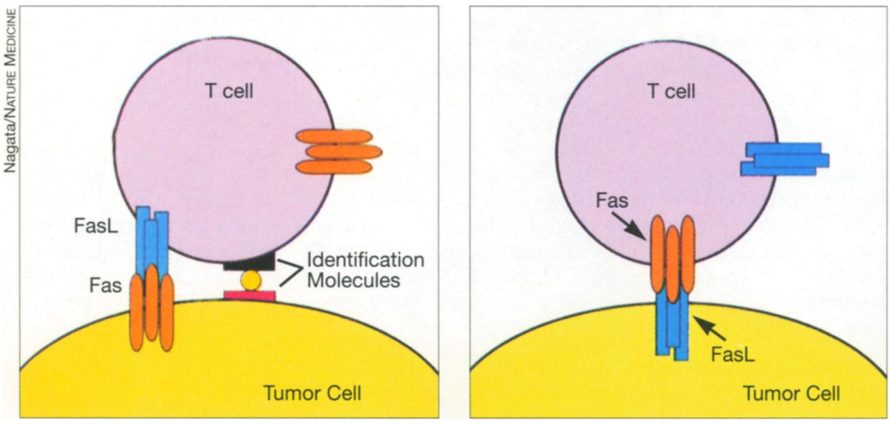
Natural-Born Killers

Some cancer cells not only dodge immune cells, they kill them

By DAN VERGANO

At least once each day, a person's immune system snuffs out a cell that has taken a turn down the path leading to cancer. For decades, physicians assumed that the immune system and such cells play a game of cat and mouse, in which the renegade cells hide from pursuing immune cells, or lymphocytes, and stealthily breed to form tumors.

Apoptosis, also called cellular suicide, is an orderly means by which the body removes unnecessary cells—during development, for example. It is also the weapon of choice for immune cells protecting the body (SN: 11/21/92, p. 344). These guardians induce apoptosis by attaching to surface molecules that act as self-destruct buttons. Biologists have long known that cancer cells sometimes stop displaying these surface molecules or alter their chemistry so that binding to the surface proteins no longer triggers self-destruction.



A T cell recognizes a Fas-equipped tumor cell by its identification molecules and induces cell death (left). A tumor cell without Fas but with FasL kills a T cell (right).

Recent research, however, reveals an unexpected twist to the game: Wielding proteins that trigger death in immune cells, some cancer cells turn on their pursuers and destroy them.

"Tumors can kill lymphocytes," says Peter R. Galle of the University of Heidelberg in Germany, who explains that this finding reverses the conventional model of interactions between the immune system and tumors.

To identify cancers, immune cells search for irregularities that mark cells as damaged, mutated, or foreign. Tumor cells can duck this search in a number of ways. They may fail to secrete identifying proteins, called antigens, that would alert the immune system to their presence, or they may surround themselves with proteins that ward off inspection.

Results from several research groups now indicate that tumors can also go on the offensive by co-opting a process that immune cells use to destroy other cells and to limit their own numbers.

Some guardian lymphocytes, particularly T cells, wield a molecule called Fas ligand (FasL) against outlaw cells. When FasL docks with Fas, a receptor molecule on many cell surfaces, apoptosis results. After finishing their work, T cells turn on each other; they bind to Fas receptors to prevent a rampage against healthy cells, as sometimes happens in the liver of alcoholics.

Tumor cells exploit this self-limiting aspect of the immune mechanism, according to Galle. He and his colleagues at the German Cancer Research Center in Heidelberg found that human liver cancer cells can produce FasL. This molecule allows them to kill T cells and perhaps create zones where tumors can grow free of immune system interference, according to a report in the December 1996 Nature Medicine.

"We were stimulated to look for this by recent findings about immune-privileged sites in the body," says Galle. Cells in the eyes and testes, for example, normally express FasL to keep lymphocytes from interfering with their functions. Galle and his colleagues reasoned that if there exists a gene for shutting out the immune system, some cancers may have figured out how to exploit it. In their study, which examined liver cancer tumors containing low concentrations of Fas, nearly 43 percent expressed FasL.

