Does Egg Beckon Sperm When the Time Is Right?

New findings suggest that the human egg sends a chemical signal to the sperm when it is ready to be fertilized

THE DANCE OF SPERM AND EGG REMAINS ONE of the great mysteries of human reproduction, as dimly understood as the mating ritual that precedes it. Now comes a new study suggesting that at the time of ovulation, the egg may release a chemical signal that beckons the sperm to make its final sprint up the fallopian tube to the site where fertilization occurs. The evidence, while preliminary and indirect, is the first indication that the sperm and egg communicate before they actually come into contact.

"There has long been a question of whether the sperm can be attracted to the egg in mammals. It has been demonstrated in sea urchins. Now we have a suggestion that it does occur in humans," says Gregory Kopf, a reproductive biologist at the University of Pennsylvania, who calls the study "very exciting."

Exciting as they may be, the data are still merely suggestive, caution the authors, who include Michael Eisenbach and Dina Ralt of the Weizmann Institute in Israel, Shlomo Mashiach of Tel Aviv University, and Dana Thompson and David Garbers of the University of Texas Southwestern Medical Center in Dallas. They have yet to identify the sperm-attracting chemical, which they detected in the follicular fluid that bathes the maturing egg. Nor do they know whether the factor is actually released by the egg or by some of the surrounding cells. What's more, tracking it down will be a daunting task, says Garbers, and success is far from assured.

Nonetheless, the researchers are hot on the factor's trail, because finding it could open the door to new treatments for some cases of infertility and to new approaches to contraception. Practical implications aside, studies of the factor also promise to illuminate some of the long-standing questions about human fertilization, such as how the final meeting between egg and sperm is synchronized, and why so few sperm, just 200 or so out of perhaps 300 million in a typical ejaculation, make it to the site of fertilization.

The discovery of the human attractant, which is described in the April issue of the *Proceedings of the National Academy of Sciences*, is a direct outgrowth of David Garbers' work on egg and sperm communication in sea urchins. In 1981 Garbers and his colleagues purified a peptide released by sea urchin eggs that stimulates sperm motility. The obvious question then was whether human eggs release a similar substance. Garbers originally hoped to use molecular techniques to find out, by using the gene encoding the sea urchin peptide to ferret out the corresponding gene in humans. Garbers' hopes were dashed, however, when he and others found that the active peptide varies dramatically in structure among different sea urchin species. That meant that the human sperm attractant, if it existed, would be very different from the sea urchin peptide, so those techniques would not work.

Eisenbach learned about Garbers' work several years ago at a meeting in Miami on chemotaxis—the movement of an organism toward a chemical signal. Eisenbach, who studies chemotaxis in bacteria, was intrigued by the possibility that human sperm might respond to chemical signals and was "astonished" to hear how little was known. He then proposed to spend 3 months in Garbers' lab learning about sperm and seeing if the two researchers could find another way to get at the question, a collaboration that continued after Eisenbach returned to Israel.

The researchers settled on a relatively simple experimental tack. They obtained fluid from the egg follicles of 40 women undergoing in vitro fertilization at the Sheba Medical Center in Israel. Then the researchers put sperm in the bottom wells of a modified chemotaxis chamber and follicular fluids or a control solution in the top wells and measured how many sperm swam to the top.

In about half the cases, sperm accumulation was far higher in follicular fluid than controls. The clincher came when the investigators compared their results to the outcome of the in vitro fertilizations. They found "an almost perfect correlation" between the eggs that were fertilized and the follicular fluids that attracted sperm, says Garbers. Adds Eisenbach: "It is very tempting to speculate that in some cases, couples may be infertile because of faulty communication between the sperm and the egg."

So why the caution displayed by the team? "Though our preliminary data show there probably is something there, we know essentially nothing about it," explains Garbers. They have yet to learn the nature of the signal or where it comes from, the egg or the surrounding cells. The authors also point out that they have not yet demonstrated chemotaxis but simply the accumulation of sperm in follicular fluid, though chemotaxis is the likely explanation.

These uncertainties notwithstanding, the investigators have come up with a working hypothesis: The putative chemoattractant may be a way to select the relatively small number of sperm that are in the proper physiologic condition to fertilize the egg. The factor may also synchronize sperm behavior with ovulation. Other investigators have shown that in some mammals, sperm accumulate in the female reproductive tract near the isthmus of the fallopian tube, where they remain relatively motionless for hours. But once ovulation occurs, they become motile again and within minutes rendezvous with the egg. Eisenbach and Garbers speculate that it is this as-yet-unidentified factor that signals the "good" sperm to get moving, while it or other substances repel the "bad" sperm.

Proving that, however, will mean getting their hands on the elusive factor. The problem is that it is active in the follicular fluid for a short time. And if the sea urchin chemoattractant is any guide, it is likely to be present in the fluid in vanishingly small amounts. Says Garbers: "The question is, can we get enough follicular fluid for chemical purification?" And if more than one chemical turns out to be involved, says Garbers, then the biochemistry moves beyond the merely difficult to the level of "a complete nightmare." Nonetheless, Eisenbach has already plunged into the experimental morass, and Garbers plans to do so soon. ■ LESLIE ROBERTS

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