312
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Kaposi Sarcoma Herpesvirus: New Perspectives

With 29 Figures and 14 Tables

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Chris Boshoff, MRCP, Ph.D.

University College London
Wolfson Institute for Biomedical Research
Gower Street
London WC1E 6BT
UK

e-mail: c.boshoff@ucl.ac.uk

Robin A. Weiss, Ph.D.

Wohl Virion Centre
Division of Infection and Immunity
University College London
46 Cleveland Street
London W1T 4JF
UK

e-mail: r.weiss@ucl.ac.uk

Cover Illustration:
Juan Chang and Patrick Moore receiving the Koch Prize for their discovery of Kaposi's sarcoma-associated herpesvirus in 1994. Also shown is a KSHV virion from chapter by O'Connor and Kedes, p. 43. and a photograph of Moritz Kaposi. Background shows an histological image of a Kaposi's sarcoma tumor.

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Preface

Moritz Kaposi (born Moritz Kohn 1837, Kaposvár, Hungary; died 1902, Vienna) succeeded his father-in-law, Ferdinand von Hibra (1816–1880) to become one of the foremost dermatologists in the German-speaking world. His remarkable clinical acumen is evident from his descriptions of systemic lupus erythematosus (1869), idiopathic multiple pigmented sarcoma of the skin (1872 Kaposi sarcoma), and xeroderma pigmentosum (1882). His name change from Kohn to Kaposi (1871) reflects his professional ambitions to be distinguished from the other *Kohns* working in the Vienna Medical Faculty at the time. Although we now associate Kaposi sarcoma occurring in eastern European and Mediterranean populations (*classic Kaposi*) with an indolent disease, the cases first described by Kaposi had an aggressive clinical course, including some with fatal systemic disease. Underlying illness (*krankheit*) might have contributed to a more immunosuppressive state (Kaposi 1872).

From the 1940s onwards, various workers observed similar vascular tumours in sub-Saharan Africa, including an aggressive lymphadenopathy in children (endemic Kaposi) (Ackerman 1962; Oettle 1962). It remains to be established whether this lymphadenopathic disease in African children represents primary infection with Kaposi sarcoma-associated herpesvirus (KSHV). In the 1970s, the introduction of organ transplantation with its related iatrogenic immunosuppression resurrected this tumour as an important cause of morbidity and even mortality (Penn 1979). The Italian dermatologist Giraldo suggested in 1972 that herpesviruses could be involved in the pathogenesis of Kaposi sarcoma, after they showed by electron microscopy herpes-type viral particles in cells cultured from these tumours (Giraldo 1972). They subsequently identified these virions as cytomegalovirus.

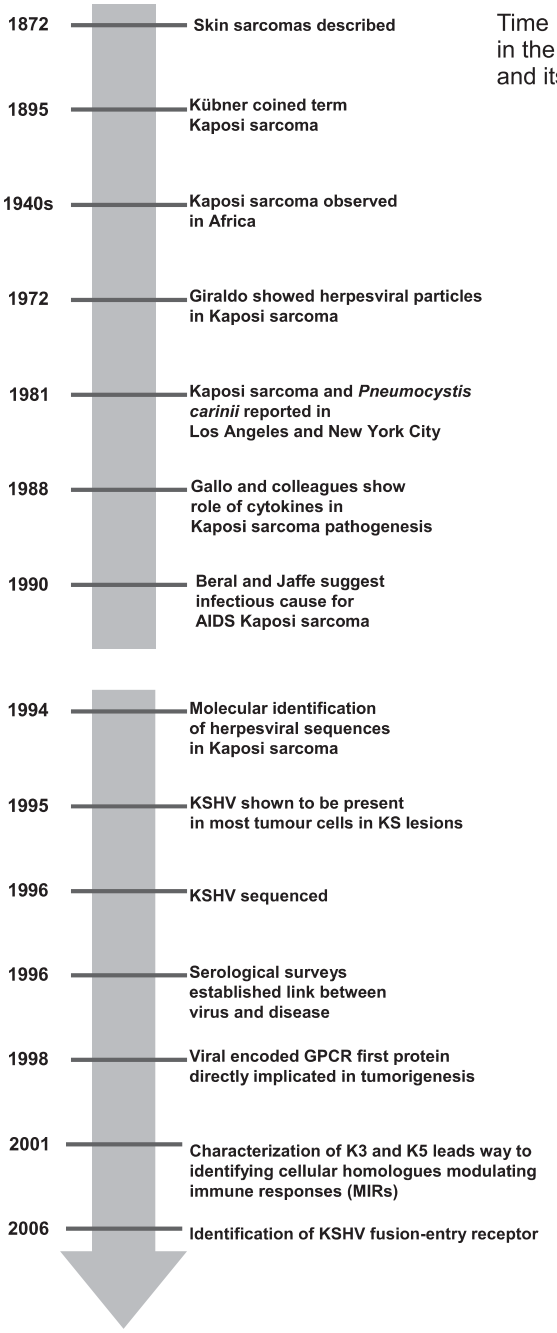
The reports from New York City and Los Angeles in 1981 of Kaposi sarcoma and *Pneumocystis carinii* pneumonia by the Centers for Disease Control in Atlanta heralded the AIDS pandemic (Friedman-Kien 1981). In 1981, about 48% of gay men with AIDS presented with or developed Kaposi sarcoma during the course of their illness. The incidence of AIDS-related Kaposi sarcoma in 1990 in this population was less than 15%. It is still unclear whether this is mainly

