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Biomedical basis of the Barker hypothesis uncovered

A research group at Inselspital, Bern University Hospital and the University of Bern has published an extensive study on prenatal causes of kidney disease in adults in *Nature Communications*. The findings reveal that the serum protein fetuin-A plays a key role in attenuating local inflammation and microcalcifications in the fetal kidney, which have consequences for kidney function later in adulthood. The study results provide indications for clinical use of fetuin-A in kidney diseases.

According to the Barker hypothesis (Hales and Barker 1992) (also referred to as “small baby syndrome”), infants with too low body weight have an increased risk of suffering from cardiovascular diseases, high blood pressure, diabetes and chronic kidney diseases in adulthood. According to this hypothesis, fetal protective mechanisms enable adaptation to unfavorable intrauterine conditions (chronic oxygen or nutrient deficiency) and allow for fetal survival. At the same time, however, they lead to permanent structural and functional strains and changes into adulthood. The comprehensive study recently published in *Nature Communications* now clarifies central mechanisms of this phenomenon.

Fetuin-A plays a key role

Under the program of the Swiss National Centre of Competence in Research (NCCR) Kidney Control of Homeostasis (Kidney.CH) funded by the Swiss National Science Foundation, the research team has developed a mouse model of reduced growth attributable to fetal oxygen deprivation (fetal hypoxia). First of all, they demonstrated that fetal hypoxia causes local inflammation and microcalcifications with tissue damage in the kidney, resulting in a more rapid decline in renal function in adulthood. The experimental findings thus confirmed the Barker hypothesis. Concomitantly, the lack of oxygen activates the gene for the serum protein fetuin-A ectopically in the kidney, beyond the previously known site of expression in the liver. This is in line with the known function of Fetuin-A to protect the vascular system from calcification.

Furthermore, the study demonstrates a considerable number of previously unknown functions of fetuin-A in the kidney. These include preventing calcification and fibrotic changes of the kidney soft tissue, as well as inhibiting inflammatory processes. In addition, the research team was able to show that fetuin-A not only carries out these functions during development, but also protects against fibrotic remodeling of kidney tissue after acute oxygen deprivation in fully developed kidneys.

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Fetuin-A with significant, pharmacological potential

The versatility of the effects of fetuin-A was initially just as surprising as the fact that kidneys are particularly affected by it. The study provides strong evidence that fetuin-A could play an important role in treating kidney damage caused by oxygen deficiency as well as after reperfusion of an ischemic circulatory disorder. First author **Stefan Rudloff** explains: "*The discovery that fetuin-A is produced ectopically outside the liver under oxygen deprivation in the fetal kidney was a surprising initial finding for us. The further we extended the research the clearer became the significance of fetuin-A not only in coping with the damage caused by oxygen deprivation in the fetal phase, but also in adulthood*."

Translational research and development facilitated by sitem-insel

The research team of Prof. Uyen Huynh-Do and Stefan Rudloff at the Department of Nephrology and at the Department for Biomedical Research at the University of Bern can rely on very favorable conditions in terms of environment. The follow-up project will be funded by the "Research Acceleration Initiative 2020" (RAI 2020) of the research department of CSL Behring as one of the three winners of the RAI 2020 funding. **Prof. Uyen Huynh-Do,** who heads the study, emphasizes: *"Without the funding and the network of NCCR Kidney.CH this study would not have been possible. The future, close collaboration with the research department of CSL Behring as an industrial partner is facilitated by sitem-insel (Swiss Institute for Translational and Entrepreneurial Medicine), where translational research and development is taken very seriously and is actively supported. Thanks to the proximity of the department of Nephrology, the university's research facilities at DBMR and CSL Behring as the industry partner, it was now possible to launch a subsequent translational project that builds on the newly published research data.*"

Experts:

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- CSL Behring «Biologics Research Center»
- sitem-insel - Swiss Institute for Translational and Entrepreneurial Medicine
- Swiss National Centre of Competence in Research (NCCR) Kidney Control of Homeostasis (Kidney.CH)