Viral replication impedes the efficacy of a targeted therapy against virus-induced lymphomas

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Kaposi's sarcoma herpesvirus (KSHV) is a human tumor virus and an etiological agent for Kaposi's sarcoma and primary effusion lymphoma (PEL). PELs are aggressive lymphomas with reported median survival time shorter than six months after diagnosis.

Researchers at the University of Helsinki discovered that spontaneous induction of KSHV lytic replication in tumors drastically attenuated the p53-dependent apoptotic response not only to a targeted therapy (Nutlin-3) but also to genotoxic anti-cancer agents.

The findings by the research groups of Päivi Ojala (Institute of Biotechnology & Research Programs Unit) and Pirjo Laakkonen (Research Programs Unit, Univ. of Helsinki) provide valuable in-depth knowledge on the use of reactivation of p53 as a highly selective treatment modality for the virally-induced lymphoma. The project involves scientists from the Genome-Scale Biology and Molecular Cancer Biology Research Programs.

TP53 gene encodes a transcription factor (p53) that plays a central role in protecting cells from tumor development by inducing cell-cycle arrest or apoptosis via a complex signal transduction network referred to as the p53 pathway. TP53 gene is mutated or deleted in 50% of all malignant tumors. A potent strategy for restoration of p53 function is based on the inhibition of the interaction of p53 with its negative regulator MDM2 via

a selective small-molecule inhibitor of the p53–MDM2 interaction, the Nutlin-3.

PEL is a non-Hodgkin type lymphoma latently infected with KSHV, and it manifests as an effusion malignancy in Kaposi's sarcoma patients. There are no current therapies effective against the aggressive KSHV-induced PEL. 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.

Majority of the PELs appear to have an intact TP53 gene suggesting that genetic alterations are not selected for during PEL tumorigenesis. Earlier report from the same researchers showed that Nutlin-3 selectively induces massive apoptosis in PEL cells leading to efficient anti-tumor activity in a subcutaneous xenograft model for PEL (Sarek et al. 2007, Journal of Clinical Investigation).

Here they report viral lytic replication as a factor, which can hamper the otherwise efficient apoptotic response of p53 restoration in vivo. Spontaneous induction of viral lytic replication in the tumors drastically attenuated the Nutlin-3-induced p53-dependent apoptotic response. Attenuation of the cell death response in the lytic PEL cells was not restricted to p53 reactivation by the MDM2 inhibitor Nutlin-3, but was also observed upon induction of apoptosis by genotoxic agents. Importantly, the undesired resistance was overcome and the sensitivity of cells to Nutlin-3-induced apoptosis was restored by inhibition of viral replication.

The study was published yesterday in the *Oncogene*.

More information: Sarek, S., Ma, L., Enbäck, J., Järviluoma, A.,

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Sarek G., Kurki S., Enbäck J., Iotzova G., Haas J., Laakkonen P., Laiho M., and Ojala P.M. 2007. Reactivation of the p53 Pathway as a Novel Treatment Modality for KSHV-induced Lymphomas, J. Clin. Invest. 117(4):1019-28.