Medical & healthcare, Drug development, Livestock industry

Development of infertility model mice and search for target factors for the development of infertility treatment and contraceptive drugs

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

Abstract

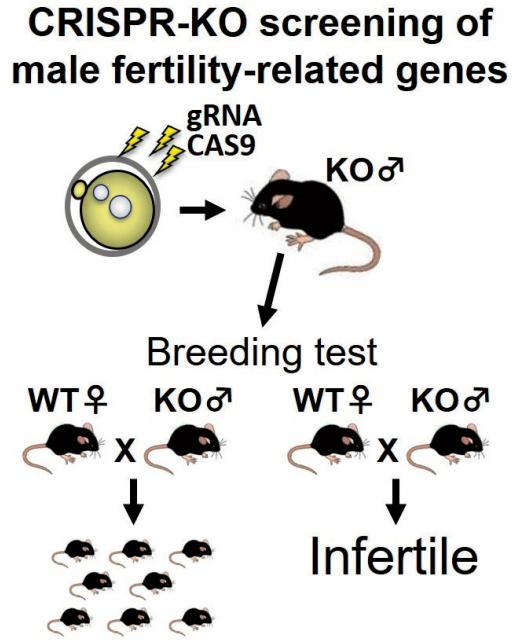
In our laboratory, we are conducting research to investigate the causes of male infertility and to develop male contraceptive drugs. Specifically, we use the latest genome editing technology to generate gene-knockout (KO) mice that target genes are expressed specifically in the testis, and analyze their phenotypes. When male infertility is observed, we elucidate the molecular mechanism and investigate the relationship with human infertility in cooperation with clinical researchers. In addition, for critical factors that control spermatogenesis and sperm function, we are working with Prof. Martin Matzuk at Baylor College of Medicine in the U.S. to develop non-hormonal male contraceptives by screening DNA-encoded small molecules.

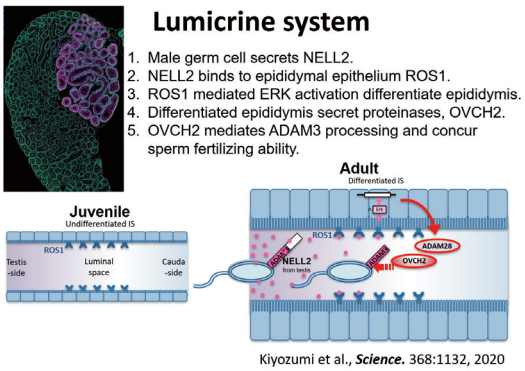
Background & Results

In mammals, it is said that there are more than 23,000 protein-coding genes, but there are about 1,000 genes that are specifically or abundantly expressed in the testis. We generated KO mice using the CRISPR/Cas9 genome editing method and conducted mating tests. As a result, we showed that 93 of the 321 testis-specific genes are essential for male fertility. For example, in 2015, we showed that sperm-specific calcineurin is essential for sperm motility, and that its inhibitors can induce temporary male infertility; in 2020, we showed that NELL2 factor produced in the testis go through the luminal space of the male reproductive tracts and regulates the differentiation of neighboring tissue (epididymis, responsible for sperm maturation). In combination with GWAS analysis of male infertility patients and KO mice studies, we elucidated the DNA8 is indispensable for sperm flagella formation and male fertility. In addition, we found that deficiency of ARMC12 causes defective formation of the sperm mitochondrial sheath, and that IZUMO1, FIMP, SOF1, TMEM95, SPACA6, and DCST1/2 are essential factors for sperm-egg fusion. Currently, we are collaborating with Professor Matzuk Martin at Baylor College of Medicine in the U.S. to develop male contraceptives through screening of DNA-encoding small molecules that bind to these essential factors.

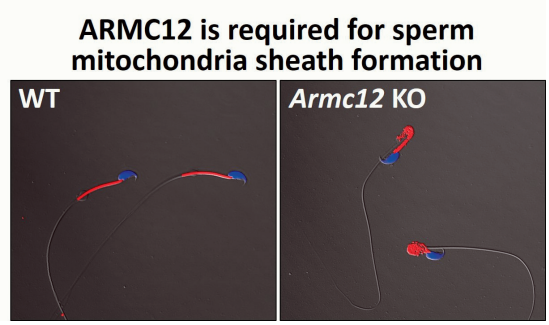
Significance of the research and Future perspective

Family planning requires the cooperation of men as well as women, but currently, the only contraceptives on the market are targeted at women. In addition, about one in six couples suffers from infertility, while about 40% of pregnancies are said to be unintended. Through safe and secure control of reproduction, we hope to lead to a society that provides gender equality, health and welfare to all people. In addition, the application of this technology to the efficient breeding of livestock animals is expected to contribute to a hunger-free society and to the conservation of rare animals.





Kiyozumi et al., ***Science.*** 368:1132, 2020



Patent

Treatise

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Keyword genome editing, reproductive medicine, family planning