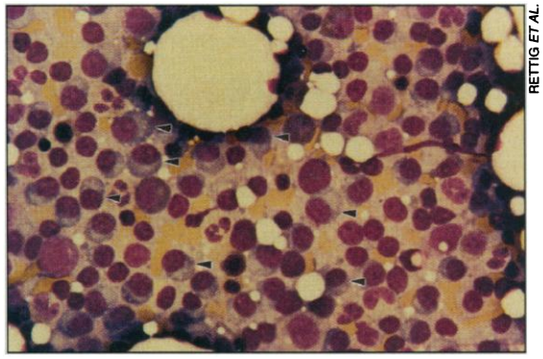
Causing Cancer by Remote Control?

Kaposi's sarcoma–associated herpesvirus may help drive the growth of the bone marrow cancer multiple myeloma, but from within neighboring cells, not the tumor cells themselves

Add another trick to the sinister repertoires of viruses. For decades, researchers have been pursuing a trail of early clues suggesting that viruses might be culprits in human cancers. Only in a few malignancies have scientists been able to finger a viral suspect, however. Now, a group of researchers may have detected viral fingerprints on another cancer, a bone marrow tumor called multiple myeloma. But the group has found that in this case, the virus may contribute to tumor growth in a novel way, working behind the scenes like a cellular puppet master.

On page 1851, a research team led by oncologists James Berenson and Matthew Rettig of the Veterans Affairs West Los Angeles Medical Center reports linking multiple myeloma to Kaposi's sarcoma–associated herpesvirus. KSHV is already under suspicion as the cause of Kaposi's sarcoma, a cancer that afflicts many AIDS patients. But unlike the malignant cells of Kaposi's and all the other cancers thought to be caused by viruses, multiple myeloma cells—derived from the bone marrow's antibody-producing plasma cells—don't seem to carry the virus. Instead, the Los Angeles team has found evidence that KSHV is lurking in adjacent dendritic cells, a subset of macrophages found in the bone marrow microenvironment.



RETTIG *ET AL.*

Helped by a virus? This bone marrow from a myeloma patient is packed with tumor cells.

In those cells, the virus appears to crank out its own version of a human protein called interleukin-6 (Il-6) that is known to stimulate myeloma cell growth. This, the researchers propose, is what propels the runaway growth of myeloma tumors, or, as Berenson describes it, "The soil, the dendritic cell, is putting out a bunch of fertilizer, and that makes the seed, the tumor cell, germinate."

That kind of remote control, says Yuan Chang, who studies KSHV at Columbia University in New York City, is a "novel mechanism" for virally caused cancer: "This is really exciting, if [the authors] are right." The finding could also steer researchers to new therapies for multiple myeloma, which strikes 13,000 people every year in the United States alone and usually kills its victims within 3 years. Drugs to block Il-6 might be one therapeutic avenue, and Berenson also suggests that it might be possible to devise therapies that specifically target the virus-infected dendritic cells themselves.

Attacking the virus with drugs or a vaccine might also stave off full-blown multiple myeloma in the estimated 1 million people who have been diagnosed with an apparent precursor condition called monoclonal gammopathy of undetermined significance (MGUS). Others who might benefit are AIDS patients, especially homosexual men, who have a high risk of becoming infected with KSHV and getting Kaposi's sarcoma.

Rettig and Berenson say that they were inspired to look for the virus in the nonmalignant bone marrow cells of multiple myeloma patients by the Chang team's discovery of a KSHV protein that closely resembles human Il-6, both structurally and functionally (*Science*, 6 December 1996, p. 1739). The Columbia workers also postulated that the viral Il-6 could feed tumor cell growth in Kaposi's sarcoma. At the time, however, there was no evidence that KSHV was involved in multiple myeloma. Further, when researchers, including Chang's group and that of Rettig and Berenson, looked for signs of KSHV in bone marrow samples from myeloma patients using the polymerase chain reaction (PCR)—a gene amplification technique that picks up very small amounts of specific DNAs—they detected no trace of KSHV DNA.

