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Modulating the antioxidant defenses to potentiate oncolytic virotherapy in prostate cancer

Rongtuan Lin, David Olagnier and **Rassin Lababidi**
McGill University, Canada

Oncolytic viruses (OVs) are novel anticancer agents that infect and effectively kill cancer cells but not normal cells. Although tumor growth is delayed or eliminated in numerous animal models following treatment with OVs, several cancer models remain partially or completely resistant to viral oncolysis. To overcome this resistance, experimental strategies are now combining OVs with different cytotoxic compounds to improve OV efficacy. Our laboratory has previously demonstrated that OV replication can be bolstered by co-administration of other chemical agents such as Triptolide, a natural molecule derived from the medicinal herb. In the current study, we investigated the capacity of sulforaphane (SFN); an anti-cancer compound naturally occurred in cruciferous vegetables with demonstrated potent antioxidant and possible anti-inflammatory actions to enhance vesicular stomatitis virus (VSV) oncolysis in OV-resistant cancer cells. We ultimately demonstrate that the resistant PC3 prostate cancer cell line can be sensitized to VSV by addition of SFN. Indeed, SFN dose-dependently enhances the replication of VSV. Neither VSV (MOI 0.1) nor SFN (20 uM) alone are toxic against PC3 cells *in vitro*; however, in combination they greatly increased the oncolytic capacity of VSV by reducing cancer cell viability and promoting apoptosis-mediated cell death. Furthermore, the potentiation of VSV oncolysis by SFN is dependent on the production of ROS and is associated with the induction of autophagy. SFN is known to induce phase II antioxidant genes via Nrf2 activation, which regulates ROS levels and stimulates autophagy in prostate cancer cells. Mechanistically, SFN inhibited the innate antiviral response by blocking the type-1 interferon (IFN) signaling pathway, through the activation of the Nrf2 transcription factor. Exogenous Nrf2 expression inhibits Interferon-Stimulated Response Element (ISRE) promoter activity in a dose dependent manner following virus infection or IFN treatment. Taken together, these results demonstrate for the first time the synergic effect of SFN and VSV and indicate that SFN treatment increases VSV replication and the subsequent apoptosis of tumor cells by inhibiting IFN signaling. We are currently investigating the molecular mechanism involved in VSV-induced oncolysis by Nrf2 activators and evaluating the therapeutic potential of the combination of OV and Nrf2 activators in a mouse model of prostate cancer.

Biography

Rongtuan Lin is an Associate Professor in the Department of Medicine at McGill University and a Project Director of the Molecular Oncology Group at the Lady Davis Institute for Medical Research. He has received his PhD from Concordia University and completed Post-doctoral training at the Lady Davis Institute for Medical Research. He made important contributions in the fields of interferon signaling and innate antiviral immunity. He has a highly successful laboratory research program with 100 scientific publications, which have been cited more than 5,500 times. He was a recipient of a Chercheur-boursier Senior and Junior 2 from Fonds de la Recherche en Sante du Quebec. In 1996 and 1998, he has received the Milstein Young Investigator Award from the International Society for Interferon and Cytokine Research.

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