Biomedical basis of the Barker hypothesis uncovered

February 2 2021

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According to the Barker hypothesis (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.

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."

More information: Stefan Rudloff et al, Fetuin-A is a HIF target that safeguards tissue integrity during hypoxic stress, *Nature Communications* (2021). DOI: 10.1038/s41467-020-20832-7

Provided by Inselspital, Bern University Hospital