Still, the finding of a viral Il-6 intrigued the Los Angeles researchers enough to entice them to look more specifically at the cells in the bone marrow stroma, a mix of cell types that provide support for developing plasma and other cells. "There was a large body of evidence saying that Il-6 was a very important and necessary growth factor for the persistence and propagation of myeloma," Rettig says. "And we knew that Il-6 is, for the most part, produced in the stromal cells."

But because those cells are sticky and present in low numbers compared to neighboring malignant plasma cells, they are hard to get hold of. So Rettig and Berenson grew bone marrow samples under cell culture conditions that killed off the malignant cells but nurtured the nonmalignant stromal cells. The researchers then did PCR testing on both the uncultured bone marrow samples, made up of predominantly malignant cells, and on the stromal cell–enriched cultured cells.

In the case of bone marrows obtained from 10 normal individuals and from 16 patients with blood cancers other than myeloma, both the uncultured and cultured cell samples came up negative. And as in the past, the researchers detected no KSHV DNA in uncultured bone marrow cells from all of the 15 myeloma patients tested. But all their stromal cells tested positive for the virus. "We have identified the virus consistently in 100% of myeloma patients," says Berenson. "That percentage, in and of itself, is amazing." Rettig and Berenson then went on to identify the virus's host cells as macrophage-derived dendritic cells, based on specific markers the cells carry on their surfaces.

What's more, when the researchers looked at bone marrow samples from eight patients with MGUS, the myeloma precursor condition, they detected KSHV DNA in the dendritic cells from two. Because that is the same proportion—25%—as the fraction of people with MGUS who go on to develop myeloma itself, the observation raises the question of whether it's the virus that determines who will progress to the cancer—or something else that is yet unidentified.

Another question Rettig, Berenson, and their colleagues have tackled is how KSHV might be stimulating tumor cell growth from adjacent cells. Their answer involves Il-6, whose messenger RNA was detected in infected dendritic cells from three out of three myeloma patients, but not in dendritic cells from two normal controls.

But while researchers such as Chang are excited by the Los Angeles team's findings, they have reservations, partly because of

past failures to detect KSHV in myeloma patients. Rettig doesn't see a conflict. "The bone marrow itself contains so few dendritic cells that the sensitivity of even a PCR assay was not adequate to detect any virus," he says, adding that finding the virus required culturing the cells to enrich the dendritic population.

Yet the culturing step itself raises concerns because what happens in culture may not reflect what is occurring in the cells of human beings, researchers say. Charles Rabkin, who studies the epidemiology of HIV-related cancers at the National Cancer Institute in Bethesda, Maryland, calls the new findings "extremely interesting," but worries that the dendritic cells Berenson's group studied may have been contaminated with the virus after their removal from the patients or that the virus, although present, may not actually cause myeloma.

Berenson and Rettig respond that contamination is very unlikely, as they did not detect KSHV in any of the samples from normal individuals or from patients with other cancers, even though all the samples were handled the same way. But even better evidence against contamination comes from as yet unpublished work in which their group looked for—and found—KSHV DNA in uncultured biopsies of bone marrow cells that were analyzed directly after removal from myeloma patients.

Even with this evidence, however, an epidemiological conundrum posed by a link between KSHV and Kaposi's sarcoma needs to be sorted out. It is not clear whether groups prone to that cancer—Ashkenazi Jews and AIDS patients—have an increased risk of multiple myeloma, says Rabkin. That could mean that either the virus isn't involved in myeloma, or that an additional, as yet unidentified, factor is needed to tip a person over the edge so that the cancer can develop.

In trying to resolve these issues, the researchers can look to the estimated 1 million people in the United States thought to have MGUS. They should make it possible to determine, for example, whether progression to myeloma correlates with signs of infection, such as having antibodies to the virus. Berenson says his group plans to test frozen blood samples from MGUS patients, some of whom have already developed myeloma.

Other studies are likely to follow as well, Rabkin predicts. That is because proving a virus is the sole cause of cancer can be inherently difficult. The different bits of information often conflict. "But as far as KSHV is concerned," Rabkin says, "this paper adds another piece to the puzzle ... one that I think will be followed up."

