Complex Role of NK cells in regulation of OV-Bortezomib therapy

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ABSTRACT

Oncolytic viruses such as herpes simplex virus-1 (oHSV) are genetically modified to target and kill cancer cells while not harming healthy normal cells and are currently under multiple clinical trials for safety and efficacy [1]. Bortezomib is a peptide-based proteasome inhibitor and is an FDA-approved drug for myeloma and mantle cell lymphoma. Yoo et al (2) have previously demonstrated that bortezomibinduced unfolded protein response (UPR) in many tumor cell lines (glioma, ovarian, and head and neck) up-regulated expression of heat shock protein 90 (HSP90), which then enhanced viral replication through promotion of nuclear localization of the viral polymerase in vitro. This led to synergistic tumor cell killing in vitro, and a combination treatment of mice with oHSV and bortezomib showed improved anti-tumor efficacy in vivo [2]. This combination therapy also increased the surface expression levels of NK cell activating markers and enhanced pro-inflammatory cytokine secretion. These findings demonstrated that the synergistic interaction between oHSV and bortezomib, a clinically relevant proteasome inhibitor, augments the cancer cell killing and promotes overall therapeutic efficacy. Therefore, there is a sound ground for combining these agents in a clinical trial. In the present paper we investigated the role of NK cells in combination therapy with oncolytic virus (OV) and bortezomib. NK cells display rapid and potent immunity to metastasis and hematological cancers, and they overcome immunosuppressive effects of tumor microenvironment. We developed a mathematical model, a system of PDEs, in order to address the question of how the density of NK cells affects the growth of the tumor [3]. We found that the anti-tumor efficacy increases

when the endogenous NKs are depleted, and also when exogenous NK cells are injected into the tumor. These predictions were validated by our in vivo and in vitro experiments.

REFERENCES

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