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The cellular deacetylase SIRT1 is a promising therapeutic option against HPV-associated cancer

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Abstract

Human papillomaviruses (HPVs) cause 5% of all cancers worldwide. HPV-associated cancers rely on the concerted action of the viral oncoproteins E6 and E7 in dampening the host cell defense response, ensuring successful cell proliferation. The canonical pathway consists of E6-mediated degradation of the tumor suppressor p53 by proteasome. As p53 is rarely mutated in HPV-associated cancers, functional restoration of this tumor suppressor should halt HPV-driven tumorigenesis. We have demonstrated the existence of a novel SIRT1-dependent circuit whose disruption leads to restoration of a functional p53 in HPV-transformed cells. Specifically, we show that pharmacological or genetic SIRT1 inhibition restores a transcriptionally active K382-acetylated p53 in HPV^+ but not HPV^- cell lines. Furthermore, SIRT1 inhibition by the specific inhibitor EX527 (Selisistat) promotes G_0/G_1 cell cycle arrest and reduces cell viability and clonogenicity of HPV^+ *vs* HPV^- cells. Lastly, EX527 treatment increases the sensitivity of HPV^+ cells to sublethal doses of standard genotoxic agents, such as doxorubicin and cisplatin. Enhanced sensitivity to the anticancer activity of cisplatin also occurs in an *in vivo* tumorigenicity assay based on subcutaneous injection of syngeneic C3.43 cells, harboring an integrated HPV16 genome, in C57BL/6J mice. This sensitization is likely due to restoration of a functional p53 as shown by immunohistochemistry of tumors from EX527-treated mice.
Altogether, our findings indicate that SIRT1 inhibition is an effective host-targeted therapy against HPV-driven cancer that may increase the effectiveness of existing anticancer treatments.