CELL BIOLOGY

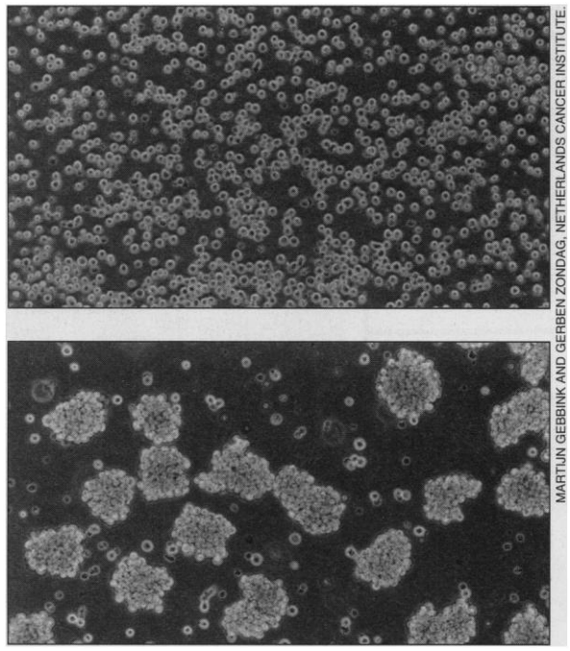
Things Start Getting Sticky For a Cell Surface Enzyme

Cells, just like people, must band together to get things done—to form skin, say, or liver or muscle. They do so by means of adhesion molecules on their surface that identify like cells and grip onto them. And like people, cells need to take action once they have found their comrades: They may need to differentiate into more complex cell types or simply stop growing, a process called contact inhibition that is lost in cancerous cells. In normal cells, it seems, a signal must pass from at least some of the adhesion molecules to the cell's interior, telling it what to do. But so far, details of how this occurs have been slow to emerge.

Now two teams of researchers have traced a circumstantial link between adhesion and signaling by showing that an enzyme believed to play an important role in signaling within the cell, a so-called receptor protein tyrosine phosphatase (RPTP), can act as an adhesion molecule. A cell making one kind of RPTP, these researchers have found, can recognize and bind to another cell bearing the same kind of molecule. While it isn't clear what kind of signaling follows the recognition, the finding is "very interesting," says Edmond Fischer of the University of Washington, a pioneer of the booming tyrosine phosphatase field and co-winner of last year's Nobel Prize in Physiology or Medicine. It's plausible, too, he adds. "One already knew that some of these [tyrosine phosphatase] receptors shared homologies with adhesion molecules. So it was a good bet that several of them would form interactions among themselves."

Tyrosine phosphatases, discovered in the late 1980s, get their name from the enzymatic role they perform inside cells: Removing phosphate groups from tyrosine residues of proteins. The better-known counterparts of the tyrosine phosphatases, the family of enzymes called protein tyrosine kinases, play the opposite role, adding phosphate groups to tyrosine residues and thereby regulating cell growth and differentiation. Because they act on the same kinds of biochemical switches as the tyrosine kinases, the tyrosine phosphatases are thought to play an equally important role in controlling cell growth and differentiation (*Science*, 15 February 1991, p. 744).

To their surprise, investigators have found that many of the tyrosine phosphatases have structures characteristic of transmembrane receptors—molecules that receive signals on the outside of the cell membrane and relay them to the cell interior. But while the extracellular parts of the different RPTPs are very diverse and so probably respond to different molecules, the search for these ligands has been slow. The new work shows that for at least some RPTPs, the missing ligand is the receptor itself. "The ligand for this receptor PTP appears to be a molecule of the same type expressed on the surface of an adjacent cell," says Nicholas Tonks of the Cold Spring Harbor Laboratory, who was the first researcher to succeed in purifying a tyrosine phosphatase 5 years ago.



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Self-selection. Insect cells genetically engineered to express a human receptor tyrosine phosphatase on their surface recognize and adhere to one another, forming clumps *(above)*, while control cells stay separate *(top)*.

One of the groups, Susann Brady-Kalnay, Andrew Flint, and Tonks at Cold Spring Harbor, announced its findings in the *Journal of Cell Biology*. The other, based at the Netherlands Cancer Institute and headed by Wouter Moolenaar, published its results in last week's issue of the *Journal of Biological Chemistry*. Both groups demonstrated the enzyme's capacity for adhesion by introducing a gene for a human receptor tyrosine phosphatase, RPTPμ, into insect cells that are not normally "sticky" in themselves. The cells producing the RPTPμ and displaying it on their surfaces clumped together dramatically, while control cells did not. In addition, Jan Sap, who works in the group headed by Josef Schlessinger at New York University, has unpublished work showing that a closely related molecule, RPTPκ, also has adhesive properties.

What's more, the Dutch researchers, in collaboration with the New York University group, took a further step. In a still unpublished experiment, they mixed insect cells expressing RPTPμ with cells expressing RPTPκ and gently shook them. The two types of cells promptly sought out their own kind, forming two distinct sets of clumps, despite the fact that RPTPμ and RPTPκ are structurally very similar. "This shows that these cell-cell interactions are highly specific and makes us feel confident that the molecules are bona fide cell-recognition receptors," says graduate student Martijn Gebbink of the Amsterdam group, who was the first to clone RPTPμ.

So far, nobody is certain how the adhesion of RPTP might affect its enzymatic activity inside the cell. One hunch is that adhesion may not alter the activity of receptor phosphatases directly, but may have an indirect effect. Says Tonks: "Maybe what happens is that the aggregation reaction links two RPTPμ molecules on opposing cells, thereby restricting where they can go in the membrane and thus indirectly controlling the activity of the enzyme."

Further insights may have to wait until researchers identify the enzyme's target proteins inside the cell, says Tony Hunter of the Salk Institute in San Diego, and these are now high on everyone's priority list for future work. Although the new findings have raised high hopes that biologists may soon unravel the bonds that hold cells together and how such bonds direct cellular responses, Hunter cautions that the secrets of cells' social lives are still a long way off.

–Felix Eijgenraam

Felix Eijgenraam is a science writer with the Dutch newspaper NRC Handelsblad *in Rotterdam.*

Additional Reading

Martijn F.B.G. Gebbink *et al.*, "Cell-Cell Adhesion Mediated by a Receptor-like Protein Tyrosine Phosphatase," *J. Biol. Chem.* **268**, 16101–16104 (1993).

Susann M. Brady-Kalnay, Andrew J. Flint, and Nicholas K. Tonks, "Homophilic Binding of the Receptor-Type Protein Tyrosine Phosphatase, PTPμ, Can Mediate Cell-Cell Aggregation," *J. Cell Biol.* **122**, 961–972 (1993).

E.H. Fischer, H. Charbonneau, and N.K. Tonks, "Protein Tyrosine Phosphatases: A Diverse Family of Intracellular and Transmembrane Enzymes," *Science* **253**, 401–406 (1991).