**Cadherin as a tumor suppressor**

Cancer cells become far more dangerous when they gain the ability to metastasize and colonize other parts of the body. But to start moving, the rogue cells have to break away from their neighbors. Walter Birchmeier (now at the Max-Delbrück-Center of Molecular Medicine in Berlin, Germany) and colleagues discovered how, showing that some cancer cells down-regulate a surface receptor that locks adjacent cells together.

The protein, known as E-cadherin, had caught the eye of developmental biologists such as Francois Jacob and Gerald Edelman because it enables the early embryo to keep its shape. Birchmeier recalls. His group tested whether E-cadherin (previously known as uvomorulin) altered the stickiness of dog kidney epithelial cells. In culture, the cube-shaped cells normally pack closely together and resemble a cobblestone street. Adding an antibody that latches onto E-cadherin spurred the cells to break up and take on a ragged, irregular shape (Behrens et al., 1989). Moreover, the cells could infiltrate a layer of collagen and burrow into chunks of chick heart, signs that they had severed their moorings and become invasive. The researchers then infected normal dog kidney cells with an oncogene-carrying virus and saw the same transformation—the cells dispersed and began metastasizing. The notion that pro-growth oncogenes could promote cancer was familiar at the time, Birchmeier says, but “the idea that you lose something to become invasive was relatively new.” The work also demonstrated that cells could become invasive even if they weren’t cancerous.

In a follow-up study, Birchmeier’s group linked E-cadherin to human cancers (Frixen et al., 1991). They analyzed cell lines from many different carcinomas—epithelial tumors that are the most prevalent type of cancer in humans—and found that the invasive lines lacked E-cadherin. What’s more, reinstalling the gene for E-cadherin reigned in the cells’ wanderlust. Birchmeier and colleagues later discovered that an oncogene called v-src didn’t alter the expression of E-cadherin. However, it did increase the number of phosphate groups stuck to E-cadherin and the bridging protein β-catenin, which connects E-cadherin to the cytoskeleton (Behrens et al., 1993). These results revealed that it’s possible to reduce cell stickiness not only by reducing the amount of E-cadherin but also by altering the protein’s structure. ML Behrens, J., et al. 1989. J. Cell Biol. 108: 2435–2447.

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**Active neuronal death**

Take away their supply of nerve growth factor (NGF), and neurons lose the will to live. In 1988, the conventional wisdom held that the cells wasted away because NGF helped keep metabolism churning. After all, NGF is a trophic factor, meaning that it literally “nourishes” the cell. But neuroscientist Eugene Johnson (Washington University, St. Louis) and colleagues suspected that the molecule instead prevented neurons from committing suicide—a controversial assertion that they confirmed with some simple experiments. The issue was important. Johnson says, because droves of surplus neurons perish during development, and uncovering the requirements for cell survival might clarify how this attribute helps wire the nervous system. The knowledge might also reveal measures for sparing neurons jeopardized by stroke and neurodegenerative diseases.

Johnson and colleagues reasoned that if NGF were essential for metabolism, shutting down protein or messenger RNA synthesis would speed the cells’ demise. But if NGF stalled a cell-killing mechanism that required fresh mRNA and proteins, halting their production would delay death. To test their hypothesis, the researchers cultured neurons and then added antibodies that neutralized the NGF (Martin et al., 1988). After about a day of deprivation, the cells started to shrink and their membranes began to seethe. The medium showed a surge in adenylate kinase, a protein normally confined to the cytoplasm, demonstrating that the neurons were spilling their guts. But a dose of cycloheximide, a protein synthesis inhibitor, proved to be a balm for the neurons. “Cells without cycloheximide were toast, and cells with cycloheximide were beautiful,” recalls Johnson. Moreover, little adenylate cyclase leaked from treated cells, further evidence that they remained whole. Treating NGF-deprived cultures with actinomycin-D, an RNA synthesis blocker, also derailed cell death. The results “changed how people thought about what trophic factors do and how cells die,” says Johnson. Neurons weren’t pining away; they were killing themselves.

Although other researchers had performed similar experiments, their results had been unclear, Johnson recalls. His group, however, made a fortunate choice. Other workers had studied neurons that required a constant supply of new proteins, and the cells died swiftly after translation or transcription halted. But the sympathetic neurons Johnson and colleagues examined could endure a four-day hiatus from protein making, possibly because they were postmitotic. His group went on to map the sequence of events in a neuron’s death, showing that the cell-slaying program eventually reaches a point of no return (Deckwerth and Martin, 1993). The invention of PCR allowed his lab to identify some of the genes that orchestrate neuron suicide (Estus et al., 1994). ML Deckwerth, T.L., and E.M. Johnson. 1993. J. Cell Biol. 123:1207–1222.

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