Identification of a protein that regulates sperm acrosome reaction

Department of Experimental Genome Research, Research Institute for Microbial Diseases

Associate Professor Haruhiko Miyata Researchmap https://researchmap.jp/hmiyata?lang=en

Professor Masahito Ikawa Researchmap https://researchmap.jp/read0054910?lang=en

Abstract

Sperm heads contain a vesicle called the acrosome. The membrane of the acrosome fuses with the sperm plasma membrane and the contents of the acrosome are released through an exocytosis called the acrosome reaction (Figure 1), which is important for spermatozoa to fertilize eggs, but its regulatory mechanism is unknown. In this study, we focused on FER-1, a protein essential for fertilization in nematodes. Among six FER-1-like proteins in mice, we generated mice deficient in FER1L4, FER1L5, or FER1L6 because the functions of these proteins were unknown. The results revealed that FER1L5 is important for the acrosome reaction and male fertility (Figure 2).

Background & Results

An exocytosis called the acrosome reaction that occurs during sperm transit through the female reproductive tract is essential for fertilization with eggs. In the acrosome reaction, the fusion of the membrane of the vesicle (acrosome) with the sperm plasma membrane leads to the release of the acrosome contents, but its regulatory mechanism has long been unknown. In this study, we focused on FER-1, a protein essential for fertilization in nematodes. Unlike human or mouse spermatozoa, nematode spermatozoa move by extending projections called pseudopods like amoeba. Pseudopod extension is mediated by an exocytosis, and FER-1 was identified as an essential protein for this exocytosis. There are six FER-1-like proteins in mice. While DYSF is known to be involved in muscular dystrophy, OTOF in deafness, and MYOF in muscle cell fusion, it was not known whether FER-1-like proteins are involved in mammalian sperm function. Therefore, we generated mice deficient in FER1L4, FER1L5, or FER1L6, which have unknown functions and are strongly expressed in testes. When each deficient male mouse was mated with wild-type females, only FER1L5 was found to be important for male fertility. No obvious abnormalities were found in the morphology or motility of FER1L5-deficient spermatozoa, but FER1L5-deficient spermatozoa could not fertilize eggs even with in vitro fertilization. Further analyses revealed that FER1L5-deficient spermatozoa in the female reproductive tract could not undergo the acrosome reaction. Even a calcium ionophore, which is a strong inducer of the acrosome reaction by increasing intracellular calcium concentration, could not induce the acrosome reaction in FER1L5-deficient spermatozoa, indicating that FER1L5 is essential for the acrosome reaction.

Significance of the research and Future perspective

Because no other deficient spermatozoa have been reported in which the acrosome reaction does not occur as much as in FER1L5-deficient spermatozoa, the identification of FER1L5 is expected to be a breakthrough in clarifying the regulatory mechanism of the acrosome reaction. Further functional analysis of nematode FER-1 is also expected to provide new insights into the acrosome reaction in mammalian spermatozoa. Since FER1L5 is known to be present in human spermatozoa, it is possible that dysfunction of FER1L5 may lead to infertility in men. Understanding the regulatory mechanism of the acrosome reaction by FER1L5 is expected to lead to the elucidation of the etiology of male infertility and the development of new diagnosis and treatment methods.

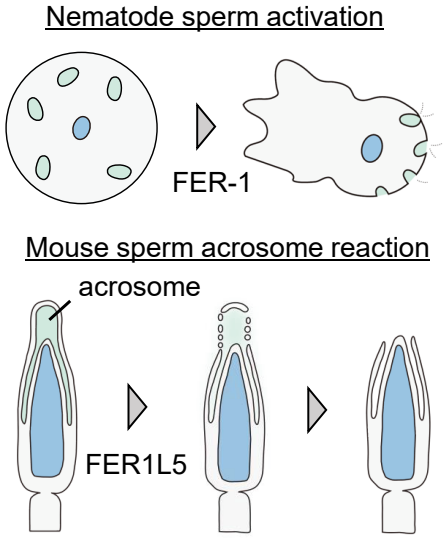

Figure 1. Exocytosis in nematode and mouse sperm

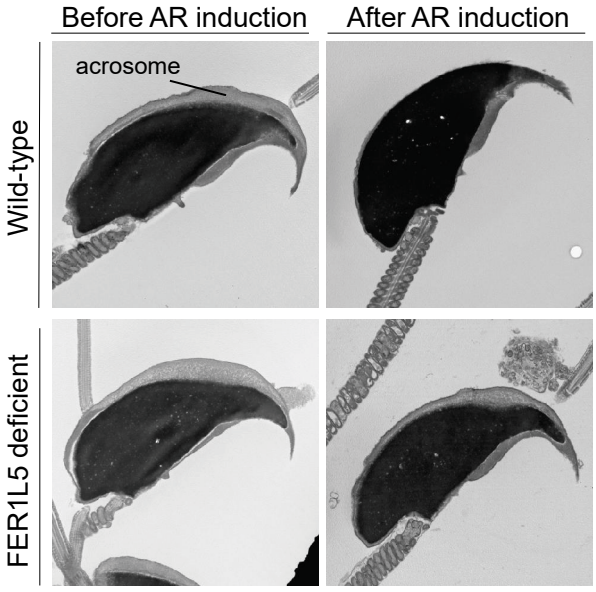

Figure 2. No acrosome reaction (AR) occurs in FER1L5 deficient sperm

Patent

Treatise Morohoshi, Akane; Miyata, Haruhiko et al. Testis-enriched ferlin, FER1L5, is required for Ca^{2+}-activated acrosome reaction and male fertility. Science Advances. 2023, 9 (4), eade7607. doi: 10.1126/sciadv.ade7607

URL

Keyword male infertility, sperm, acrosome reaction, exocytosis