Kaposi's Sarcoma Puzzle Begins to Yield

The sarcoma appears to be critically dependent on growth factors for its survival, possibly opening the way to new therapies

KAPOSI'S SARCOMA used to be an obscure skin cancer, known to few outside the dermatology community. Then the AIDS epidemic struck, and Kaposi's leaped to a new prominence. Approximately 15% of AIDS patients have the sarcoma, which makes it 20,000 times more common in the AIDS population than in the population at large. But why so many AIDS patients come down with Kaposi's has always been a mystery.

Now, evidence accumulated over the past year or two is beginning to solve that puzzle. It indicates that the AIDS virus fosters the development of the tumors by causing the production of growth-stimulating factors on which the sarcoma is critically dependent.

By identifying the tumor's Achilles' heel—its growth factor dependency—these findings could lead to new forms of treatment. Drugs that block the synthesis or action of the growth factors may knock out or at least suppress the tumor growth. "It's very exciting," says dermatologist Bijan Safai, a Kaposi's expert at Memorial Sloan-Kettering Cancer Center in New York, who has been caring for AIDS patients since the very beginning of the epidemic. The sarcoma may be, he predicts, "the first disease of mankind that is going to be treated by manipulation of growth factors."

The idea that growth factors might be needed for Kaposi's development dates back to work done about 2 years ago by Robert Gallo, Shuji Nakamura, S. Zaki Salahuddin, and their colleagues at the National Cancer Institute. At the time, the researchers were trying to grow Kaposi's tumor cells in laboratory culture to look for signs of viral infection. Afer some trouble getting the cells to grow, they found that an unidentified, and possibly novel, growth factor produced by activated T cells would do the trick (see *Science*, 21 October 1988, p. 376).

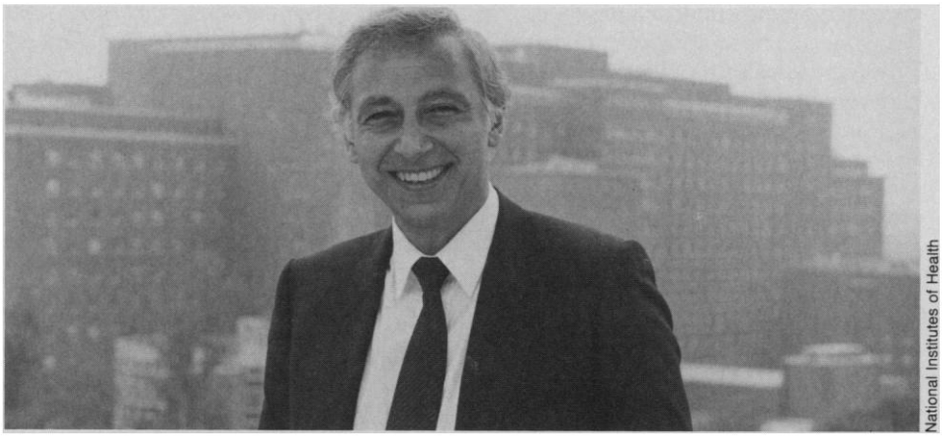
Kaposi's sarcomas contain several cell types. But with the aid of the T cell factor, the NCI workers were able to culture the one that they believe is the actual Kaposi tumor cell, which is called the spindle cell because of its shape. The researchers then learned that the cultured cells themselves produce large quantities of growth factors, especially the two known as interleukin-1β and basic fibroblast growth factor. That finding suggested that Kaposi's sarcoma cells can help perpetuate their own abnormal growth once the tumors are triggered.

Further evidence that the spindle cell is the Kaposi's tumor cell and that growth factors are important in the sarcoma development came from experiments in which the Gallo group transplanted the cultured cells into nude mice. "The mice developed lesions near the cells," Gallo says, "that looked like early Kaposi's sarcomas of human origin, but were of mouse origin." When the human cells eventually died off, the mouse lesions disappeared, too, presumably because they had been deprived of the necessary growth factors.

Although those results pointed to the importance of growth factors in Kaposi's development, they left many questions unanswered: What is the growth factor made by activated T cells that permits the Kaposi's cells to grow? And does that factor have a role in triggering Kaposi's in patients? A particular conundrum is that, although activated T cells generally produce the factor, cells infected with a leukemia virus called human T cell lymphotrophic virus type 2 (HTLV-II) proved to be the richest source, whereas T cells infected with the AIDS virus itself were much less active in producing growth stimulators for Kaposi's cells. So maybe the factor made by the HTLV-II–infected cells has nothing to do with actual Kaposi's tumors.

