insideblood

● ● ● **CLINICAL TRIALS**

KSHV: forgotten but not gone

Patrick S. Moore and Yuan Chang UNIVERSITY OF PITTSBURGH CANCER INSTITUTE

Thirty years ago, Kaposi sarcoma (KS) arose as a prominent manifestation of the AIDS epidemic. Seventeen years ago we discovered the virus that causes KS,[1] Kaposi sarcoma–associated herpesvirus (KSHV), and within a year KSHV had been also shown to be the likely cause of AIDS-associated primary effusion lymphoma (PEL)[2] and most cases of multicentric Castleman disease (MCD).[3]
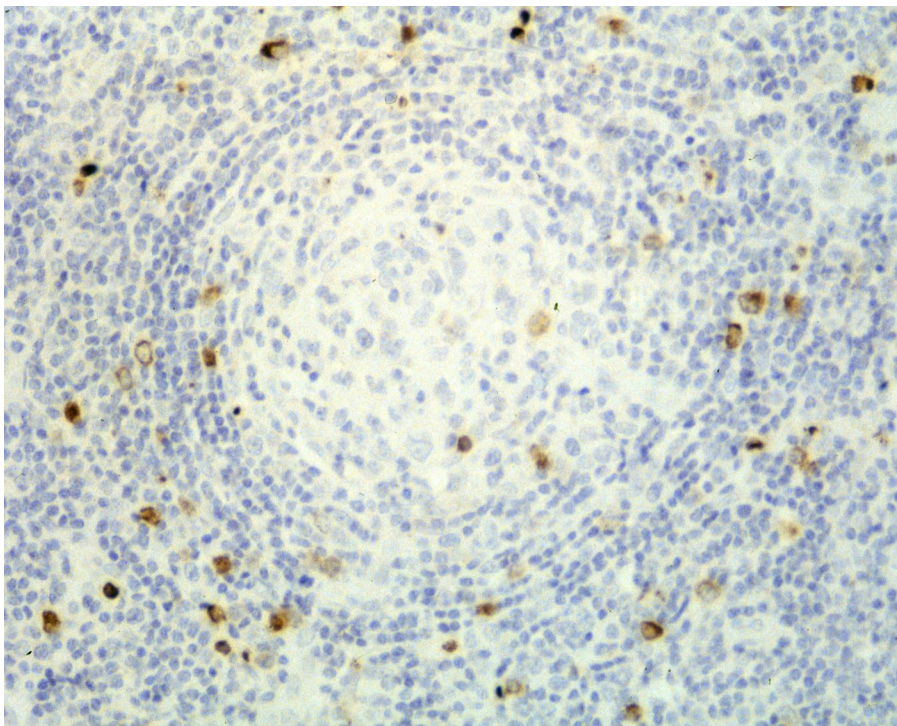
KSHV-infected cells expressing vIL-6 within an adventitious germinal center in a multicentric Castleman disease tumor. Illustration courtesy of C. Parravicini.

Since then, almost no progress has been made in treating the virus that causes these tumors. In this issue of *Blood*, for the first time, Uldrick et al describe a long overdue approach to MCD therapy based on direct targeting of KSHV.[4]

There are now 7 known human cancer viruses but only scattered efforts to developed drugs specifically targeting them. The successes of the human papillomavirus and hepatitis B virus vaccines make clear that virus-oriented therapies have the potential to be major success stories in cancer management. If a virus causes a tumor, why are most pharmaceuticals targeting the host cancer cell instead of the causative virus? The most important reason is economics: 1 in 5 cancers worldwide has an infectious origin, with most cases concentrated in poor and developing countries.

But to be fair to the pharmaceutical industry, drugs against viral cancers are also difficult to make. Almost all current antivirals target viral replication machinery. The most well-known antiviral drug is acyclovir, a nucleoside analog activated by the herpes simplex thymidine kinase enzyme. This viral protein is only expressed during active viral replication to replicate viral DNA and for this reason acyclovir is effective against cold sores but not against latent virus in trigeminal or sacral ganglia. Acyclovir reduces symptoms but does not cure the underlying disease.

Similarly, viruses in most tumor cells are latent as well. If viruses in cancer cells did actively replicate, host innate and adaptive immune responses would kill the cell before it could grow into a clinically apparent tumor, and for most viral cancers there is no target that can be hit with available drugs. Ganciclovir, for example, is remarkably effective in randomized clinical trials to prevent KSHV replication and KS[5,6] but has no effect once KS tumors emerge.[7]

The study by Uldrick et al looks at this problem in a different way—are there any other KSHV-related tumors in which actively replicating virus can be targeted? Castleman disease is a B-cell lymphoproliferative disorder driven by IL-6 over-expression and in KSHV-related MCD, only a small percentage of tumor cells are actually KSHV-infected (see figure). KSHV-infected MCD cells are surrounded by uninfected B cells forced to multiply by cytokine-induced mitogenesis, which make up the bulk of MCD tumors and are responsible for most MCD symptoms and sequelae. Viral replication machinery plays a key role in MCD because KSHV-encoded vIL-6 is amplified as part of the virus's replication program (although the KSHV vIL-6 gene can be activated in different ways and should not be called a "lytic KSHV gene").

Uldrick et al exploit this to develop a viral chemotherapy regimen against MCD. The work extends previous studies suggesting that antivirals can improve MCD patient survival.[8] In their pilot study, Uldrick et al use the ganciclovir prodrug, valganciclovir, together with zidovudine (AZT) to precisely target 2 viral enzymes involved in viral DNA synthesis, the viral phosphotransferase and thymidine kinase, respectively—a first in KSHV oncology. These drugs can potentially be paired with other standard chemotherapies to further improve outcome for this disease that otherwise has a dismal prognosis.

