

Reviewer's report

Title: KSHV/HHV-8 and HIV infection in Kaposi sarcoma development

Version: 1 **Date:** 24 August 2006

Reviewer: Thomas Schulz

Reviewer's report:

General

This is a relatively short review on Kaposi sarcoma and KSHV/HHV8, which, in my view, attempts to cover too broad a field and therefore does not do justice to many of the aspects of KS and KSHV/HHV8 that it touches. The authors are well known for their work on the histopathology of KS and are therefore in a very good position to review this aspect of KS biology. Since there are already several recent reviews on the molecular virology of KSHV/HHV8, but none on the histopathology and tumour biology of KS, it would be better if the authors focussed on this part of their review. This part contains many interesting aspects, worth to be discussed in context and to be brought to the attention of the many virologists working in this field, whereas the molecular virology sections are too cursory to be of wide interest.

When revising the sections on the histopathology and cytogenetics of KS the authors should take care not to overinterpret some of the findings reported in the literature. In my view this applies for example to their paragraphs on the role of HIV-1 Tat and of bFGF in KS pathogenesis (see some specific examples below).

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. p.5 KSHV miRNAs: most miRNAs are encoded between K12 and orf71, only 2 miRNAs are located in the kaposin gene, as stated.
2. p.5: there is no evidence that the region upstream of K12 and downstream of orf71, which contains most miRNAs, has transforming properties. Of course, miRNAs may contribute to the oncogenic effects of KSHV, but so far there is no direct evidence for this, except for their expression during latent persistence. However, miRNAs are probably best left out of the review, if this is to be focussed on the histopathology and cytogenetics of KS, as suggested above.
3. p.8: the authors pick up the suggestion, made in reference 56, that KSHV/HHV8 may behave as an integrating oncovirus. Since there is no evidence for an integration of a herpesvirus genome into cellular genomes (other than events that are considered aberrant and dead-end integration events) this suggestion should clearly be treated with a lot of caution. The evidence in reference 56 does, in my view, not really support this assertion and a critical appraisal may be required in such a review.
4. p.9, relative lack of antibodies to Tat in AIDS KS vs. asymptomatic HIV-infected patients: the authors follow the interpretation in this paper that antibodies to Tat may protect against KS development thereby supporting a role for HIV-1 Tat in KS pathogenesis. The problem with this report is that no antibodies to KSHV/HHV8 were measured, i.e. if the majority of asymptomatic HIV-1-infected patients had not been infected with KSHV/HHV8 one would not expect them to develop KS.
5. Cytogenetics: The authors should mention that none of the available cell lines derived from KS lesions contain KSHV. While they may have harboured KSHV originally it is also possible that they are derived from a minor cell population in the KS lesion and that any cytogenetic abnormality in these cell lines does not reflect the situation of the majority of KSHV/HHV8 - infected cells in the KS lesion.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

p.4: "angiogenesis" (typo)

p.5: "envelop glycoprotein gb" (typo)

p.6: "in lesions later may ulcerate" - better: "...may later ulcerate..".

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.