have no effect. If that result holds up, the next step will be to test whether the inhibition occurs with mutant proteins, and whether it kills neurons.

If such a mechanism does occur, the fact that GAPDH binds to both huntingtin and DRPLA raises the possibility that it could be a common mechanism for all the glutamine-repeat diseases. Huda Zoghbi of Baylor College of Medicine in Houston and her collaborators, Pennsylvania's Fischbeck and Harry Orr of the University of Minnesota, have unpublished findings that bolster that notion. They have found that GAPDH binds at least two other glutamine-repeat proteins.

But even if this hypothesis proves true, other important questions will remain, such as how each disease targets a different set of neurons even though each glutamine-repeat protein is widely expressed in the brain, and GAPDH is in every cell. "There may be other proteins that are cell-specific that interact with these glutamine-containing proteins and enhance the interaction with GAPDH," Zoghbi suggests. The HAP-1 protein discovered by Ross's group might be one such protein. But for researchers trying to get to the bottom of glutamine-repeat diseases, the protein hunt is certainly not over.

–Marcia Barinaga

IMMUNOLOGY

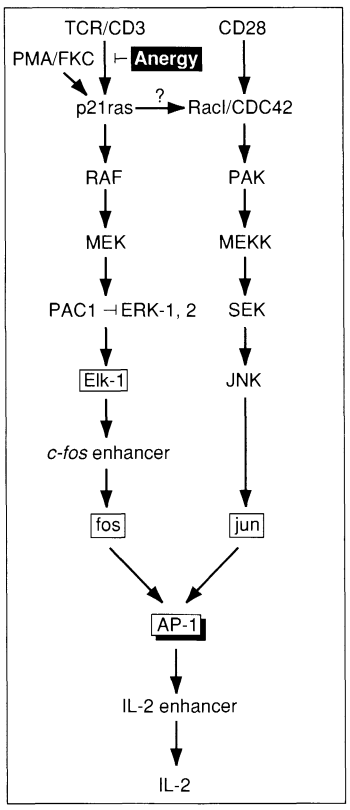
T Cell Inactivation Linked to Ras Block

Like nuclear missiles, the immune system's key regulatory cells, the T cells, won't go into action against an enemy unless they are triggered by several signals at once. Indeed, cell culture studies show that if a T cell receives only one of the two signals it needs, it becomes paralyzed—unable to divide or produce certain growth factors vital for making immune responses. How this state, known as anergy, is achieved has long puzzled researchers, but two groups, one led by Frank Fitch of the University of Chicago and the other by Daniel Mueller of the University of Minnesota in Minneapolis, report new results in this issue that may help solve the puzzle (see pp. 1272 and 1276).

Both teams' results imply that the cause of anergy lies in a block early in the Ras signaling pathway, one of the pathways most widely used to control growth and differentiation in a diverse range of cells and tissues. "This is strong evidence pointing us toward the block," says immunologist Art Weiss of the University of California, San Francisco. The finding is not only shedding light on the biochemical underpinnings of anergy, but by doing so may help resolve a long-standing debate among immunologists.

Although many believe that anergy may help prevent the immune system from mounting an attack on normal body tissues by putting self-reactive T cells out of action, others have suspected that it's just a laboratory artifact. By pinpointing a specific alteration in one of the cell's major control pathways as the cause of anergy, the new work bolsters the view that it does play an important physiological role. "I don't think anergic cells are playing dead. It looks as if they're doing things with a real function in the immune response," says Mueller. And beyond its implications for immunology, the work will also help understand operation of the Ras pathway itself.

The two groups came to their conclusions by different routes. Mueller's wanted to pin down how the production of a key immune system growth factor, interleukin-2 (IL-2), is blocked in anergic cells. The team took its starting cues from previous work by Michael Lenardo's team at the National Institute of Allergy and Infectious Diseases indicating that the shutdown in IL-2 production is due to the failure of the transcription factor called AP-1 to turn on the IL-2 gene, as it normally does when a T cell is activated (*Science*, 21 August 1992, p. 1134).



SOURCE: D. MUELLER

Locked up? A Ras block may inhibit both paths leading to IL-2 production.

Either of two signaling pathways could be responsible for this failure, because anergy ensues when a T cell that has received one signal from an antigen fails to receive a "costimulatory" signal from the so-called B-7 molecules on specialized antigen-presenting cells. To try to find out where the failure originates, Mueller says, "we decided to start in the nucleus [where AP-1 acts] and work outwards toward the membrane" along the two signaling pathways. The strategy paid off when the Mueller group showed that in fact inhibition of the activity of enzymes in both pathways appears to be contributing to the decreased IL-2 production characteristic of anergy.

Meanwhile, Fitch's group had picked up on a blockage in the pathway starting with the T cell's antigen receptor. Previous work from their laboratory had shown that two proteins are markedly less active in anergic T cells than in activated cells. "We suspected these might be the mitogen-activated protein kinases ERK-1 and ERK-2," says Fitch, referring to two enzymes that help transmit signals through the T cell receptor pathway. Their latest experiments confirmed that hunch, and with the ERK pathway now clearly shown to be involved in anergy, the results suggested a key role for one of its most prominent members: the Ras protein, which is the product of the cancer-causing *ras* oncogene and normally passes signals from the T cell receptor to other components in the ERK pathway.

Fitch's group looked directly at Ras activity in both normal and anergic cells that they stimulated with antibodies. They found that while this stimulation produced a marked increase in activated Ras in normal T cells, there was no accumulation of the active form of Ras in anergic cells. This indicates an early block in the pathway, Fitch says. Confirming that, both teams treated anergic cells with a chemical called phorbol myristate acetate (PMA), which activates Ras directly. The result: PMA restores normal function, showing that downstream of Ras the pathway could still operate. Finding a block in Ras activation also makes sense in view of the Mueller group's finding that the activity of the costimulatory pathway, whose signals are picked up by the CD28 protein on T cells, is also reduced in anergic cells. Ras "cross-talks" with that pathway, and so loss of its function in one could also inhibit the other.

To complete the anergy picture, researchers will now want to find just what blocks Ras activation in anergic cells. There are plenty of candidates: Ras is known to have several regulators, and previous studies have also found changes in a number of other molecules in the early steps toward anergy. And there's good reason to push on with the search, says immunologist Ron Germain, at the National Institutes of Health, as the payoff is likely to be a better understanding of both anergy and operation of the Ras pathway generally. "Whatever the real role of anergic T cells," he says, "they are going to tell us something important about signaling."

–Nigel Williams