But then again it might, although views differ about the factor's chemical nature. Steven Miles of the University of California School of Medicine, Los Angeles, Diane Logan of the Ottawa Regional Cancer Centre, and their colleagues suggest that it might be a protein called interleukin-6. Interleukin-6 is a so-called cytokine, one of a family of proteins—interleukin-1β is also a member—that perform several activities, such as stimulating the growth and differentiation of immune cells, that help the body to fight off infections.

The UCLA workers began considering interleukin-6 as a candidate for the factor discovered by Gallo's group, Miles says, because the molecular weights of both are similar, in the 27,000 to 30,000 range. Moreover, Elizabeth Breen and Otoniel Martiínez-Maza of UCLA have shown that the cytokine concentrations go up in patients infected with the AIDS virus.



Why do Kaposi's sarcomas grow? *Robert Gallo thinks he knows; the AIDS virus produces a protein that is at the root of the problem.*

So Miles and Logan looked for interleukin-6 in the fluid in which T cells infected by HTLV-II had been grown, and they found it there. They also looked for the cytokine in cultured Kaposi's sarcoma cells, including one line obtained from the Gallo group. "Interleukin-6 was off the scale, the highest levels we have ever seen," says Miles.

But a significant question remained: Even if interleukin-6 was present in the Kaposi's cells, could it really have any role in their growth? Conventional wisdom said no. Kaposi's tumors may arise from endothelial cells, the type of cell that lines the blood vessels and also the vessels that carry the lymph around the body. And although normal endothelial cells produce interleukin-6, they do not respond to it. Nevertheless, Miles and his colleagues have strong evidence that interleukin-6 does stimulate the growth of the Kaposi's cells.

They find indications, for example, that

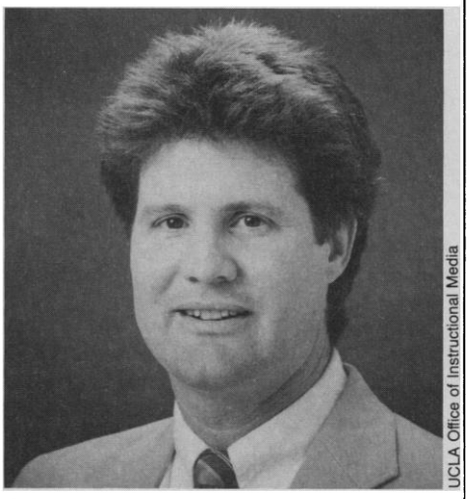
Kaposi's cells make much more of the interleukin-6 receptor, the molecule to which the cytokine must bind to produce its cellular effects, than do normal endothelial cells. Moreover, the increased production of interleukin-6 and its receptor are not limited to cells growing in culture. Miles and Logan also detect it in Kaposi's tumor tissue taken from patients, but not in adjacent normal skin. "[Kaposi's] cells make interleukin-6 in vitro and respond to it. That probably occurs in people as well," Miles says.

Miles's suggestion that interleukin-6 is important for Kaposi's development does not conflict, incidentally, with the Gallo group's earlier finding that the tumor cells make large amounts of the growth stimulators interleukin-1β and basic fibroblast growth factor. They all might be involved, working either independently or in conjunction with one another. Interleukin-1β, for example, is a potent stimulator of interleukin-6 synthesis.

The Gallo group meanwhile has also been trying to pin down the identity of the Kaposi's growth factor produced by HTLV-II–infected T cells—and they don't think that it is interleukin-6. They have purified the factor, which is a protein, Gallo says, and find that it is much more effective than interleukin-6 in stimulating the tumor cell growth. The T cells could well be producing two—or more—proteins with the ability to stimulate Kaposi's cell growth, but more work will obviously be required to sort out this situation and determine which, if any, is active in Kaposi's patients.

But, assuming that growth factors have a key role in stimulating the growth of Kaposi's cells, what does all this have to do with HIV, as the AIDS virus is called? Recent work by the Gallo group may provide an answer. Earlier this month at a meeting on HIV and AIDS held in Keystone, Colorado, Gallo reported that he and his colleagues Barbara Ensoli of NCI and Flossie Wong-Staal of the University of California, San Diego, have found that the *tat* protein, the product of one of the major regulatory genes of the AIDS virus, is itself a growth factor for Kaposi's cells. (The data are in press in *Nature*.) It stimulates their growth about twofold, and as the NCI researcher points out, "Any growth stimulation is significant. It can be the difference between normal growth and leukemia."

