742 MULTI-ARMED MYXOMA VIRUS INDUCES POTENT ANTI-TUMOR RESPONSES IN VITRO AND IN VIVO

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Background Myxoma virus (MYXV) has been shown to selectively infect cancer cells in humans in vitro and inhibit tumor growth in mice. The genome of MYXV is large and amenable to engineering for expression of multiple transgenes. We armed MYXV with mouse or human IL-12 and human decorin. IL-12 is an immune modulator. Cellular responses to decorin include tumor cell intrinsic signaling effects, tumor matrix remodeling, and inhibition of the TGF-beta pathway. We hypothesized that MYXV armed with decorin and IL-12 would be an effective anti-tumor therapy. The current work describes the oncolytic activity and transgene expression, following exposure to armed MYXV in human cancer cell lines in vitro and efficacy in in vivo in murine models, as single agents and in combination with immune checkpoint inhibition.
Methods Cytotoxicity was measured by a cell viability assay. ELISAs were used to detect transgene expression, Caspase-3 activation, and TGF-beta induced SMAD phosphorylation. Mouse tumor models were treated with vehicle control or the indicated virus.
Results MYXV carrying payloads of decorin and mouse IL-12 (vMYX-mIL-12/Dec) or human IL-12 (vMYX-hIL-12/Dec) were tested. Human tumor cell lines infected with vMYX-hIL-12/Dec in vitro showed independent effects when levels of transgene expression and cytotoxicity were compared, suggesting that oncolytic activity and transgene expression differentially contribute to MYXV activity. Virus-free supernatants derived from infected cells suggested a decorin specific response in caspase-3 activation, and inhibition of TGF-beta signaling. Human IL-12 is not active on mouse immune cells giving the opportunity to evaluate the role of decorin in tumor regression. B16-F10 murine melanoma mice treated with vMYX-mIL-12/Dec showed a robust response while vMYX-hIL-12/Dec showed an intermediate anti-tumor response suggesting decorin has cancer inhibitory activity and synergized with IL-12. We tested anti-PD-1 and vMYX-mIL-12/Dec in the colon adenocarcinoma model MC38. We observed that the combination for multi-armed MYXV with an immune checkpoint inhibitor showed dramatically reduced tumor growth and improved survival.
Conclusions Our data demonstrates that MYXV with IL-12 and decorin payloads have cytotoxic activity in vitro and inhibit tumor growth in vivo. Cellular responses to decorin in vitro included inhibition of processes intrinsic to tumor progression. In mouse tumor models decorin played a role in inhibiting tumor progression and synergized with IL-12 implying the combination has immune-modulatory activity. Interestingly, MYXV with IL-12 and decorin payloads significantly synergized with anti-PD-1 in preventing tumor growth, suggesting a potentially new approach towards anti-cancer therapy.
Ethics Approval All studies and procedures involving animals were carried out under the institutional guidelines of Translational Drug Development Institutional Animal Care and Use Committee

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