INSIGHT INTO HUMAN CONGENITAL ABNORMALITY

Congenital absence of the uterus and vagina in humans, also known as Rokitansky-Kuster-Hauser (RKH) syndrome, is characterized by utero-vaginal atresia in an otherwise phenotypically normal female with a normal 46,XX karyotype. In this syndrome, anomalies of the genital tract range from upper vagina atresia to total Mullerian agenesis with urinary tract abnormalities (*Development and Disease*. 2007;134:1799-1807).

Although a mutation in the wingless type 4 (Wnt4) gene has been identified in 1 isolated patient with a phenotype similar to RKH syndrome, no association between Wnt4 and RKH syndrome has been proven, and the disease etiology still remains to be elucidated.

Interestingly, in a research article recently published in *Development* (2007;134:1799-1807), Iizuka-Kogo and colleagues report a mouse knockout for the discs large homolog 1 (Dlgh1), which presents a phenotype that clearly resembles the human congenital absence of the uterus and vagina associated with other variable Mullerian duct abnormalities.

The authors of the study successfully generated mutant mice null for the Dlgh1 gene, which is a mammalian homolog of the *Drosophila* tumor suppressor Discs large 1 and a member of the membrane-associated guanylate kinase scaffolding proteins. In *Drosophila*, Discs large 1 is important for cellular polarity establishment, cell-cell adhesion integrity, and regulation of cellular proliferation. In mammals, Dlgh1 has been known to be expressed in epithelial and neuronal cells and has been reported to be involved in nephrogenesis, cell-cell adhesion of intestinal epithelial cells, cell cycle inhibition in cervical cancer and cultured cells, cellular polarization of astrocytes, and localization and clustering of glutamate receptors at the synaptic membrane. Therefore, Dlgh1 has been considered to function as a scaffolding protein and is known to interact with various other proteins.

In this study, Iizuka-Kogo et al analyzed the phenotypes of the Dlgh1 knockout mice to elucidate its functions in developing epithelial tissues. As such, the authors focused on the development of the urogenital tract, in which the proper organization of epithelial tissues is crucial for normal morphogenesis.

Iizuka-Kogo and colleagues observed that the Dlgh1-deficient mice developed various abnormalities in their renal and urogenital organs, which occurred at various stages of development, indicating that Dlgh1 plays a crucial role in these tissues.

In the mutant animals, the kidneys and ureters were hypoplastic, and the lower ends of the ureters were ectopic. Contrary to what was expected, loss of Dlgh1 function in the developing ureters did not disrupt cell-cell junctional complexes but did impair cellular proliferation in the epithelium, suggesting a novel role for Dlgh1 in regulating epithelial duct formation and morphogenesis during mammalian development.

The vagina and seminal vesicle, which are derived from the lower part of the Mullerian and the Wolffian duct, respectively, were absent. In addition, the uterine cervix was aplastic. This suggests that there is an obstruction of the Mullerian ducts, caused by their impaired down growth in the Dlgh1 mutant animals.

In sum, the findings shown by Iizuka-Kogo et al not only present new insights into the function of Dlgh1 but also clearly demonstrate that Dlgh1 plays a crucial role in the development of the urogenital system in mammals. Moreover, the results presented by the authors strongly suggest that Dlgh1 function is impaired at the onset of urogenital development, potentially contributing to congenital abnormalities, such as RKH syndrome. The role of Dlgh1 as a potential etiology for this disease certainly deserves further examination.

REFERENCE

1. Iizuka-Kogo A, Ishidao T, Akiyama T, Senda T (2007). Abnormal development of urogenital organs in Dlgh1-deficient mice. *Development and Disease* 134, 1799-1807.

SEARCH FOR A MALE CONTRACEPTIVE

The search for a male contraceptive that is concomitantly safe, effective, and reversible upon treatment abandonment has been long ongoing.

A novel chemical entity, Adjudin (1-(2,4-dichlorobenzyl)-1H-indazole-3-carbohydrazide, formerly known as

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