Both drugs are approved for human use with other viral infections having more favorable pharmaco-economic indices than KSHV. In some African countries hard hit by AIDS, however, Kaposi sarcoma accounts for the majority of adult cancers reported to cancer registries. In Southeast Asia, EBV–containing nasopharyngeal carcinoma is a major unmet public health problem. Despite the effectivenesss of papillomavirus vaccines, cervical cancer remains a major killer throughout the developing world, and 4000 women die from it annually in the US. For KSHV and most other cancer viruses, the problem is not that there is no possible viral drug target. KSHV latency-associated nuclear antigen 1 is needed by the virus to maintain its genome in every tumor cell. Finding drugs to target these latent viral proteins is more an economic than a scientific issue. In the words of the astronaut Gus Grissom, "No bucks, no Buck Rogers."

Rates of KS in developed countries have dramatically fallen with the development of effective antiretroviral therapy for HIV/AIDS, reducing the urgency to develop new control approaches to KSHV tumors. The current respite in KSHV-related disease, however, may be only temporary. Antiretroviral therapy does not affect latent, life-long KSHV infections and so resurgence of KSHV-related tumors with aging of the current HIV/AIDS population can be expected. We have not used this quiet time wisely.

This study by Uldrick et al provides a key lesson that antiviral chemotherapy in KSHV tumors can work—but only because of MCD's unusual pathoetiology. MCD acts more like a smoldering virus infection than a neoplasm. If new classes of antivirals were to be developed targeting latent cancer virus oncoproteins, there is promise that remarkable

clinical outcomes could emerge. These drugs could lead to cures instead of palliation for some viral infections. They might also be far less toxic than current cancer chemotherapies because they target foreign proteins—much like the miraculous antibiotics of the 1940s. The study reported in this issue *Blood* is an important first step in this direction.

Conflict-of-interest disclosure: The authors hold patents related to KSHV that have been assigned to Columbia University. ■

REFERENCES

1. Chang Y, Cesarman E, Pessin MS, et al. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science*. 1994;265(5192):1865-1869.

2. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. *N Engl J Med*. 1995;332(18):1186-1191.

3. Soulier J, Grollet L, Oksenhendler E, et al. Kaposi's sarcoma-associated herpesvirus-like DNA sequences in multicentric Castleman's disease. *Blood*. 1995;86(4): 1276-1280.

4. Uldrick TS, Polizzotto MN, Aleman K, et al. High-dose zidovudine plus valganciclovir for Kaposi sarcoma herpesvirus-associated multicentric Castleman disease: a pilot study of virus-activated cytotoxic therapy. *Blood*. 2011; 117(26):6977-6986.

5. Martin DF, Kuppermann BD, Wolitz RA, Palestine AG, Li H, Robinson CA. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med*. 1999;340(14):1063-1070.

6. Casper C, Krantz EM, Corey L, et al. Valganciclovir for suppression of human herpesvirus-8 replication: a randomized, double-blind, placebo-controlled, crossover trial. *J Infect Dis*. 2008;198(1):23-30.

7. Krown SE, Dittmer DP, Cesarman E. Pilot study of oral valganciclovir therapy in patients with classic kaposi sarcoma. *J Infect Dis*. 2011;203(8):1082-1086.

8. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman disease with ganciclovir treatment. *Blood*. 2004;103(5):1632-1634.

● ● ● **IMMUNOBIOLOGY**

Comment on Barao et al, page 7032

Unlicensed natural born killers

Andreas Lundqvist and Richard Childs   KAROLINSKA INSTITUTET; NATIONAL INSTITUTES OF HEALTH

In this issue of *Blood*, Barao and colleagues describe repopulation of Ly49G2 single-positive NK cells after congenic hematopoietic stem cell transplantation (HSCT) that appear fully functional, having tumor cytolytic capacity despite recipients lacking MHC molecules thought necessary to license them.

Natural killer (NK) cells are innate lymphocytes capable of killing tumors and virus-infected cells. Their function is regulated through a variety of different receptors. In humans, the largest group of receptors belongs to the killer Immunoglobulin-like family, or KIRs. Although structurally different from KIRs, mice possess Ly49 receptors that share similar functional characteristics; both KIRs and Ly49 receptors are composed of members possessing inhibitory or activating properties that regulate the function of the NK cell on binding its cognate MHC class I ligand. Although cell subsets lacking inhibitory receptors for self-MHC have been observed in both man and mouse, in vitro studies have shown that these potentially autoreactive NK-cell populations are in most cases hyporesponsive. In contrast, NK cells whose inhibitory receptors interact with self-MHC class I acquire functional competence, a process referred to as licensing.[1] Such licensed NK cells are immunologically competent and

are capable of responding to stimuli in vitro and in vivo.

In this issue of *Blood*, Barao et al investigated whether licensing plays a role in the reconstitution of NK cells bearing different Ly49 receptors in mice undergoing HSCT.[2] Initial experiments focused on transfer of bone marrow cells in congenic C57BL/6 mice (H-2b–positive). In these mice, Ly49G2 single-positive NK cells are considered unlicensed because of their inability to bind H2b. Contrary to expectations, early NK-cell repopulation after HSCT was dominated by Ly49G2 single-positive NK cells. Remarkably, these unlicensed NK cells were phenotypically mature and were not hyporesponsive, lysing tumor targets to a similar degree as licensed NK-cell controls. When experiments were repeated in mice on an H-2d background, a selective expansion of Ly49G2 single-positive NK cells was again observed. Thus, it appears that NK-cell repopulation early after HSCT is dominated by Ly49G2 single-