RENAL PHYSIOLOGY

MAGED2 mutations in transient antenatal Bartter syndrome

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Antenatal Bartter syndrome is an inherited disorder characterized by renal salt wasting and fetal polyuria, resulting in severe hydramnios and premature delivery. Findings now identify loss-of-function mutations in *MAGED2* as a cause of polyhydramnios and a transient form of antenatal Bartter syndrome associated with inappropriate expression of the sodium–chloride transporters NKCC2 and NCC. “In this study we show for the first time that *MAGED2* is required in the hypoxic fetal renal medulla to allow proper expression of two critical salt transporters,” says researcher Martin Kömhoff. “Our findings add a new level of complexity to the regulation of these transporters.”

Although virtually all forms of antenatal Bartter syndrome persist, some cases are transient with spontaneous resolution of symptoms

shortly after birth. Kömhoff explains that his interest in transient antenatal Bartter syndrome developed after encountering a family in which three pregnancies with male offspring were complicated by early-onset polyhydramnios and prematurity. One fetus died whereas the two living infants had a Bartter-like syndrome, with substantial salt wasting and polyuria that resolved within a few weeks.

“Recognition of a possible X-linked transmission in this as well as other families led to X chromosome exome sequencing and the identification of mutations in *MAGED2* in 13 individuals from seven families,” he says. “In addition, we identified *MAGED2*-mutations in two additional families from a cohort of women who had experienced idiopathic polyhydramnios but with no evidence of transient Bartter syndrome in their male offspring.”

Using immunohistochemistry, the researchers examined the renal expression of NKCC2, NCC and uromodulin in the deceased fetus from the case family. “This analysis showed intracellular retention and reduced apical expression of the sodium transporters, whereas uromodulin stained normally,” says Kömhoff.

“The effects of knockdown and overexpression of *MAGED2* on the heterologous expression of the transporters in HEK296 cells confirmed our immunohistochemical findings.” To determine how *MAGED2* affects expression of the transporters, Kömhoff and colleagues compared the interactome of wild-type and mutant *MAGED2*, identifying differential binding of the cytoplasmic chaperone Hsp40 and Gsa to the two forms of *MAGED2*. “Altered Hsp40 and Gsa activity fits with intracellular retention and reduced apical expression of the two transporters,” notes Kömhoff.

The reason why this particular form of Bartter syndrome is transient is not known. “We speculate that increasing tissue oxygen levels in the renal medulla and adenylate cyclase activity during the last trimester of pregnancy might reduce the dependence of Hsp40 and Gsa on *MAGED2* activity, which would explain the resolution of all symptoms,” says Kömhoff.

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