It was logical to suspect that the *tat* gene product might be a growth factor for Kaposi's cells, Gallo says, in the light of results obtained about 18 months ago by Gilbert Jay, who was then at NCI but has since moved to the Laboratory of Virology of the American Red Cross in Rockville, Maryland, Paul Luciw of the University of California, Davis, and their colleagues. When these researchers introduced the *tat* gene into mice, the animals developed skin tumors that looked very much like the Kaposi's sarcomas of humans. In addition, Alan Frankel of the Whitehead Institute in Cambridge, Massachusetts, has found that HIV-infected cells release the *tat* protein, so it could come into contact with Kaposi's cells or their precursors.



Another Kaposi's maven. *Steven Miles focuses on the cytokine interleukin-6.*

In fact, Gallo now thinks that the Kaposi's growth stimulatory activity produced by T cells infected by the AIDS virus is due to the *tat* protein made by the cells. The NCI workers do not yet know how the protein stimulates the tumor cells' growth, however. It may do so indirectly. The *tat* protein can activate gene expression, perhaps including the genes encoding interleukin-6 or the other cytokines implicated in the growth of Kaposi's cells.

Jay also favors the idea that the *tat* protein contributes to Kaposi's development indirectly by stimulating growth factor production. He points out that the AIDS virus is present in the Langerhans cells of the skin epidermis and that the viral proteins are being made there. That would put both the *tat* protein and any growth factors it might induce in the right place to foster the development of Kaposi's tumors.

Gallo maintains, however, that the *tat* protein may have a direct growth stimulatory effect. He points out that it works on Kaposi's cells at very low concentrations—only about one-thousandth of what it takes to get gene activation. He thinks that the *tat* protein may provide the initial stimulus for Kaposi cell growth, possibly aided by the cytokine produced by activated T cells, with an additional boost from the growth factors made by the Kaposi's cells themselves.

But even if the AIDS virus contributes as now postulated to Kaposi's, it may not be the sole cause of the sarcoma. "Many patients have HIV, but don't have Kaposi's sarcoma," Safai points out. "There's really more than one factor involved. You need a pathological agent, a specific genetic background, and an imbalance of the immune system. When you have them all together, you have Kaposi's sarcoma."

Some researchers even suspect that the AIDS virus is not the primary pathological agent for Kaposi's. In the 20 January issue of *Lancet*, for example, Alvin Friedman-Kien of New York University Medical Center and his colleagues described the cases of six homosexual men who came down with Kaposi's, but were not infected with HIV.

In an analysis published in that same *Lancet* issue, Valerie Beral, Harold Jaffe, and their colleagues at the Centers for Disease Control in Atlanta concluded that the epidemiological data on Kaposi's distribution suggest that it is caused by a sexually transmitted pathogen other than the AIDS virus. They found, for example, that the sarcoma is more common in people infected with the AIDS virus by sexual contact rather than by contaminated needles or blood.

The proposed "Kaposi's virus" may have entered the same population in which the AIDS virus is endemic so that the two are often transmitted together. The HIV may then make conditions right for Kaposi's development by causing growth factor production, and possibly by suppressing the body's immune defenses against cancer. "Something else may start the process," Miles explains, "and HIV may just give it a push."

But he notes that other viruses could also stimulate production of cytokines such as the interleukins-1β and -6 that promote Kaposi's cell growth, even without the AIDS virus's help. The cytokines are, after all, a part of the body's defenses against infections. "We're beginning to realize how complicated [Kaposi's development] is," Miles says. "You may have many different pathways to get to Rome."

The discovery of the tumor's dependence on growth factors has, meanwhile, opened the door to new strategies aimed at treating the sarcoma. In fact, the Gallo group is collaborating with a group of Japanese scientists on studies of a natural product they have isolated. It inhibits Kaposi's sarcoma growth in an animal test system, and the researchers are hoping to move the drug toward trials in human patients. So the next question is, will this or other agents that block growth factor activity work? "We've learned so much," Safai says, "but there's still a lot we don't know. That's the bottom line." ■ JEAN MARX