LTX-315, an oncolytic peptide, increases anticancer immunity mediated by CTLA4 blockade in an interleukin-2 receptor beta chain-dependent manner

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ABSTRACT

Intratumoral immunotherapeutics aim at enhancing local immunosuppression as well as reactivating and enhancing systemic anticancer T cell functions without inducing side effects. LTX-315 is a first-in-class oncolytic peptide–based local immunotherapeutic that meets these criteria by inducing a type of malignant cell death that elicits anticancer immune responses. Here, we show that LTX-315 rapidly reprograms the tumor microenvironment by decreasing the local abundance of immunosuppressive Tregs and myeloid-derived suppressor cells and by increasing the frequency of polyfunctional Th1/Tc1 cells with a concomitant increase in the local immunosuppression as well as reactivating and enhancing systemic anticancer T cell functions without inducing side effects. LTX-315 is a cationic peptide with oncolytic properties following intralesional administration in mice and humans. It mediates its anticancer activity against a wide variety of histological tumor types in a T cell-dependent manner by inducing cell death endowed with immunogenic properties. In this preclinical study, we found that LTX-315 can be active against sarcomas that poorly respond to CTLA4 blockade, and that the sequential combination of anti-CTLA4 mAb followed by LTX-315 is synergistic, either using systemic or local delivery of anti-CTLA4 mAb, with a mechanism involving IL-2 receptor beta chain-dependent manner. One of the salient features of LTX-315 is that it can be administered locally, by injection into malignant lesions to locally stimulate anticancer immune responses that suppress the growth of distant tumors, and hence mediate abscessal responses. Moreover, we have accumulated data suggesting that LTX-315 can be advantageously combined with CTLA4 blockade, in particular if CTLA4 blockade precedes or is concomitant to the local administration of LTX-315.