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Metabolic Profiling of Glucocorticoid Deficiency: A "Fishing" Expedition

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Adrenal insufficiency (AI) is a life-threatening metabolic disorder in humans leading to severe symptoms such as fatigue, abdominal pain, infection, reduced heart rate as well as decreased blood pressure. On a pathophysiological level AI is defined as impaired synthesis of various adrenal hormones including the glucocorticoid hormone cortisol [1]. Current therapeutic strategies are routinely based on cortisol replacement by oral drug therapy. However, this therapy is far downstream of the disease triggering mechanism, since reduced adrenal hormone synthesis can be caused by the impairment of various signaling pathways in different organs. Glucocorticoid hormone replacement reduces morbidity and mortality in AI patients, nevertheless, this therapeutic approach is non-curative and associated with severe adverse side effects [2,3]. To extend our knowledge of AI and to optimize current therapeutic strategies, more mechanistic insights of genetic and molecular pathways and networks involved in this severe metabolic disorder are pivotal.

In the last two decades the zebrafish has been established as an excellent tool to decipher the genetic as well as molecular underpinnings of various human diseases, including metabolic or cardiovascular disorders [4–6]. Interestingly, several studies comparing development and function of the endocrine systems demonstrated a high degree of similarity between humans and zebrafish. Thus, important metabolic key molecules in the endocrine system especially the stress axis were dissected in detail in zebrafish [7,8]. As in humans, glucocorticoid hormones play an important role in the response to intrinsic or extrinsic stress triggers in zebrafish and are released by the interrenal gland, the homolog of the adrenal gland in humans. Mitochondrial glucocorticoid synthesis in zebrafish depends on proper Fdx1b function, which is a paralogue of human FDX1 (ferredoxin 1). Remarkably, in 2016 Griffin and co-workers established a stable *fdx1b*-deficient zebrafish mutant line, demonstrating limited glucocorticoid synthesis leading to a dysfunctional stress axis and primary adrenal insufficiency [9].

Recently published in *EBioMedicine* [10], using their *fdx1b*-deficient zebrafish mutant line, Weger and coworkers now analyzed the impact of impaired mitochondrial glucocorticoid biosynthesis on metabolism and gene expression and compared their findings to a zebrafish model of secondary adrenal insufficiency (rx3 strong) but also to metabolic data derived from patients suffering from primary adrenal insufficiency.

They found that *fdx1b*-deficient zebrafish show increased glutamine levels as a consequence of reduced glucocorticoid-dependent transcription of liver and intestine specific glutaminases (*gls2a* and *gsl2b*) and thereby impaired glutaminolysis. Moreover, biosynthesis of the important antioxidant and cell signaling molecule glutathione was significantly reduced in Fdx1b mutant zebrafish leading to increased levels of oxidative stress markers as well as increased up-regulation of genes involved in DNA repair. Also, the authors found that post-transcriptional regulation of enzymes that are crucial for *de novo* purine biosynthesis (*paics* and *atic*) strongly depends on glucocorticoids. Finally, the authors compared metabolic profiles derived from *fdx1b*-deficient zebrafish (primary adrenal insufficiency), from rx3 strong mutant zebrafish (secondary adrenal insufficiency) and from patients with primary hypocorticolism. Interestingly, the authors identified overlapping but also distinct changes of metabolic and transcriptional profiles with a higher degree of similarity between *fdx1b*-deficient zebrafish and patients suffering from primary adrenal insufficiency compared to rx3 strong mutant zebrafish. These findings further strengthen the role of fdx1b mutant zebrafish as a valid animal disease model for human primary adrenal insufficiency.

Diagnosis and therapy of adrenal insufficiency in patients are still far from being optimal. The interpretation of cortisol levels as readout for adrenal function, particularly in diverse clinical situations, is often challenging. In this context, the development of novel specific biomarkers *e.g.* by detailed metabolic and transcriptional profiling would significantly improve the efficient diagnosis of adrenal insufficiency. Furthermore, current steroid replacement in AI patients is unable to fully restore the physiological feedback mechanisms of the hypothalamic-pituitary-adrenal axis. Also, circadian as well as pulsatile hormone secretion is not reconstituted by this therapeutic strategy. A detailed understanding of the pathogenesis of adrenal insufficiency, particularly the metabolic peculiarities of primary and secondary adrenal insufficiency might help to develop therapeutic strategies that specifically target these metabolic differences thereby providing a tailored therapy for patients with primary and secondary adrenal insufficiency.

In conclusion, the study by Weger and colleagues provides novel interesting insights into the metabolic and transcriptional profiles in zebrafish models of primary and secondary adrenal insufficiency, particularly the authors demonstrate distinct but also overlapping metabolic and transcriptional changes in the two animal models of glucocorticoid deficiency. Further studies in patients suffering from

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adrenal insufficiency will be necessary to validate these findings and to prove causality, paving the way for the development of novel diagnostic procedures and targeted therapeutic strategies to efficiently treat adrenal insufficiency in humans.

Disclosure

The authors declared no conflicts of interest.

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