"This could be a crucial thing in how tumors reappear after their first treatment," suggests Galle.

The cells in his team's study had been treated with anticancer drugs. He theorizes that in some cases, the stress of chemotherapy fosters the development of tumor cells that can kill immune cells, echoing earlier findings that only the most aggressive cells appear in second-generation tumors (SN: 4/6/96, p. 216).

"A good tumor cell has FasL," says Jurg Tschopp of the University of Lausanne in Switzerland. In a recent study, Tschopp collaborated with researchers at the Ludwig Institute of Cancer Research in Lausanne and the University of Geneva to investigate skin cancer cells from seven patients. All of the cancerous cells expressed FasL, whereas healthy skin cells from the same patients expressed only Fas.

"We were surprised," says Tschopp. "We had been looking at the other side of the battle to see if melanomas didn't express Fas." In fact, a lab technician on the Swiss team discovered the cancer's cell-killing capability by accident, while measuring FasL as a control during experiments.

To test their findings, the researchers introduced FasL-expressing melanomas into mice. Normal mice developed tumors rapidly, but a mutant strain, bred to have immune cells lacking Fas, developed cancers at a much lower rate, the researchers report in the Nov. 22, 1996 Science.

"There's a selection process at work here," says Tschopp. He suggests that tumor cells may express FasL to knock off competing lines of tumor cells as well as to get at lymphocytes. In the aftermath of incompletely successful therapy,

the surviving cancer cells struggle to reassert themselves against the body. Killing a competitor means more resources for the nascent tumor, he says.

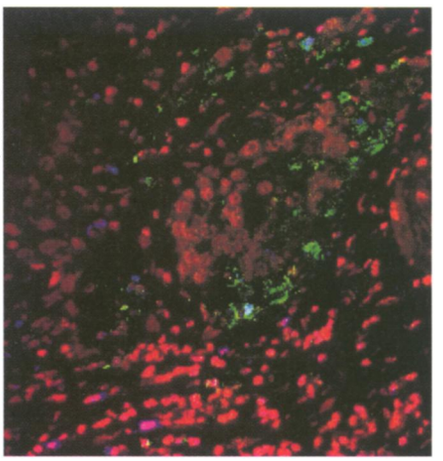
Cancers may kill T cells by using molecules other than FasL, suggests Claude D. Gimmi of the Dana Farber Cancer Institute in Boston. Her research team found that some lines of breast cancer cells were patrolled by an unusually small number of T cells. Mammary glands normally express small amounts of an antigen called Death Factor-3 (DF3)/MUC1, which causes apoptosis in activated T cells. Perhaps, the scientists reasoned, the breast cancer cells overexpressed that molecule.

To test their hypothesis, Gimmi and her colleagues removed DF3/MUC1 from tumor cells in the test tube and watched T cells proliferate rapidly amidst the disarmed cancer. Then, they compared lymphocyte proliferation in three lines of breast cancer cells that don't carry the death factor molecule to one that does. T cell apoptosis occurred only in the tumor cells armed with the DF3/MUC1, they report in the December 1996 NATURE MEDICINE.

"It wouldn't surprise me if we find other, as-yet-undiscovered mechanisms that will be kind of startling," says Dan L. Longo of the National Institute on Aging in Baltimore. "But, in retrospect, we'll say it makes sense. The tumor is trying to adapt to a hostile environment."

In Longo's view, tumors evade the immune system by using a combination of methods to avoid or disarm T cells. Complicating the search for a cancer cure, it's likely that no two malignancies employ the same mix of methods, even within the same type of cancer. Future therapies may hinge on discerning each growth's distinct weapons and disarming the rogue cells case by case.

Whatever means healthy cells use to dampen the immune response are probably taken up by tumors and pressed into expanded service, says Longo. "If there's a gene in the repertoire, cancer will find a way to use it."



Galle/NATURE MEDICINE

In studies of liver cancers, stained apoptotic T cells (blue) float lifelessly amid FasL-expressing tumor cells (green). Normal liver cells are colored red.