due to a fall in the seroprevalence of Kaposi sarcoma-associated herpesvirus (KSHV or HHV8) in this population, or whether these were related to other disease-associated risk factors. The particular symmetrical distribution of AIDS–related Kaposi sarcoma on the skin, high rate of mucosal membrane, lymph node and visceral involvement, provoked various hypotheses regarding the pathogenesis of this disease: tissue-specific temperature or oxygen tensions might favor KS tumour cell proliferation, or attraction of infected cells by specific chemokine-rich environments could favor these sites of disease. The demonstration that solid epithelial cancer micrometastases could be attracted to specific organs by chemokines corresponding to the specific chemokine receptors expressed on such cancer cells, favors a hypothesis where circulating Kaposi tumour cells, or KSHV-infected cells, home-in on specific organs. Underlying HIV infection might influence the distribution of such chemokines and certainly promotes the aggressiveness of the disease.

Robert Gallo and his team were among the first to culture cells from AIDS-related Kaposi sarcoma, and they introduced the concept of an autocrine and paracrine driven tumour, where cytokines stimulate the growth of this malignancy (Salahuddin 1988; Ensoli 1989). A contemporary of Kaposi, Virchow proposed in 1863 that cancerous tumours occur at sites of chronic inflammation (Balkwill 2001) and in 1986 Dvorak speculated that tumours are wounds that do not heal (Dvorak 1986). The model of a tumour landscape, where inflammatory cells produce cytokines and other growth factors which contribute to the initiation and maintenance of tumour growth has since become a major focus of cancer research. Interestingly, Kaposi sarcoma lesions also display the Kübner phenomenon (tumour develops at sites of an old injury).

Epidemiological studies by Harold Jaffe and Valerie Beral in the early years of the AIDS epidemic suggested that an infectious agent other than HIV was the culprit causing Kaposi sarcoma (Beral 1990). However, their suggestion that such an infection is mainly transmitted by the faecal-oral route was probably incorrect.

Patrick Moore (epidemiologist to the City of New York), and his wife Yuan Chang (pathologist at Columbia University), used representational difference analysis to identify sequences of a new herpesvirus in 1994 (Chang 1994). The technique of representational difference analysis was first described by Lisitsyn and Wigler (Lisitsyn 1993). They employed this polymerase chain reaction subtraction technique to successfully identify a sequence that clearly belonged to a herpesvirus genome, but was distinct from previously characterized herpesviruses. KSHV is the second human oncogenic virus to be identified by molecular techniques, the first being human cervical papillomavirus in 1983 by Harald zur Hausen and colleagues.



Time Line: Important events in the history of Kaposi sarcoma and its associated virus

Since the identification of two sequences from KSHV, we have learned much about this pathogen as reflected in this book. As it turned out, KSHV itself encodes for a number of cytokines, and induces cellular cytokine secretion, contributing to tumour growth. Moreover, KSHV vFLIP targets the IKK-NFκB axis to encourage the inflammatory microenvironment observed by Gallo and his colleagues. KSHV continues to elucidate both mechanisms of viral oncogenesis, and cellular and immune pathways involved in non-viral driven neoplasia.

We bring together here various experts in their respective fields, addressing some key aspects of KSHV biology, and we are grateful for their contributions.

