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KSHV-mediated ROS induction defines novel therapeutic targets in Kaposi's sarcoma

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Background

Kaposi's sarcoma herpesvirus (KSHV) is the etiological agent of Kaposi's sarcoma (KS). Understanding the interplay of viral and host factors in KS carcinogenesis is critical for the rational development of new therapies. Reactive oxygen species (ROS) have a recognized broad function in oncogenesis mediated by signaling cascades leading to the Rac1 activation of NADPH oxidases (Nox) [1]. ROS play a role in cell cycle regulation and angiogenesis, yet the specific molecular events linking ROS and these cancer hallmarks are still elusive. KSHV encodes a constitutively active G protein-coupled receptor (vGPCR) [2], which triggers KS-like sarcomagenesis via Rac1 [3]. It has been shown that Rac1-activated mutant induces tumors resembling Kaposi's sarcoma by a ROS-mediated mechanism in transgenic mice [4,5]. Moreover, Rac1 is overexpressed in AIDS-KS lesions and in KSHV-infected mECK36 tumors, pointing to a role for KSHV-induced Rac1-mediated production of ROS in KS pathogenesis [5]. The current study explored the induction of oxidative stress pathways in the KSHV-induced mouse model mECK36.

Results

vGPCR expression led to the upregulation of the c-sis/PDGFB oncogene in a dose-dependent manner in mECK36. PDGFB upregulation was dependent on Rac1 and ROS since it was suppressed by the Rac1 inhibitor EHT1864 and the ROS scavenger N-acetyl cysteine (NAC). PDGF activated oxidative signaling in a Rac/Nox/ROS-dependent manner in latently infected cells, leading to the upregulation of important genes for proliferation and angiogenesis, such as c-Myc and VEGFA through the activation of the STAT3 transcription factor. Treatment with antioxidant NAC and PDGF receptor inhibitors (imatinib and sunitinib) proved effective in inhibiting KSHV-induced tumorigenesis in the mECK36 mouse model.

Conclusions

Our results show a novel KSHV-driven oncogenic mechanism mediated by PDGF-B, whereby KSHV infection induces and exploits ROS production. ROS can be targeted therapeutically by using the NAC antioxidant or FDA-approved PDGF receptors inhibitors. Imatinib clinical responses in AIDS-KS could be due to PDGF-receptor inhibition of ROS production and warrant further clinical trials and molecular exploration of these new molecular therapeutic and prevention targets in AIDS-KS.

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