QnAs with Peter N. Devreotes

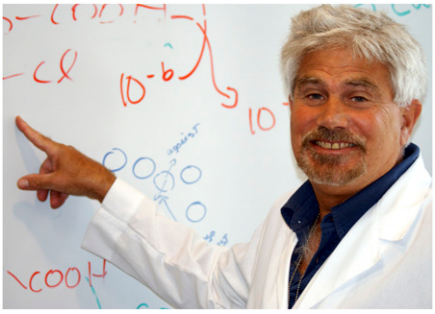
Peter N. Devreotes, a professor of cell biology at Johns Hopkins University who was elected to the National Academy of Sciences in 2005, studies how animal cells navigate their physical environments using a process called chemotaxis, which helps cells move away from or toward chemical cues. First described in the late 1800s, this deceptively simple process of directed movement could help researchers answer weighty questions surrounding human diseases such as cancer and arthritis. Devreotes tells PNAS that a short-lived, soil-dwelling microbe that performs chemotaxis might hold many of those answers.

PNAS: Why is chemotaxis important to animal cells?

Devreotes: Sensing chemical gradients in cellular environments is crucial to both embryos and adults. Chemotaxis happens in a range of animals, from starfish to people. It's been observed in immune cells like macrophages, neutrophils, and dendritic cells; in endothelial cells, which line blood vessels; and in cells involved in wound healing. Primordial germ cells [which give rise to eggs and sperm] use chemotaxis to reach the gonads from their place of origin in the developing embryo. Axons of neurons in the embryo use chemotaxis to reach their targets. Cells of the fish lateral line [a sense organ that helps fish detect movement in water] display chemotaxis during the embryonic stage.

PNAS: For decades researchers have studied chemotaxis using the amoeba *Dictyostelium*. What makes it such an attractive model for chemotaxis?

Devreotes: *Dictyostelium* amoeba moves, well, in an amoeboid way, which is very similar to the movement of immune cells. Because the amoeba shows a chemotactic response resembling mammalian chemotaxis, it's a good model for the process. What's more, the molecular features of the chemotactic system seem to be highly conserved between *Dictyostelium* and mammals, even though they sense different kinds of chemicals; and the amoeba provides a range of genetic tools for studying chemotaxis. The field has advanced to a point where you can quickly generate *Dictyostelium* mutants lacking many combinations of genes; I think the current record is about seven gene deletions in a single amoeba. Further, the amoeba is easy to observe with high-resolution imaging techniques and easy to grow in the lab for biochemical experiments. So, *Dictyostelium* is as good a model for chemotaxis as yeast is for cell division, and the fruit fly, for development.



Peter N. Devreotes.

PNAS: So how do cells navigate through external chemical gradients?

Devreotes: They use an internal compass. We've found that cells performing chemotaxis use G protein–coupled receptors distributed across the cell surface to respond to external chemical gradients. The receptors engage a signaling network and the cytoskeleton to bring about biased movement of cells within the gradient. Amoeboid cells put out pseudopods [membranous, feet-like protrusions] to move. The cells move even in uniform chemical milieus, but, when surrounded by gradients, the lifetime and position of the pseudopods change in tune with the gradient to help the cells move up the gradient. We've identified some parts of this compass but not others.

PNAS: One of those parts goes by the mellifluous name "pianissimo." Tell us what it does.

Devreotes: About 15 years ago, a graduate student, Mei-Yu Chen, who happened to be a piano player, discovered a mutant amoeba showing defective signaling, and hence defective chemotaxis. Because the signal in this mutant wasn't strong enough, she named it pianissimo after a musical notation meaning "soft." While we were looking for the precise function of the pianissimo protein, Michael Hall from the University of Basel, Switzerland, identified a yeast signaling protein complex, called TORC2, whose signature component turned out to be the yeast counterpart of pianissimo. That finding suggested that TORC2 likely played a role in chemotaxis. We now know that a series of kinase enzymes in a signaling network, of which TORC2 is a part, controls chemotaxis. So our discovery of pianissimo helped uncover one of two well-known biochemical pathways controlling chemotaxis.

PNAS: What is the other pathway?

Devreotes: The other pathway is controlled by a phospholipid called PIP3, which is produced at the cell's leading edge during chemotaxis. An enzyme, called PI3-kinase, makes PIP3, and another enzyme, called PTEN, destroys it. When my postdoc Miho Iijima eliminated PTEN, she found that PIP3 spread along the cell surface, instead of accumulating at the cell's leading edge, which, of course, led to pseudopods in all the wrong places. That interferes with directional movement; the cells still move in the direction of the gradient, but they grope because of all the lateral pseudopods. Other researchers artificially activated PI3-kinase in neutrophils and found that the neutrophils started to migrate. So it's clear that PIP3 is an important player.

PNAS: In your PNAS inaugural article (1) you describe a model simulating the behaviors of chemotactic cells. Can you explain the model?

Devreotes: Without a surrounding gradient, cells respond to stimuli for a while, then stop responding until the stimuli are refreshed or altered. This is a form of adaptation. In the presence of a gradient, however, they continue to respond for as long as the gradient is around. Ten years ago, postdoc Carole Parent and I proposed that an interplay of excitatory and inhibitory signals within cells controls their adaptation as well as their response to gradients. According to that model, the excitatory signal persistently overrides the inhibitory signal at the front of cells, whereas the reverse is true for the back of cells; but that model could not explain all of the behaviors of chemotaxing cells. Our model in the inaugural article ties the excitation–inhibition paradigm, the actin cytoskeleton, and the cells' signaling network to explain the dynamic behavior of chemotaxing cells.

PNAS: Your pursuit of chemotaxis is propelled by more than scientific curiosity. What are its clinical implications?

Devreotes: Chemotaxis is important in inflammation, which is implied in a number of ailments like asthma, arthritis, and atherosclerosis. So controlling chemotaxis, and thus inflammation, has obvious uses. Because of the number of pathways involved, any attempt to control chemotaxis would likely call for mixtures of compounds. The other important scenario is cancer metastasis. There's proof that spreading cancer cells use chemotaxis to move out of blood vessels and into target tissues. So the implications for cancer treatment are also obvious.

Prashant Nair, *Science Writer*

1. Xiong Y, Huang CH, Iglesias PA, Devreotes PN (2010) Cells navigate with a local-excitation, global-inhibition-biased excitable network. *Proc Natl Acad Sci USA* 107: 17079–17086.