The message of these findings is that the conventional picture of a hypervigilant immune system is "dead wrong," according to Drew Pardoll of Johns Hopkins University in Baltimore. He argues that many healthy cells manipulate lymphocytes to keep T cells from latching onto their surfaces and destroying them.

"There's a tendency to focus on just one mechanism du jour," says Pardoll. He predicts that researchers will find tumors employing up to 10 stratagems to dodge the immune response. Discovering and cataloging every one offers the best hope of eventually giving physicians the upper hand in the battle against cancer.

If tumors avoid the immune system by failing to produce Fas, Tschopp argues, an effective therapy might be to force the cancer cells to produce that surface molecule. In cases where malignancies have FasL on their surfaces, injected antibodies might lock onto the molecule, gumming it up before it can wreak havoc. "Now we know the means to fight back," Tschopp says.

Other researchers also see medical promise in unearthing cancer's evasive tactics. "Actually, I'm very excited," says Pardoll. "We can now really study what's going on in tumors and intervene at a molecular level." □

Physics

Peeking inside an electron's screen

Standard references and textbooks describe an electron as a stable elementary particle. Typically, they specify values for its mass, electric charge, and spin, and they sometimes mention vaguely that an electron's charge appears concentrated in a point. However, there's both more and less to an electron than such a bare-bones description indicates.

According to modern quantum theory, the space surrounding an electron is not empty but filled with a boiling sea of so-called virtual particles, which continually blink into existence in oppositely charged pairs, then almost immediately disappear again. Since the 1930s, theorists have proposed that these virtual particles cloak the electron, in effect reducing the charge and electromagnetic force observed at a distance.

By forcing electrons and positrons (the oppositely charged, antimatter counterparts of electrons) to collide head-on at sufficiently high energies, researchers have now penetrated the virtual-particle screen and made the first measurements confirming that an electron's electromagnetic influence increases as the distance from the particle's central core decreases.

"As we probe the cloud, getting closer and closer to the core charge, we see less of the shielding effect and more of the core," says David S. Koltick of Purdue University in West Lafayette, Ind. "This means that the electromagnetic force from the electron as a whole is not constant but rather gets stronger as we go through the cloud and get closer to the core."

Koltick and his coworkers report their findings in the Jan. 20 PHYSICAL REVIEW LETTERS.

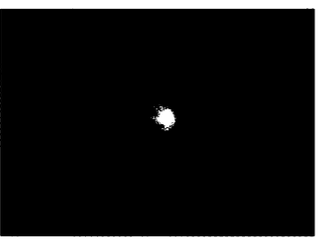
The experiment was performed by members of the TOPAZ detector group at the TRISTAN particle accelerator of the National Laboratory for High Energy Physics in Tsukuba, Japan. The accelerator was operated at an energy of 57.77 gigaelectronvolts to enable them to penetrate the screen without creating other particles.

From their data, the researchers obtained a value of the fine structure constant, a number that characterizes the inherent strength of the electromagnetic force. As expected theoretically, the newly obtained value of 1/128.5 is significantly larger than the 1/137 observed for a fully screened electron.

"Ours is a clean measurement of the electromagnetic effect," Koltick says. In higher-energy experiments at other accelerators, the effect is swamped by additional factors, including the strong force, which holds neutrons and protons together in an atomic nucleus and binds quarks into protons and neutrons. Those factors make it difficult to distinguish the relative contributions of the nuclear and electromagnetic forces.

"The observed properties of an electron derive from an interplay between the particle and the vacuum," Koltick notes. "We have to go much deeper to learn more about the 'bare' electron."

Pulling aside the virtual-particle curtain opens up new possibilities for revealing the naked truth about electrons. — *I.P.*



Dennis Harp/Purdue

Artist's visualization of an electron as a central core (bright spot) surrounded by a cloud of virtual particles, which appear and disappear in pairs—one particle positively charged (blue) and the other negatively charged (yellow). Faint white lines radiating from the electron core represent its electric field.