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Human Endogenous Retrovirus Type K promotes proliferation of Merlin-negative schwannoma and meningioma which can be inhibited by anti-retroviral and anti-TEAD drugs

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Abstract 1164: Human endogenous retrovirus type K promotes proliferation of Merlin negative schwannoma and meningioma which can be inhibited by anti-retroviral and anti-TEAD drugs

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Abstract

Deficiency of the tumor suppressor Merlin causes the development of schwannoma, meningioma and ependymoma tumors. These can occur spontaneously or in the hereditary disease Neurofibromatosis type 2 (NF2). Merlin mutations are also relevant in a variety of other tumors. Currently available treatments are surgery or radiosurgery which are only partially effective, with tumors frequently reoccurring and in case of meningioma often as a higher grade. There is an urgent need for effective drug treatments.In this study, we investigated the role of Human Endogenous Retrovirus Type K (HERV-K) and its targetability in Merlin negative schwannoma and meningioma tumors by using tissues and primary cells isolated form patients employing immunohistochemistry, immunocytochemistry, western blotting and proliferation assays.

We demonstrate that HERV-K proteins are overexpressed in Merlin negative schwannoma and all meningioma grades. Furthermore, we implicate $CRL4^{DCAF1}$ and YAPT/EAD Hippo pathway in this overexpression and suggest that exosome transport of the HERV-K Envelope (Env) protein might contribute to schwannoma development. We also show that: (i) Ectopic overexpression of HERV-K Env in normal Schwann cells increased proliferation and upregulated the transcription factor c-Jun. Env overexpression also increased activity of the extracellular signal-regulated kinase 1/2 (pERK1/2), a known mitogenic pathway in schwannoma. (ii) An anti-Env monoclonal antibody decreased pERK1/2 and reduced proliferation of schwannoma cells. iii) FDA-approved retroviral protease inhibitors Ritonavir, Atazanavir and Lopinavir decreased pERK1/2 and cyclin D1 and reduced proliferation of schwannoma and grade I meningioma cells.

We provide evidence for HERV-K Env contributing to the development of NF2-associated schwannomas and meningiomas. Considering the urgent need of drugs to treat NF2, we suggest the trialling of antiretroviral protease inhibitors, and consideration of anti-HERV-K Env immunotherapy, as well as TEAD-specific inhibitors in these patients. The above treatments would also be potentially beneficial for patients with other tumors caused by Merlin deficiency.

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