β-adrenergic receptor inhibitor and oncolytic herpesvirus combination therapy shows enhanced antitumoral and antiangiogenic effects on colorectal cancer

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Abstract

Oncolytic viruses (OVs) are considered a promising therapeutic alternative for cancer. However, despite the development of novel OVs with improved efficacy and tumor selectivity, their limited efficacy as monotherapeutic agents remains a significant challenge. In this study, we explored the effect of propranolol, a nonselective β-blocker, on the antitumor efficacy of the T1012G virus in colorectal cancer models. A cell viability assay showed that cotreatment could induce synergistic killing effects on human and murine colorectal cell lines. Moreover, cotreatment caused sustained tumor regression compared with T1012G monotherapy or propranolol monotherapy in human HCT116 and murine MC38 tumor models. Additionally, propranolol treatment did not produce a positive effect on viral replication in vitro or in vivo. Western blotting showed that cotreatment significantly enhanced the expression of cleaved caspase-3 in HCT116 and MC38 cells compared with the propranolol or T1012G alone. In addition, propranolol or T1012G treatment induced a 35.06% ± 0.53% or 35.49% ± 2.68% reduction in VEGF secretion in HUVECs (P¡0.01/P¡0.01). Cotreatment further inhibited VEGF secretion compared with the monotherapies (compared with propranolol treatment: 75.06% +- 1.50% decrease, compared with T1012G treatment: 74.91% +- 0.68%; P¡0.001, P¡0.001). Consistent with the in vitro results, in vivo data showed that cotreatment could reduce Ki67 and enhance cleaved caspase 3 and CD31 expression in human HCT116 and murine MC38 xenografts. In summary, β-blockers could improve the therapeutic potential

of OVs by enhancing oncolytic virus-mediated killing of colorectal cancer cells and antiangiogenic effects on colorectal tumors.

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