CCDC183 is Essential for Axonemal Compartmentalization during Spermiogenesis

Keisuke Shimada[1] and Masahito Ikawa[1,2,3]

1. Department of Experimental Genome Research, Research Institute for Microbial Diseases, Osaka University, Osaka, Japan

2. Regulation of Host Defense Team, Center for Infectious Disease Education and Research, Osaka University, Osaka, Japan

3. Laboratory of Reproductive Systems Biology, The Institute of Medical Science, The University of Tokyo, Tokyo, Japan

Sperm flagellum plays a crucial role in male fertility. By using a flagellum as a driving force, spermatozoa travel long distances to reach female gametes. An axoneme, a motility apparatus composed of a “9+2” microtubule arrangement, is found throughout the sperm tail except for the endpiece. The “9+2” arrangement is composed of nine outer doublets surrounding a pair of single central microtubules.

Axoneme extension from the distal centriole localized on the cell surface causes the plasma membrane to protrude from the cytoplasm. The centriole then migrates and associates with the nuclear envelope to bridge the plasma membrane with the nucleus. The centrioles and nucleus then move toward the cell surface on the opposite side. This causes an inward folding of the centriole-associated plasma membrane called cytoplasmic invagination, which allows compartmentalization of the flagellum. Although this cytoplasmic invagination and axonemal compartmentalization in early spermatids has been observed for a long time, it has not been studied in depth until now.

Here, we generated *Ccdc183* knockout mice using the CRISPR/Cas9 system to reveal the protein function of the testis-specific protein CCDC183 in spermiogenesis. We demonstrated that CCDC183 absence causes male infertility with morphological and motility defects in spermatozoa. Owing to the lack of CCDC183, centrioles after elongation of axonemal microtubules do not connect to the cell surface and nucleus during spermiogenesis, which causes subsequent loss of cytoplasmic invagination around the flagellum. This results in abnormal compartmentalization of the axoneme, and cytosol-exposed axonemal microtubules collapse during spermiogenesis. In addition, ectopic localization of accessory structures, such as the fibrous sheath and outer dense fibers, and abnormal head shape as a result of abnormal sculpting by the manchette are observed in *Ccdc183* knockout spermatids. Our results indicate that CCDC183 plays an essential role in axonemal compartmentalization to form functional spermatozoa during spermiogenesis.