University College London *Chris Boshoff and Robin A. Weiss*

Table 1 Twenty of the most cited articles on Kaposi sarcoma herpesvirus

	Article	Estimated number of citations (2006)
1.	Chang Y et al. (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869	1950
2.	Cesarman E et al. (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. NEJM 332:1186–1191	880
3.	Russo JJ et al. (1996) Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). PNAS 93:14862–14867	735
4.	Whitby D et al. (1995) Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 346:799–802	570
5.	Moore PS et al. (1995) Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. NEJM 332:1181–1185	555
6.	Gao SJ et al. (1996) KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med 2:925–928	527
7.	Moore PS et al. (1996) Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. Science 274:1739–1744	505
8.	Renne R et al. (1996) Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nat Med 2:342–346	499

Table 1 (continued)

	Article	Estimated number of citations (2006)
9.	Kedes DH et al. (1996) The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): Distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med 2:918–924	464
10.	Boshoff C et al. (1995) Kaposi's sarcoma-associated herpesvirus infects endothelial and spindle cells. Nat Med 1:1274–1278	415
11.	Simpson GR et al. (1996) Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 348:1133–1138	403
12.	Bais C et al. (1998) G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. Nature 391:86–89	390
13.	Lennette ET et al. (1996) Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. Lancet 348:858–861	365
14.	Gao SJ et al. (1996) Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. NEJM 335:233–241	351
15.	Moore PS et al. (1996) Primary characterization of a herpesvirus agent associated with Kaposi's sarcoma. J Virol 70:549–558	351
16.	Rettig MB et al. (1997) Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients. Science 276:1851–1854	346
17.	Nador RG et al. (1996) Primary effusion lymphoma: A distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpesvirus. Blood 88:645–656	346
18.	Staskus KA et al. (1997) Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (Spindle) tumor cells. J Virol 71:715–719	292
19.	Boshoff C et al. (1997) Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. Science 278:290–294	279
20.	Kledal TN et al. (1997) A broad-spectrum chemokine antagonist encoded by Kaposi's sarcoma-associated herpesvirus. Science 277:1656–1659	249

References

1. Ackerman LV, Murray JF (1962) Symposium on Kaposi's sarcoma, Acta Union Internationalis Contra Cancrum. Karger, Basel
2. Bais C, Santomasso B, Coso O, Arvanitakis L, Raaka EG, Gutkind JS, Asch AS, Cesarman E, Gershengorn MC, Mesri EA (1998) G-protein-coupled receptor of Kaposi's sarcoma-associated herpesvirus is a viral oncogene and angiogenesis activator. Nature 391:86–89
3. Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? Lancet 357:539–545
4. Beral V, Peterman TA, Berkelman RL, Jaffe HW (1990) Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet 335:123–128
5. Boshoff C, Endo Y, Collins PD, Takeuchi Y, Reeves JD, Schweickart VL, Siani MA, Sasaki T, Williams TJ, Gray PW, Moore PS, Chang Y, Weiss RA (1997) Angiogenic and HIV-inhibitory functions of KSHV-encoded chemokines. Science 278:290–294
6. Boshoff C, Schulz TF, Kennedy MM, Graham AK, Fisher C, Thomas A, McGee JO, Weiss RA, O'Leary JJ (1995) Kaposi's sarcoma-associated herpesvirus infects endothelial and spindle cells. Nat Med 12:1274–1278
7. Cesarman E, Chang Y, Moore PS, Said JW, Knowles DM (1995) Kaposi's sarcoma-associated herpesvirus-like DNA sequences in AIDS-related body-cavity-based lymphomas. N Engl J Med 332:1186–1191
8. Chang Y, Cesarman E, Pessin MS, Lee F, Culpepper J, Knowles DM, Moore PS (1994) Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. Science 266:1865–1869
9. Davies JNP, Loethe F (1962) Kaposi's sarcoma in African children. Acta Union Internationale Contra Cancrun 18:394–399
10. Dvorak HF (1986). Tumours: wounds that do not heal. Similarities between tumor stroma generation and wound healing. N Engl J Med 315:1650–1659
11. Ensoli B, Nakamura S, Salahuddin SZ, Biberfeld P, Larsson L, Beaver B, Wong-Staal F, Gallo RC (1989) AIDS-Kaposi's sarcoma-derived cells express cytokines and autocrine and paracrine growth effects. Science 243:223–226
12. Friedman-Kien AE, Laubenstein L, Marmor M et al. (1981) Kaposi's sarcoma and pneumocystis pneumonia among homosexual men – New York and California. Morbidity Mortality Rep 30:305–308
13. Gao SJ, Kingsley L, Hoover DR, Spira TJ, Rinaldo CR, Saah A, Phair J, Detels R, Parry P, Chang Y, Moore PS (1996) Seroconversion to antibodies against Kaposi's sarcoma-associated herpesvirus-related latent nuclear antigens before the development of Kaposi's sarcoma. New Engl J Med 335:233–241
14. Gao SJ, Kingsley L, Li M, Zheng W, Parravicini C, Ziegler J, Newton R, Rinaldo CR, Saah A, Phair J, Detels R, Chang Y, Moore PS (1996) KSHV antibodies among Americans, Italians and Ugandans with and without Kaposi's sarcoma. Nat Med 8:925–928
15. Giraldo G, Beth E, Haguenau F (1972) Herpes-type virus particles in tissue culture of Kaposi's sarcoma from different geographic regions. J Natl Cancer Inst 49:1509–1513

