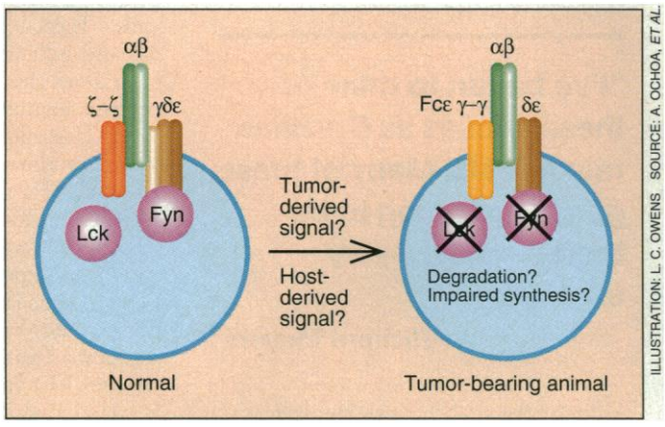
Do Tumor-Altered T Cells Depress Immune Responses?

From surgery to radiation to chemotherapy, physicians attack cancer in a variety of ways —all of which can be pretty hard on the body. This all-out assault often makes seemingly simple questions tough to answer. Take, for example, the question of whether cancerous tumors depress the patient's immune system. The evidence is strong, though perhaps not persuasive to all, that people with cancer have weaker immune responses. But is that a result of the tumors themselves or of the therapy directed toward them?

Now, new results obtained by a group at the National Cancer Institute's (NCI) Frederick Cancer Research and Development Center provide direct—and surprising—evidence of immunological changes that may help resolve the issue. On page 1795, the team, which is led by immunologist Augusto Ochoa, reports that the long-term presence of cancerous tumors can alter the structure of a key molecule on the surface of the T cells of the immune system, thereby disrupting the cells' internal signals and possibly leading to depressed immune responses. While most of the work has been done with mice, where the immunosuppressive effects of tumors are more clearcut than in humans, preliminary results indicate that T cells from human cancer patients have the same abnormality. "What we have here is a form of immunosuppression that is really unexpected," says immunologist Dan Longo, director of the center's Biological Response Modifiers Program and a coauthor of the paper. "This may give us the first insight into how tumors shut down the immune system," Ochoa adds.

The implications of the discovery could be enormous. The NCI group, for instance, speculates that tumors release some soluble factor that brings about the change, an alteration in the T cell receptor, a complex of several proteins the cells use to recognize and respond to foreign antigens. If that hypothetical molecule can be identified, physicians may be able to block its effects, possibly allowing them to strengthen cancer patients' immune defenses and improve their odds of surviving aggressive treatment. Moreover, the discovery could help boost fledgling efforts toward cancer immunotherapy, which has so far worked better in animals than it has in humans. Even more speculative, says Longo, is the chance that the knowledge may help improve organ transplantation or therapies for autoimmune diseases, if the molecule can be used to suppress unwanted immune system activity.

Because the stakes are so high, the finding so unexpected, and the mechanism behind the changes still unresolved, other cancer researchers are hesitant to embrace the finding before it's confirmed. "I don't understand the results. It's a mystery to me," admits T cell expert Jeffrey Bluestone of the University of Chicago. "This is just so surprising and amazing that your first response is that it can't be true," says oncologist Drew Pardoll of Johns Hopkins University Medical School, who is nonetheless convinced from talking with the NCI group that their work is solid. "It's definitely going to stimulate a lot of activity in other laboratories," Pardoll adds.



T cell alterations. Replacement of CD3 zeta (ζ) chains leads to reduction of the gamma (γ) chain and loss of the Fyn and Lck kinases.

The result took the NCI-Frederick team by surprise, too. Their original goal, Ochoa explains, was to try to use immune cells to attack tumors better. To that end, Ochoa and Longo, along with immunologists John O'Shea and Daniel McVicar, and surgeons Hiromoto Mizoguchi and Cynthia Loeffler were experimenting with an antibody to a T cell surface molecule called CD3 to see if the antibody would boost T cell activities against tumor cells. The researchers chose the antibody because it was known to activate T cells by virtue of its ability to bind CD3, a complex that usually contains five protein chains (the gamma, delta, and epsilon chains, plus two identical zeta chains), and is in contact with the actual T cell receptor in the cell membrane. While it's the T cell receptor that recognizes foreign peptides presented by other cells and normally starts the signaling process leading to an immune response, the associated CD3 can also initiate an immune response when appropriate molecules bind to it.

