hydrocarbon groups at each corner (the legs). Earlier this year, the researchers succeeded in moving around individual porphyrins deposited on a metal sample with the ultrafine probe of a scanning-tunneling microscope, a device that can read a surface's atomic contours. (*Science* 12 January, p. 181).

In the study reported at the conference, the researchers discovered that the 4-poster porphyrins adopted different conformations on different metallic surfaces, as the legs of the molecules bent to adapt to the spacing of the atomic rows on the metal surfaces as well as the amount of electrical attraction between the mattress and the various surfaces. On copper, for example, the legs were oriented roughly in squares, while on silver they were positioned in long rectangles. On gold, the porphyrins adopted two different shapes, and the researchers were able to take before-and-after snapshots of the transition.

When they briefly heated a sample of gold coated with porphyrins, the individual porphyrin molecules adopted a rectangular shape. But after heating the sample for another 20 min, the same porphyrins stretched into longer rectangles. The researchers believe that the extra heat allowed the porphyrin molecules to wiggle into a more energetically stable binding position, in which the long axis of the rectangular porphyrins straddled the rows of gold atoms.

The next step is to see whether researchers can understand how precise conformational changes influence properties such as the ability of the molecules to conduct electrical charges. If they succeed, techniques for mastering shape shifting could trigger some technological shifts as well.

–Robert F. Service

APOPTOSIS

Life-Death Balance Within the Cell

When it was first identified more than two decades ago, tumor necrosis factor (TNF) seemed like a promising cancer killer. Indeed, this signaling molecule, which is made by cells of the immune system, was named for its ability to shrink tumors. But researchers soon learned—much to their disappointment—that TNF doesn't kill most types of cancer cells. Now, three research teams, in separate reports in this issue, have unmasked the reason for its fickleness.

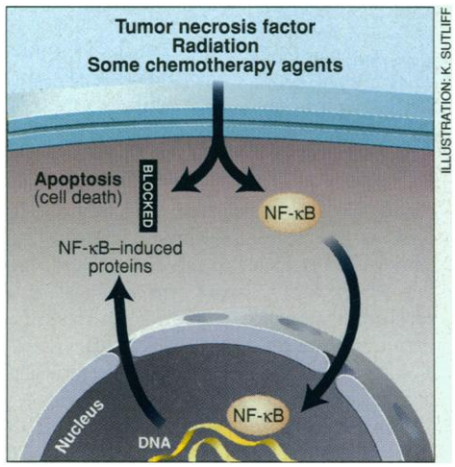
As many researchers have suspected, TNF undermines its own killing powers. Even though it triggers a biochemical pathway that leads to the programmed form of cell suicide known as apoptosis, it also activates a key molecule that can block this very pathway, and so sets up a delicate life-death balance within the cell. And these findings have again raised hopes for potential therapies, for the researchers also show that disrupting the protective mechanism makes cells much more vulnerable to killing, not only by TNF but also by radiation and a chemotherapy drug. "The data are crying out for clinical trials," says cell-death researcher Vishva Dixit, of the University of Michigan.

The first clues to TNF's dual nature came several years ago when a number of groups observed that cells treated with drugs that block protein synthesis are more easily killed by TNF. "Clearly genes were being turned on that could protect against cell death," says David Goeddel, who studies TNF at Tularik, Inc., in South San Francisco. Researchers suspected those genes may be getting switched on by a protein called nuclear factor kappa B (NF-κB), which is activated by TNF and, in turn, turns on genes involved in the body's response to inflammation, infection, and stress.

That idea gained support last year when David Baltimore's group at the Massachusetts Institute of Technology reported that knockout mice missing NF-κB die before birth, apparently of a massive die-off of liver cells. That implied that NF-κB protects embryonic liver cells from committing suicide, but, says Baltimore, "we couldn't generalize it" to other cell types, since other parts of the embryos seemed fine.

Then Gail Sonenshein's group at Boston University Medical School reported earlier this year that inhibiting NF-κB causes the B cells of the immune system to die of apoptosis. But her findings weren't generalizable either, because B-lymphocytes are a special case: NF-κB is always active in these cells, whereas in most other cell types it is bound up in the cytoplasm by an inhibitor molecule called IκB, which must be destroyed for NF-κB to be activated.

The new papers, from Baltimore's group (p. 782), Inder Verma's team at the Salk Institute in San Diego (p. 787), and Albert Baldwin's group at the University of North Carolina (p. 784), broaden the earlier findings and link them to the TNF puzzle. Baltimore's group treated cells taken from NF-κB knockout mice with TNF, and compared their response to that of cells from normal mice. The normal cells were fine, but those lacking NF-κB died. Baldwin's and Verma's groups took a different approach: They introduced into a variety of cultured tumor and nontumor cells a mutant form of IκB that acts as a "super-repressor," keeping NF-κB irreversibly shackled in the cell's cytoplasm. With NF-κB out of the picture, TNF could kill all the cell types. Goeddel and Michael Karin, of the University of California, San Diego, have similar results in press. As Sonenshein puts it, "there appears to be quite a general role for NF-κB in [preventing] apoptosis."



Suicide prevention. NF-κB turns on protective proteins that can help cells resist death.

Baldwin's group has already begun to explore the implications of that role for cancer therapies, many of which work by triggering cell suicide. Noting that radiation also activates NF-κB, Baldwin says, "I started thinking, can we make tumor cells respond better to radiation by blocking their NF-κB activation?" The answer turned out to be yes; Baldwin's team found that a human tumor cell line in which NF-κB was bound up by the IκB super-repressor was much more readily killed by radiation, and by the chemotherapy drug daunorubicin, than were normal cells.

Even cancers that at first respond well to radiation or drugs often develop resistance by turning off their suicide response, and Sonenshein thinks drugs that inhibit NF-κB, several of which are already in clinical trials for AIDS, may help turn it back on. At least some tumor cells show changes in NF-κB that could contribute to their resistance to death: Sonenshein has unpublished results that human breast cancer cells have NF-κB continuously turned on, while normal breast cells do not. If turning off NF-κB could reboot the suicide pathway in tumor cells, says molecular oncologist David E. Fisher of Harvard Medical School, that would be a boon. But he cautions that suicide may be turned off in cancer cells in a variety of ways, and not all of them may respond to NF-κB inactivation.

Fisher adds another caution: An anti-NF-κB approach would have to be tumor specific, or it might wreak havoc by increasing the killing of normal as well as cancer cells. Nevertheless, this view of cells' life-and-death balance might eventually provide a boost to cancer treatments or even help tumor necrosis factor finally live up to its name.

–Marcia Barinaga