

I have been conducting research to elucidate the mechanisms of mammalian fertilization and reproduction, with an interest in “why the number of pups per delivery differs among species” and “why the male/female ratio is 1:1” The sex of mammals is determined depending on whether a Y-chromosome-bearing sperm (Y-sperm) or an X-chromosome-bearing sperm (X-sperm) fertilizes the ovum. In 2019, for the first time in the world, we identified the protein that is found in X-sperm, but not in Y-sperm, and discovered that the sex ratio can be changed by utilizing functional differences of Y- and X-sperms. Y-sperm and X-sperm are produced in equal numbers, so the sex ratio is 1:1 in most mammals. However, Y- and X-sperms have partially different genes (not bearing the other sex chromosome). We hypothesized that Y- and X-sperms might

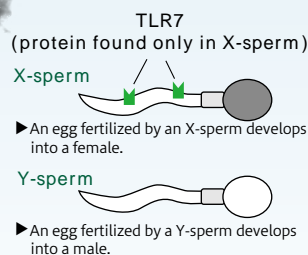
Discovered the protein “TLR7” (red portion), which is found only in a spermatozoon bearing an X chromosome (X-sperm) (Umehara et al., PLOS Biology, 2019)



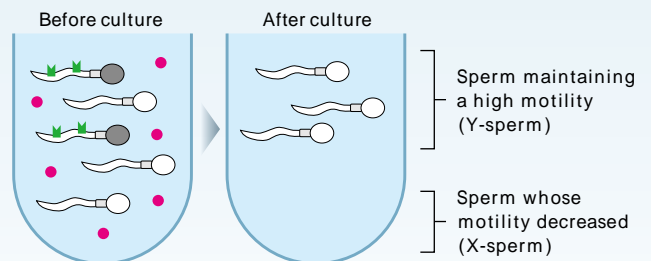
have potential functional differences to express specific proteins. To verify this hypothesis, we collected all RNAs in mouse sperm and then the sequences were analyzed. By narrowing down genes expressed from X-chromosomes or Y-chromosomes, we discovered a protein present only in X-sperm, “TLR7.” We then investigated conditions under which functional differences are demonstrated between X-sperm having TLR7 and Y-sperm not having TLR7. As a result, it has been found that under TLR7-ligand condition, the production of adenosine triphosphate (ATP), which is the primary energy carrier in all living organisms, was decreased only in X-sperm. Furthermore, the motility of X-sperm decreased and X-sperm sank to the bottom,

whereas Y-sperm showed no effect and swam up to the upper layer, exhibiting high motility. We have succeeded in the selective production of a male or female in mice and cattle by applying this method of “easily separating X- and Y-sperms” to in vitro fertilization. This research result can be summarized very simply as follows: We discovered functional differences of X-sperm and Y-sperm and succeeded in the selective production of a male or female by separating X- and Y-sperms. However, this achievement was not easily obtained. We repeated over and over the process of developing a hypothesis, creating a story to prove the hypothesis, and then executing that story. Our achievements are the result of our hard and steady research efforts over five years. In my opinion, the best part of research is the joy that we feel when we can neatly prove phenomena that surpass our hypothesis, by examining unexpected results without being disheartened by failures. Our research results have received a huge response from across Japan and abroad. In beef cattle production, the demand for male calves is higher. It is because male cattle or bulls grow bigger than females and can be sold at higher prices. In short, economic efficiency is higher for livestock farmers. The method we have developed does not require large-scale equipment. Therefore, in the future, it may become possible for individual livestock farmers to selectively produce males or females. We wish to contribute to livestock production by promoting the practical application of this technique so that it can be used at livestock production sites.

## Contributing to the world's food problems by elucidating the mechanisms of genes that determine sex



Succeeding in producing male cattle by applying the technique developed using mice to cattle (Photo provided by Oita Prefectural Agriculture, Forestry and Fisheries Research Center)



Succeeding in separating X- and Y-sperms by stimulating only X-sperm (Umehara et al., PLOS Biology, 2019)



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