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Sperm fusion protein identified

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A team of researchers has identified a sperm protein that is essential for the fusion of the sperm and egg membranes during fertilization, according to a report in this week's *Nature*. They called the protein "Izumo," after the Japanese shrine dedicated to marriage.

Masaru Okabe of Osaka University and coworkers used the fusion-inhibiting monoclonal antibody OBF13 and gene-cloning techniques to identify an antigen on mice sperm involved in fusion. "The antigen Izumo is a novel protein of the immunoglobulin superfamily," Okabe, the senior author of the study, told *The Scientist*. Proteins belonging to this family are membrane-anchored, and are usually involved in cell-cell adhesion.

Okabe has been seeking the sperm protein since 1987, when his group reported that OBF13 bound to an unknown molecule on the sperm head. Further studies revealed that the antibody did not prevent sperm binding, but did inhibit fertilization. This gave the researchers a clue as to the protein's involvement in fusion. "For the next ten years, I tried very hard to find the antigen [that OBF13 bound], but I couldn't clone the gene," explained Okabe. "Then, I rested for five years, until Noakazu Inoue, the first author of the paper, joined our group. Inoue tried the procedure again, with newer and more sensitive techniques, and succeeded."

In recent years, Okabe and his team have also studied egg proteins. In 2000 they published a paper in *Science*, reporting that CD9—a protein on the egg surface—was essential for sperm-egg fusion. A group in France also published a report presenting similar results in the same issue. "We had this egg protein involved in fusion, but on the sperm side, nothing was clear," said Okabe. "With the discovery of Izumo, the mechanism of sperm-egg fusion is now ready to be examined."

In their latest paper, the researchers established the role of Izumo in fertilization by producing a knockout mouse line. The experiments rendered unambiguous results. The mice were healthy, but the males were sterile. Their sperm bound to, and penetrated the *zona pellucida*but could not fuse with the egg.

Paul Primakoff of the University of California at Davis, who was not involved in the research, welcomed the paper, which deals with a field in which there had not been breakthroughs lately. "The fertilization processis difficult to study for many reasons," said Primakoff, "primarily because it's hard to get the number of eggs necessary for the experiments, but also because there aren't many people working in the field."

He added that no one has worked out a rapid screening method to identify proteins involved in the fusion process, which makes its study particularly hard. "Now we can start thinking about the mechanism of how this protein acts, and to formulate models on how the fusion process might occur."

"This paper will provide a jolt of energy to the field," said Richard Schultz of the University of Pennsylvania, who did not participate in the study. "Now there's a candidate molecule that is out there that might help us understand better how membranes actually fuse. I think it'll generate a lot of excitement in the field. Schultz, who wrote a related News and Views article, pointed to the potential of

Izumo as a target for non-hormonal contraception, based on Okabe's finding that human sperm also contains Izumo, and that when exposed to the antibody, sperm becomes unable to fuse with the egg.

Okabe is expecting accompanying proteins to be involved in fusion. "We think that Izumo is not the only factor affecting fusion. We just opened the door for studying the fusion mechanism," he said. "Now we have to find other factors which are also involved in fusion, using Izumo and CD9."

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