavery, Gareth	University of Birmingham	01.05.2015	30.04.2018
3707761	Odermatt, Alex	Schuster, Daniela	University of Innsbruck	01.05.2015	31.12.2018