16. Kaposi M (1872) Idiopatiches multiples pigment sarcom der Haut. Archic fur Dermatologie Syphilis 4:265–272
17. Kedes DH, Operskalski E, Busch M, Kohn R, Flood J, Ganem D (1996) The seroepidemiology of human herpesvirus 8 (Kaposi's sarcoma-associated herpesvirus): distribution of infection in KS risk groups and evidence for sexual transmission. Nat Med 2:918–924
18. Kledal TN, Rosenkilde MM, Coulin F, Simmons G, Johnsen AH, Alouani S, Power CA, Luttichau HR, Gerstoft J, Clapham PR, Clark-Lewis I, Wells TN, Schwartz TW (1997) A broad-spectrum chemokine antagonist encoded by Kaposi's sarcoma-associated herpesvirus. Science 277:1656–1659
19. Lennette ET, Blackbourn DJ, Levy JA (1996) Antibodies to human herpesvirus type 8 in the general population and in Kaposi's sarcoma patients. Lancet 348:858–861
20. Lisitsyn N, Lisitsyn N, Wigler M (1993) Cloning the differences between two complex genomes. Science 259:946–951
21. Moore PS, Boshoff C, Weiss RA, Chang Y (1996) Molecular mimicry of human cytokine and cytokine response pathway genes by KSHV. Science 274:1739–1744
22. Moore PS, Chang Y (1995) Detection of herpesvirus-like DNA sequences in Kaposi's sarcoma in patients with and without HIV infection. N Engl J Med 18:1181–1185
23. Moore PS, Gao SJ, Dominguez G, Cesarman E, Lungu O, Knowles DM, Garber R, Pellett PE, McGeoch DJ, Chang Y (1996) Primary characterization of a herpesvirus agent associated with Kaposi's sarcomae. J Virol 70:549–558
24. Nador RG, Cesarman E, Chadburn A, Dawson DB, Ansari MQ, Sald J, Knowles DM (1996) Primary effusion lymphoma: a distinct clinicopathologic entity associated with the Kaposi's sarcoma-associated herpesvirus. Blood 88:645–656
25. Oettle AG (1962) Geographical and racial differences in the frequency of Kaposi's sarcoma as evidence of environmental or genetic causes. Acta Union Internationale Contra Cancrum 18:330–363
26. Penn I (1979) Kaposi's sarcoma in organ transplant recipients. Transplantation 27:8–11
27. Renne R, Zhong W, Herndier B, McGrath M, Abbey N, Kedes D, Ganem D (1996) Lytic growth of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in culture. Nat Med 2:342–346
28. Rettig MB, Ma HJ, Vescio RA, Pold M, Schiller G, Belson D, Savage A, Nishikubo C, Wu C, Fraser J, Said JW, Berenson JR (1997) Kaposi's sarcoma-associated herpesvirus infection of bone marrow dendritic cells from multiple myeloma patients. Science 276:1851–1854
29. Russo JJ, Bohenzky RA, Chien MC, Chen J, Yan M, Maddalena D, Parry JP, Peruzzi D, Edelman IS, Chang Y, Moore PS (1996) Nucleotide sequence of the Kaposi sarcoma-associated herpesvirus (HHV8). Proc Natl Acad Sci USA 93:14862–14867
30. Salahuddin SZ, Nakamura S, Biberfeld P et al. (1988) Angiogenic properties of Kaposi's sarcoma-derived cells after long-term culture in vitro. Science 242:430–433

31. Simpson GR, Schulz TF, Whitby D, Cook PM, Boshoff C, Rainbow L, Howard MR, Gao SJ, Bohenzky RA, Simmonds P, Lee C, de Ruiter A, Hatzakis A, Tedder RS, Weller IV, Weiss RA, Moore PS (1996) Prevalence of Kaposi's sarcoma associated herpesvirus infection measured by antibodies to recombinant capsid protein and latent immunofluorescence antigen. Lancet 348:1133–1138
32. Staskus KA, Zhong W, Gebhard K, Herndier B, Wang H, Renne R, Beneke J, Pudney J, Anderson DJ, Ganem D, Haase AT (1997) Kaposi's sarcoma-associated herpesvirus gene expression in endothelial (spindle) tumor cells. J Virol 71:715–719
33. Whitby D, Howard MR, Tenant-Flowers M, Brink NS, Copas A, Boshoff C, Hatzioannou T, Suggett FE, Aldam DM, Denton AS et al. (1995) Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. Lancet 346:799–802

List of Contents

List of Contributors

(Addresses stated at the beginning of respective chapters)