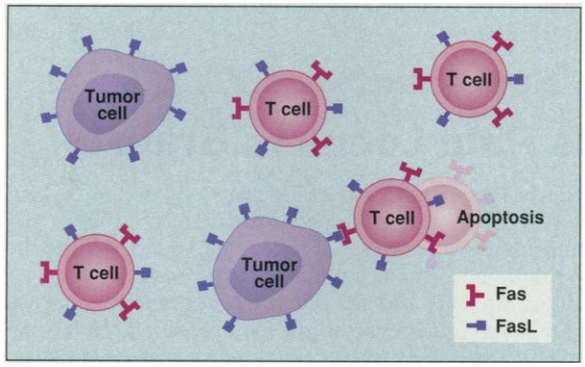
IMMUNOLOGY

Tumor Cells Fight Back to Beat Immune System

One of the biggest puzzles of cancer is why the sufferer's immune system almost always fails to eliminate the tumor. Researchers suspected that tumor cells survive by evading immune detection or damping down the immune response. But new research reported in this issue (p. 1363) suggests that at least one kind of cancer cells has a tactic that goes much further than mere evasion: They kill the immune cells that attack them. A team of Swiss researchers has shown that melanoma cells bear on their surface a molecule that induces immune cells to commit suicide through a process called apoptosis.

"It's a very interesting and significant finding," says tumor immunologist Thierry Boon of the Ludwig Institute in Brussels. As one of the researchers, biochemist Jürg Tschopp at the University of Lausanne in Switzerland, explains, "We don't understand why most [melanoma] patients are incapable of eliminating their tumors, but this new evidence may provide a clue." And by revealing the cancer cells' strategy, the results may also have laid the groundwork for foiling it, or even turning the cell killing back on the tumor itself.



Defense mechanism. Tumor cells' surfaces bear the Fas ligand (FasL), which prompts attacking T cells to commit suicide.

The new work has grown out of rapid advances over the past few years in the understanding of apoptosis, which is crucial for eliminating superfluous cells in development and for reining in immune responses. Among the most important molecules involved in delivering the death signal that initiates apoptosis is one called Apo-1, or Fas, which sits on the cell surface. When another molecule called the Fas ligand (FasL) binds to it, Fas triggers a series of events inside the cell that leads to its suicide.

Researchers soon found that many cell types express Fas on their surfaces, but FasL at first seemed to occur mainly on the immune system's activated T lymphocytes—cells designed to kill other cells. Although T cells use FasL to kill their targets by apoptosis, they can also use the Fas system to slow up an immune response. T cells all bear Fas as well as FasL, so that they can turn this molecular weapon on each other. But soon after the discovery of FasL on T lymphocytes, researchers began finding other cell types bearing the molecule. "It took some time to convince people that the molecule was not exclusive to T cells," says Tschopp.

More than that, it turned out that certain non–immune cells could use this weapon against T cells themselves. Two teams of researchers in the United States reported that cells in sites of immune "privilege"—places in the body where any inflammatory immune response could be crippling, such as the eye chamber, parts of the nervous system, and testis—express FasL. Any activated T cell bearing Fas that enters such sites would encounter cells expressing FasL and hence receive a death signal, preventing an immune response.

Over the past year, a number of scientists also reported that several tumor cell lines in the laboratory expressed FasL, although no one was sure quite what these findings meant, says immunologist Alan Haughton at the Sloan-Kettering Cancer Center in New York. But Tschopp and colleagues at the University of Lausanne, the Ludwig Institute in Lausanne, and the University of Geneva decided to investigate further. They wondered whether tumors in patients might be able to defend themselves against attack from T cells or other effector cells of the immune system by expressing FasL, just as immune-privileged cells do. They began screening patients with a number of diseases for evidence of FasL. When they tested melanoma patients, they got a clue: Out of 35 patients, 18 had FasL in their blood.

That did not prove that the cancer cells were the source of the FasL. But when the team took tumor samples from seven of the patients and stained them with antibodies against FasL, the protein showed up in all the tumors, says Tschopp. To test whether FasL was protecting the cancer from immune attack, the team used an assay that detects breaks in single strands of DNA, which are a characteristic feature of cells about to undergo apoptosis. They found the telltale breaks among the cells infiltrating the tumor. "The results suggest FasL is playing a role in defending these tumors from attack," says Tschopp.

The tumors, meanwhile, seem to be safe from their own weapon: When the team studied melanoma cell lines growing in the laboratory, they found that the cells expressed FasL but not Fas. The tumor cells could therefore deliver the death signal to cells bearing Fas, but could not receive a death signal because they expressed little or no Fas themselves, says Tschopp.

To test these ideas, the team injected tumor cells into a strain of mouse that produces no Fas. They expected that the mouse's T cells, lacking Fas, would be safe from the FasL of the tumor cells and would be able to mount an attack. As predicted, the tumor developed more slowly than in a normal mouse.

If it turns out that expression of FasL is a widespread mechanism by which melanomas, and perhaps other cancers, defend themselves against immune attack, investigators will begin looking for ways to overcome those defenses. "Tumor cells can be very smart, but these results open up new strategies for treatment and new targets," says Haughton. In theory, it may be possible to block the Fas signal pathway in tumor-infiltrating lymphocytes, block the production of FasL in tumors, or induce them to express Fas too, says Haughton. "It might not be easy in practical terms, but if the Fas reaction can be abolished, then the immune potential against these tumors we know exists could be activated," says Pierre Golstein of the INSERM-CNRS Center for Immunology in Marseilles.

Indeed, some common anti-cancer drugs may already be attacking tumors through the Fas pathway. Recent work by Claudia Friesen and colleagues at Heidelberg's University Children's Hospital and the nearby German Cancer Center, reported in the May issue of *Nature Medicine*, reveals that one anti-cancer drug, doxorubicin, enhances expression of both Fas and FasL in tumor cells. The researchers believe that Fas and FasL interact on the surface of each tumor cell and between cells, so they effectively kill themselves by apoptosis.

"Cancer immunology has been filled with false optimism for decades, but there's now a growing understanding of how the immune system might recognize cancer cells and how cancer cells might evade those responses," says Haughton. "At last, the scientific grounding for the field is becoming established."

–Nigel Williams