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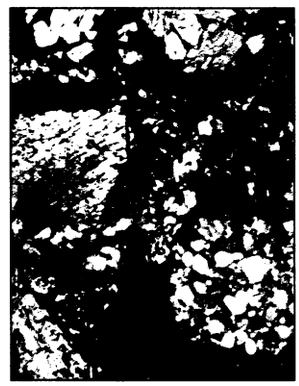
PLANETARY SCIENCE

How the Hectic Young Sun Cooked Up Stony Meteorites

WINSTON-SALEM, NORTH CAROLINA—Inspired by glimpses of the turmoil around young stars, a team of astrophysicists has presented a radically new theory of the solar system's most primitive—and perhaps most mysterious—solid objects. These meteorites, called chondrites, are thought to be shards of bodies like those that clumped together to form our planets. For more than a century, meteoriticists have puzzled over their bizarre composition—a stew of dust, roundish rocks that were "flash melted" and resolidified, and the remains of short-lived radioactive isotopes. The new theory holds that this stew was cooked up by explosive flares and powerful winds near the young sun.

As Frank Shu of the University of California, Berkeley, explained here last week when he presented his team's results at a meeting of the American Astronomical Society, the two processes, in varying combinations, could explain all the ingredients of chondrites. Flares licking at the disk of gas and dust around the young sun could have irradiated the material with energetic particles, and the heat of the flares or the glare of the young sun could account for the melting. The winds might then have blown the molten material to the outer reaches of the solar system, where it mixed with dust to form chondrites. Simply put, the mechanism "takes material trying to get on the sun, heats it up, irradiates it, and plops it back onto the disk farther out," says Donald Clayton of Clemson University in South Carolina, who organized the session at which Shu spoke.



GARY R. HUSS/CALTECH

Hot rocks. Viewed in polarized light, a section of a chondrite meteorite reveals once-molten globules called chondrules, each roughly a millimeter across.

Some astrophysicists who have sought the origins of the isotopic anomalies outside the solar system—in radiation from a nearby supernova, for example—aren't convinced that Shu and colleagues have the full story. But others are embracing the scenario, among them Clayton, who says, "In my mind, his [explanation] is the leading contender right now."

The mystery dates from the 1870s, when researchers started cutting open meteorites. Inside some of them, says Glenn MacPherson of the department of mineral sciences at the Smithsonian Institution of Washington, was something that "looks a little bit like concrete." These so-called carbonaceous chondrites consist of a dark, dusty matrix, which apparently never melted, sprinkled with once-molten rocks: centimeter-size pinkish-white ones called calcium-aluminum-rich inclusions (CAIs), and bluish-gray rocks measuring a millimeter or so, called chondrules.

Strangely, the CAIs and chondrules in any particular chondrite are almost uniform in size, as if they had been sorted like peas in a factory. Even more surprising, their crystal structures show that the CAIs were molten for periods of days and the chondrules for just hours. The cool band of the protoplanetary disk now occupied by the asteroid belt, where chondrites are thought to have originated, seems an unlikely setting for such rapid melting and freezing.

But the deepest mystery of all could be the residue of certain short-lived radioactive isotopes, found mainly in the CAIs. "There is evidence that these materials had live aluminum-26 in their crystalline structures when they formed," says MacPherson. The aluminum-26 itself is long gone—it has a half-life of just a million years—but it left identifiable decay products, as did other slightly less mercurial isotopes such as manganese-53.

Most theories have invoked separate processes to explain these physical and isotopic anomalies. A. G. W. Cameron of the Harvard-Smithsonian Center for Astrophysics in Cambridge, Massachusetts, for example, has suggested that violent "x-ray flares," like the ones now seen around young stars, might have flash-melted some material in the protoplanetary disk, while the strange isotopes might have come from a nearby supernova. The new theory, put together by Shu, Hsien Shang of Berkeley, Typhoon Lee of the Academia Sinica in Taiwan, and Alfred Glassgold of New York University, ties all the anomalies together in a single explanation. Parts of it appeared in *Science* a year ago (15 March 1996, p. 1545), but the group presented the full picture at the meeting.

It had emerged as the Hubble Space Telescope, orbiting x-ray observatories, and other instruments revealed unexpected turmoil in the disks of material that surround young stars. The observations showed jets of gas and