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Unlocking the sperm's internal compass

Study shows how a sperm's behavior shapes its swimming path.

Even without GPS units to guide them to the egg, sperm perform some impressive navigational feats. Kashikar et al. reveal several responses that enable sperm to get their bearings and steer to the egg (1).

A sperm tracks down the egg by following a gradient of chemical attractants. In the sea urchin species *Arbacia punctulata*, the attractant is the peptide resact, which sticks to receptors on the sperm's flagellum and triggers an influx of calcium (2). Sperm set their course based on these calcium surges (3). For example, a recent study by the team found that the rate of change in calcium levels dictates whether sea urchin sperm make sharp or gentle turns (4). By continually "sniffing" its surroundings and recalibrating its course, a sperm follows a circuitous path to the egg. But many of the details of how sperm navigate using resact levels remain mysterious. Researchers don't know, for example, how long a sperm samples its surroundings before heading in a particular direction or how it adjusts its sensitivity to concentrations of attractant that can vary by orders of magnitude.

Kashikar et al. set up experiments to answer questions like these. They exposed sea urchin sperm to caged versions of resact and cyclic GMP—which spurs calcium surges—that they could free with flashes of light. In this way they could stimulate the sperm at specific time intervals. The first question the researchers tried to answer was how long the sperm samples its surroundings. The team compared responses to a single full-strength flash and two half-strength flashes delivered varying times apart. The results suggest that a sperm tests its environment for between 0.2 and 0.6 seconds, integrating the stimuli it receives in that time and then computing its direction.

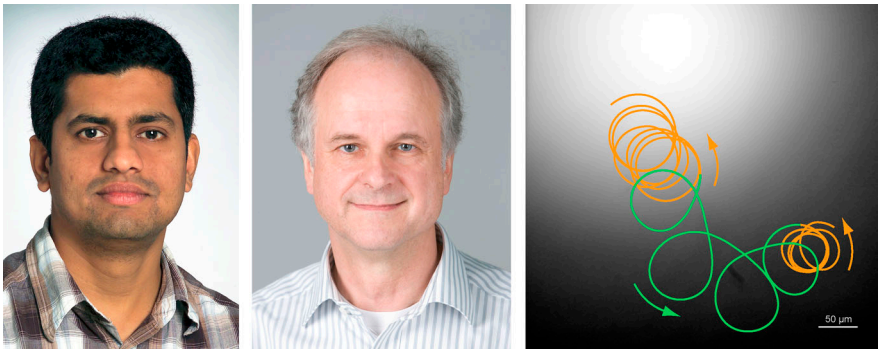
But what if another stimulus arrives after a sperm has already begun to respond? The researchers thought they knew the answer: the sperm would ignore late-arriving stimuli or add them to previous ones. Instead, the team showed that a pulse of resact or cyclic GMP one second after the original stimulus—when the calcium influx was at its peak—caused the sperm to reset. The calcium surge fizzled, and a new one began. When the researchers tracked the swimming paths of the sperm, they discovered that plunging calcium levels caused the cells to stay on a straight path for a longer period of time. The sperm then turned as calcium levels began to rise after the second stimulus.

> "We identified the different computational steps that sperm perform in order to navigate successfully."

By altering the concentration of caged resact and the strength of the light pulse, Kashikar et al. determined that a sperm can detect and count single molecules of the attractant. But that finding raises a question: as the sperm approaches the egg, resact's concentration soars, so why aren't the resact receptors swamped at close range? To find out, the researchers added resact to solutions with different background levels of the attractant. Results of these experiments suggest that sperm reduce their sensitivity as the background concentration increases, probably by tweaking the resact receptor. The scientists tested that possibility by prodding sperm with cyclic GMP, which stimulates the cells without activating resact receptors. That procedure spurred less desensitization, supporting the notion that sperm somehow dull the responsiveness of their resact receptors as the concentration of the attractant rises.

"We identified the different computational steps that sperm perform in order to navigate successfully," says senior author U. Benjamin Kaupp. By sampling their surroundings, remaining responsive to late-arriving stimuli, and adjusting their sensitivity as they near their target, sperm can home in on an egg that is 4.7 millimeters away, or about 100 times their length. Among the questions researchers still need to answer are how sperm adjust the sensitivity of their resact receptors and how the cells deal with noise that could send them astray.

Focal Point



PHOTOS COURTESY OF PETER GOLDMANN (KASHIKAR) AND U. BENJAMIN KAUPP

Nachiket Kashikar (left), U. Benjamin Kaupp (center), and colleagues (not pictured) put swimming sperm through their paces to determine how they set their course. They found that sperm test their environment for a limited time but remain attentive to stimuli that arrive after that period. They also showed that sperm respond to individual molecules of attractant but reduce their sensitivity as they approach their target. The diagram (right) of the swimming path of sperm in a gradient of attractant (indicated by shades of gray) reveals that sperm tend to swim in loops (green) where the gradient is steepest and in tighter circles (orange) where concentration changes are more gradual.

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4. Alvarez, L., et al. 2012. *J. Cell Biol.* 196:653–663.