DNA damage response confers a barrier for viral tumorigenesis

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Kaposi's sarcoma herpesvirus (KSHV) is a human tumor virus and an etiological agent for Kaposi's sarcoma (KS). KSHV infection is endemic in sub-Saharan Africa where KS is nowadays the most common malignancy, due to widespread infection with KSHV and human immunodeficiency virus (HIV). Importantly, KS also occurs in HIV-negative individuals. Researchers at the University of Helsinki, Finland, have discovered that activation of the DNA damage response in the early stages of KS development functions as an anti-cancer barrier also in virus induced malignancies.

Recent findings suggest that DNA damage checkpoints become activated in early stages of human tumorigenesis, leading to growth arrest or apoptosis and thereby hindering tumor progression. DNA hyper-replication triggered by oncogenes can induce cellular senescence, which together with the oncogene-induced DNA damage checkpoint function as an early anti-cancer barrier. The findings by the research group of Päivi Ojala, Ph.D., (University of Helsinki) demonstrate that the DNA damage checkpoint is activated during the initial stages of KSHV infection and KS tumorigenesis and this can confer a barrier to tumorigenesis also in virus induced cancers.

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KSHV displays two patterns of infection: latent and lytic phase. During latency, only a restricted set of viral genes is expressed. The KSHV

genome encodes several homologues of cellular proteins, which engage cellular signaling pathways, govern cell proliferation and modulate apoptosis. The results of this study demonstrate that one of the viral latent proteins, viral cyclin, which is a homolog of cellular D-type cyclins, induces replicative stress in endothelial cells, which leads to senescence and activation of the DNA damage response.

To support the finding early stage lesions of clinical KS specimens were analysed in the study. The results demonstrate that DNA damage checkpoint is activated in early, but not late stage lesions of clinical KS specimens. During the course of infection, the KSHV infected cells may be imposed to overcome this checkpoint, and oncogenic stress elicited by the expression of the viral cyclin may further contribute to the induction of genomic instability and malignant transformation.

Source: University of Helsinki