Altered protein seen in human cancer

A novel form of a protein found in normal cells has been detected in cells from a patient with a common type of adult leukemia, called chronic myelogenous leukemia (CML). "There is a very good chance detection of this protein form and/or its biochemical activity may eventually provide an unambiguous biochemical marker for the diagnosis of CML," says Owen Witte of the University of California at Los Angeles.

The finding also advances understanding of how genetic changes can trigger cancer. It ties together work on viral genes responsible for animal cancers and clinical studies relating cancers to chromosomal abnormalities.

A paradox of cancer research has been the observation that the cancer-producing power of many viruses comes from genes, called oncogenes, they have picked up from normal cells. In their original cellular location, these genes do no damage, and may even be essential to normal cell function. In some cases, detailed analyses have revealed subtle genetic differences between normal and malignant forms of these genes, but it has been difficult to determine how such changes induce cancer (SN: 11/13/82, p. 316).

In studies of a virus that causes leukemia in mice, scientists have found that the crucial gene, called v-*abl*, encodes a protein that catalyzes addition of a phosphate group to certain sites — the amino acid tyrosine — on proteins. Such phosphorylating, or kinase, activity also has been linked to malignancy in other cancers. The viral gene v-*abl* is closely related to a cellular gene called c-*abl*. They have the same nucleotide sequence in the region responsible for the enzymatic activity of the viral gene product. But the cellular gene product lacks this enzymatic activity in laboratory tests and has no phosphate groups attached to its own tyrosines. The scientists suspect it may have kinase activity under certain, as yet unidentified, conditions.

Human patients with CML show a characteristic chromosome abnormality. It results from a chromosomal break near one end of the c-*abl* gene and the attachment of the resultant segment to another chromosome. Witte and colleagues report that they have found in cells derived from a CML patient both the normal protein encoded by c-*abl* and an altered product that is phosphorylated, resembling the virus-encoded protein. Therefore both the leukemia caused by a virus and the leukemia caused by chromosomal translocation involve an altered protein with tyrosine kinase activity.

What is the difference between the normal protein and the ones with malignancy-inducing activity? Witte and colleagues suggest that the normal protein is regulated so that it is only active under specific conditions, different from those the scientists have investigated so far. Or the protein may only phosphorylate a specific molecule, not yet tried by the researchers. Although, Witte says, "we've added so many different things, we're sort of punch-drunk from trying."

Witte suggests the lack of control or of specificity shown by the "less finicky" malignancy-causing proteins is likely to be due to alterations of the c-*abl* genes. Such alterations may have occurred when the gene was picked up by a virus or when the gene was relocated by chromosome breakage.

Previous work indicates that the normal cellular and viral-encoded proteins are identical at one end, but at the other end the protein encoded by the viral gene lacks some amino acids. In contrast, the abnormal protein in the CML patient's cells is larger than normal. In both cases there is preliminary evidence the important change is at the same end, the amino terminal, of the molecule.

"The major scientific interest in this work is that it ties together two dominant themes, chromosomal translocations and oncogenes," Witte says. He points out that there have been instances of chromosomal translocations putting a cellular oncogene next to an inappropriate regulator, so excessive amounts of a normal protein are produced. "But here we have a structural alteration of a cellular oncogene that looks, acts and smells like the structural alteration in a viral gene," Witte says. —*J. A. Miller*

More meteorites from earth's moon?

With thousands of meteorites under study on earth, it was only last year that scientists were able for the first time to determine conclusively where *one* such rock had actually come from. Found in Antarctica's Allen Hills on Jan. 18, 1982, it was indicated by a host of analyses to be a rock from the highlands of earth's moon (SN: 3/26/83, p. 196). Now Japanese researchers have reported two more Antarctic meteorites to be probable moonrocks as well.

Both were found in the Yamato Mountains, some 3,000 kilometers from the Allen Hills and almost diametrically across the Antarctic continent. The first (now designated by its sample number, Yamato 791197) was collected late in 1979, but it was not recognized as a possible lunar meteorite until February of this year, when Keizo Yanai of Japan's National Institute of Polar Research examined it together with Klaus Keil and Jeffrey Taylor of the University of New Mexico (UNM) in Albuquerque. It looks like a typical lunar highland regolith breccia (a rock formed of fragments "rewelded" as by the pressure of a meteorite impact), says Keil, and the ratio of iron to manganese in its pyroxene and olivine minerals, according to Yanai, is consistent with a lunar origin. Oxygen isotope ratios, too, says Robert Clayton of the University of Chicago, convincingly support the case.

The other sample (Yamato 82192), described by Yanai this week at UNM at the annual meeting of the Meteoritical Society, was collected early last year, and although the oxygen-isotope measurements have yet to be completed, its texture, mineralogy and iron-manganese ratios carry the same implication: a rock from the moon.

Major questions remain: Do the three "lunar" meteorites represent three separate cases of other meteorites hitting the moon hard enough to knock fragments all the way to earth? The two Yamato samples were found about 70 km apart, so it may be at least possible that they were ejected together from the moon. Many kinds of analysis may be needed to resolve the matter, says Keil, and several researchers have expressed the hope that pieces of the Japanese meteorites will be made available to an international consortium of investigators so that their collective techniques can be brought to bear. According to Yanai, the Japanese Committee for Antarctic Meteorite Research has decided at least that a consortium approach will be used, and international participation may be invited. The committee, he says, has already received six sample requests from researchers in other countries, and the hope is that the consortium can be set up by September so that preliminary results will be ready for an Antarctic Meteorite Symposium next March in Tokyo.

One important result of identifying meteorites from the moon has been to indicate that rocks can indeed be blasted to earth from an object of the moon's mass and gravity, rather than merely from small asteroids. A number of other meteorites have yielded analyses suggesting to some researchers that they may have come from Mars — a far more difficult case to prove, since there are no equivalents to the hand-delivered Apollo lunar samples for comparison.

Even so the Martian evidence mounts. At this week's meeting, one Antarctic meteorite (EETA 79001), whose noble-gas abundances and nitrogen-isotope ratios resemble Viking lander analyses of the Martian atmosphere, was reported by Robert H. Carr and colleagues from the Open University in Milton Keynes, England, to show carbon-isotope ratios compatible with Viking's CO_2 measurements. —*J. Eberhart*