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How an AIDS-Related Cancer Unleashes Inflammation

Although new HIV treatments have drastically reduced the incidence of Kaposi's sarcoma in developed countries, it remains a health threat in many developing countries. Now, researchers have discovered one way that Kaposi's sarcoma—a cancer-like viral disease traditionally associated with AIDS—triggers severe inflammation.

Don Ganem, a Howard Hughes Medical Institute (HHMI) investigator, and HHMI associate Craig McCormick, who are both at the University of California, San Francisco, published their findings in the February 4, 2005, issue of the journal *Science*.

Ganem and McCormick dedicated the *Science* article to the memory of Robert Sadler, a former HHMI associate in Ganem's lab who discovered kaposin B. Sadler was killed in 1999 by stray bullets fired into a San Francisco nightclub.

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According to Ganem, early studies of Kaposi's sarcoma (KS) indicated that the abnormal growth of infected cells required the overproduction of cytokines—immune system proteins that trigger the cell's inflammatory response. A central question, he said, has been how does the Kaposi's sarcoma-associated herpesvirus that causes KS initiate cytokine production?

"While there are many genes in the viral genome that are capable of inducing cytokine production, the mechanism underlying this induction has remained unknown," said Ganem.

In their studies, McCormick and Ganem concentrated on one protein called kaposin B, which was discovered in Ganem's laboratory, but whose function remained unknown. "The sequence of the kaposin B gene is very unusual; there's no homology to any known gene," said Ganem. "So, we had no clue as to what the protein did. Since it was a very simple protein, we believed that it had no enzymatic function itself, but acted by binding to or activating other proteins," he said.

Thus, the researchers conducted experiments in which they isolated proteins that bound with kaposin B in the cell. That screening revealed that kaposin B binds to a protein called MK2, which is known to play a role in boosting cytokine production.

In further experiments, they discovered that the binding of kaposin B activated MK2, leading to higher levels of cytokines in the cell. Activated MK2 does this by prolonging the stability of cytokine messenger RNA—the genetic blueprint for cytokine proteins. The longer these messenger RNAs remain in the cell, the more cytokine proteins the cell's protein-making machinery is able to synthesize, said Ganem.

The activation of MK2 also increases production of blood-vessel-forming, or angiogenic factors, including the protein VEGF. The activation of angiogenesis pathways by kaposin B fits with observations made in patients with KS, Ganem noted. "If you examine lesions in a patient with KS, you'll see that they are visibly red because of all the new blood vessels that KS produces," he said.

In cell culture studies, the researchers found evidence of an "activation loop," by which kaposin B activation of MK2 promotes even further MK2 activity by other proteins. The over-production of cytokines resulting from kaposin B's binding to MK2 creates inflammation that in turn activates the regulatory protein p38. p38, in turn, further increases activation of MK2.

"We still don't know the mechanism by which kaposin B activates MK2," said Ganem. "Nor do we understand how this activation leads to activation of the upstream regulator of MK2, which is p38. Thus, while we now understand the biology of this inflammation, the details of the biochemistry still need to be worked out," he said.

While the new knowledge of kaposin B's role will contribute to understanding how the responsible virus produces cytokines, there are likely other mechanisms at work as well, Ganem emphasized. Other viral genes are also known to be involved in cytokine pathways, he said.

Developing countries—where HIV treatments are not readily available—will be most likely to benefit from potential new treatments for KS that involve inhibiting cytokine production, Ganem said. "KS has become a less urgent threat in developed countries, because two factors are needed for KS

lesions—viral infection and immunodeficiency. Effective new treatments for HIV have strikingly reduced the immunodeficiency factor in developed countries; so new cases of KS have gone down by 90 percent since 1996,” he said. There are also forms of KS not linked to HIV, Ganem added, and these studies could also lead to new treatments for those forms of the illness.