But the NCI group made a puzzling discovery. Treatment with the CD3 antibody was much more effective at battling tumors in animal models than in human patients. When they tried to figure out what caused this difference, the researchers found that mice that had had cancerous tumors for nearly a month had a sluggish T cell response to the antibody, whereas the response was normal in healthy mice or those just inoculated with tumors. The test on animals with "young" tumors had not mirrored the situation of the human cancer patients, whose tumors were quite advanced.

To track down the origins of the immune defect, the NCI workers decided to compare the signaling pathways that lead to T cell activation in spleen T cells from normal mice and those that had colon cancers for more than 26 days. They eventually found that T cells from the long-term tumor-bearing animals were defective in one of the earliest steps in the signaling pathway. In this step, enzymes called tyrosine kinases add phosphate groups to tyrosine residues on other proteins when the T cell receptor is activated. The NCI group discovered that the two key kinases, known commonly as Lck and Fyn, that bring about the reaction were absent from the T cells of the cancerous animals.

The question then became, Why were Lck and Fyn missing? Ochoa and his colleagues couldn't find an explanation in the T cell receptor itself. The two chains (designated alpha and beta) that make up the receptor were both present in normal amounts on cells from the cancerous animals. But when the researchers turned their attention to the CD3 molecule, the result was much more interesting. T cells from tumor-bearing mice had low levels of the gamma chain, and no detectable zeta chains at all. This came as a complete surprise, say the authors, since the zeta chains are needed to assemble and convey the T cell receptor proteins to the cell membrane, yet the receptors were still present in normal numbers. The researchers did find, however, that instead of the two zeta chains, the CD3 molecule in cancerous mice included two copies of a similar protein fragment from the receptor for immunoglobulin E, which apparently took their place in transporting the T cell receptor to the cell surface. The new arrangement of proteins in the CD3 molecule may exclude the gamma chain, leading to lower levels of that protein as well. Moreover, the replacement of the zeta chains with the other protein could explain why the Lck and Fyn kinases are missing, Longo says, be-

cause they apparently can't associate with the altered receptor.

Significantly, the T cell alteration appears to be a general phenomenon. The NCI team, for instance, has found the same defect in different strains of mice with different types of cancer. What's more, the changes are apparent in both of the two major types of T cells, the "killer" CD8 cells and "helper" CD4 cells, although it is only in the CD8 cells that the NCI group can observe impaired function: The CD8 cells don't "lyse" or kill other cells as efficiently as they should. How the alteration affects the performance of CD4 cells is an important issue, admit both Longo and Ochoa, and tough to resolve because it is more difficult to assess their normal function. Even more important, the NCI group has extended its work to human cancer patients and has found similar alterations of peripheral blood T cells in more than half of the approximately one dozen studied so far, although not in any of the normal controls.

As with any major new finding, this one has raised more questions than it answers. The mouse studies show that all the T cells in the animals, not just those that react with the tumor, can undergo the alteration in less than 48 hours. The researchers propose that the change is brought about by a soluble factor, which is released by the tumor into the bloodstream and can thus come in contact with all T cells. But they have few clues to how the putative factor works. Since both the zeta chains and the two kinases appear to be synthesized, Longo speculates that the hypothetical tumor substance leads to the degradation of the zeta chain and that the kinases, which can no longer couple with CD3 to preserve their form, are also degraded as a result. Of course, says Pardoll, "the big question is whether there truly is a humoral substance that can be isolated."

If there is and if it can be isolated, the challenge will then be to translate that accomplishment into the therapeutic arena. "We should be able to give a treatment that could prevent or reverse the defect," says Longo, pointing to test tube experiments showing that the altered T cells, when they are no longer in contact with the mystery substance, return to their normal state. In other cases, he hazards, such as autoimmune diseases or in organ transplantation, physicians may want to do the reverse, depressing the immune system with the hypothetical agent. Still, Longo and his co-authors agree with other cancer researchers that any such possibilities will remain conjectural until the years of work needed to understand this T cell surprise are completed. "This is just the beginning. It opens up lots of lines of inquiry," he predicts.

