

Kaposi's Sarcoma-Associated Herpesvirus Induced Tumorigenesis; How Viral Oncogenic Insults are Evaded

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Editorial

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Some viral infections in human are strongly related to cancer formation. Apart from retrovirus induced cancer formation seen in rodents and avian, virus induced cancer formation in human seems to be very complicated. In human, mainly DNA viruses such as papillomavirus, hepatitis B virus (HBV), Epstien-Barr virus (EBV), and Kaposi's sarcoma-associated herpes virus (KSHV) are etiological agents and some RNA viruses such human T-cell leukemia virus and hepatitis C virus (HCV) are involved in their specific cancer formation. It takes long time for the viruses to cause cancers and we do not have good systems to observe how the viral infection leads to cancer formation.

KSHV is belonging to gamma-herpesviridae and an agent involved in the formation of Kaposi's sarcoma (KS), primary effusion lymphoma (PEL) and multicentric Castelman's disease (MCD).

The virus infection has a very strong link with these cancers. The mechanism how the virus causes such cancers is, however, still enigmatic and remains to be elucidated. KSHV latent infection should be important in terms that this type of infection provides with an origin of the related cancers. But, many genes with oncogenic activity of this virus are lytic genes, which are expressed only in the lytic phase.

As mentioned above, virus induced carcinogenesis is very complicated and is attractive to take an insight how the virus causes related cancers [1].

KSHV expresses an extremely limited number of viral genes such as latency-associated nuclear antigen (LANA), viral cyclin (v-cyc), viral FLICE inhibitory protein (vFLIP), kaposin and viral interferon regulatory factor-3 (vIRF-3) and 17 viral microRNAs in latency. The genes build an active gene locus in the KSHV genome in latency.

Among them, v-CYC, a homolog of cellular D-type cyclins, functions as an oncogene to deregulate cellular proliferation which leads to DNA damage response (DDR) and p53 induced apoptosis. Normal cells respond to oncogenic insults and cannot be easily transformed by choosing suicide pathway through p53 [2]. If the virus survives this situation, there must be a mechanism and this is one of ways how KSHV causes cancers.

In this point a recent report from Leidal et al. [1] is attractive for an insight to link the v-CYC induced oncogenic insult with subversion of this activity by vFLIP and how the virus causes related cancers. They found that v-CYC caused autophagy induced senescence and/ or apoptosis. On the other hand, vFLIP is known for an autophagy inhibitor as well as an NF-kB activator [3,4]. And thus, vFLIP functions to evade from v-CYC induced oncogenic insult/senescence and make a direction of KSHV induced carcinogenesis.

However, we should be careful whether such a pathway happens in the natural infection course, since this kind of experiment is usually performed in over-expression system. Actually, vFLIP expression at the protein level has not been confirmed even in KSHV infected PEL cell lines and thus it is unclear whether such vFLIP activity is seen in the native situation.

In summary, a report from Liang seems to be very important to explain how KSHV causes cancers by connecting oncogene (v-CYC in this case) induced apoptosis and/or senescence [5]. Although there is no related report about the other human virus induced carcinogenesis, similar mechanisms might be stealthing.

References

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Received August 28, 2012; Accepted August 28, 2012; Published August 30, 2012

Citation: Ueda K (2012) Kaposi's Sarcoma-Associated Herpesvirus Induced Tumorigenesis; How Viral Oncogenic Insults are Evaded. J Blood Lymph 2:e109. doi:10.4172/2165-7831.1000e109

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