–John Travis

ASTRONOMY

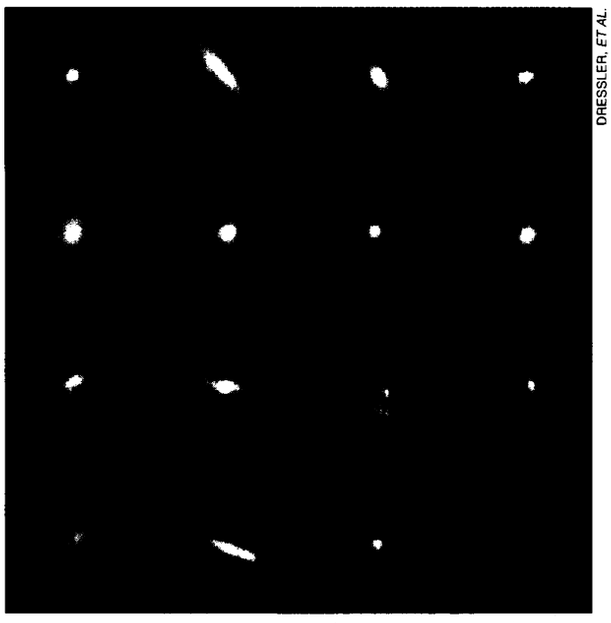
Hubble Sees a Zoo of Ancient Galaxies

Like a chalkboard seen from the back of a lecture hall, the history of galaxies has been too blurry to read. The history is there in the form of galaxies seen at such great distances that they lie a large fraction of the way back to the Big Bang. But to earthbound telescopes, those distant, early galaxies are no more than formless smudges. Now, thanks to the Hubble Space Telescope, a page in the history of galaxies has suddenly come into focus. By training the telescope on a galaxy cluster 4 billion light-years away, a team of astronomers has seen the shapes of galaxies past—and they are puzzlingly different from those of today.

In their galaxy cluster, a third of the way back to the Big Bang, Carnegie Institution astronomer Alan Dressler and his colleagues spotted all the different galaxy types seen in today's universe: elliptical, lens-shaped, and a garden of spirals. But the proportions were quite different. In this ancient cluster, code-named CL 0939+4713, spiral-shaped galaxies made up about 30% of the population, a surprising abundance considering that only about 5% of the galaxies in modern clusters are spirals.

If the cluster is typical of the earlier universe (and the researchers caution that it may not be), what could have happened to the teeming spirals between then and now? Dressler and his colleagues—Augustus Oemler of Yale University, James Gunn of Princeton University, and Harvey Butcher of the Netherlands Foundation for Research in Astronomy—think they see clues. Astronomers believe spirals are the active star-formers of the cosmos while other types of galaxies, such as the ellipticals, lie dormant, having long ago finished making new stars. And the spirals in this cluster look even more active than most—they burn bright with the characteristic blue glow of newborn, massive stars. That raises the possibility, say Dressler and his colleagues, that the fast-living spirals may simply have used up all their star-forming material and burned out. Their dim relics may be lurking unnoticed in today's clusters.

Oemler brings up another possible fate. "Some fraction of the [spirals] we see are in the process of merging," he says. "They look like galactic wrecks." Such collisions can intensify star formation, and they can also transform the shape of a galaxy. The extra spirals, says Oemler, may have vanished by crashing together into shapeless ellipticals.



DRESSLER, *ET AL.*

Denizens of the past. A different mixture of galactic species inhabited the cosmos 4 billion years ago.

Besides explaining how the spirals were weeded out, the turmoil seen in the Hubble image fits with earlier observations suggesting that the intermediate chapters of galactic history were surprisingly eventful. Analyzing the light from even more distant galaxies, astronomers had seen little of the blue that signals prolific star formation. Young as these galaxies must have been, they looked mature, their time of starbirth long past, says Oemler. In the late 1970s, though, Oemler and Butcher found many galaxies in the more modern universe that, paradoxically, looked to be in an earlier stage of evolution—bluer, more active, younger. But no one could make out their shapes until this latest observation from Hubble.

Just why these youthful galaxies should have appeared so late in cosmic history isn't clear, say other astronomers. "It's been quite difficult to produce a coherent picture [of galaxy evolution]," says Princeton astronomer Jeremiah Ostriker. The latest Hubble images can't resolve that mystery. But Dressler and his colleagues are heartened by their success. "We are beginning to see the universe when it was young and to see galaxies in the act of formation," he says.

That means a bright future for cosmic time explorers, he adds. "All these questions about galactic evolution are approachable now." And Dressler and his colleagues are hoping for an even better view after the repair of Hubble's faulty mirror, scheduled for 1993.

–Faye Flam