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The oncolytic virus ΔPK has multi-modal anti-tumor activity

Oncolytic viruses (OVs) are an emerging cancer therapeutic based on tumor cell lysis by replicating virus and the resulting release of cellular proteins [viz. tumor-associated antigens (TAAs)], which modulate tumor immunogenic cell death (ICD). OVs have a near complete absence of serious adverse events. Unfortunately, clinical efficacy is limited, apparently due to their relatively poor tumor penetration, failure to eradicate tumor-initiating cancer stem cells (CSCs), and inability to alter the strongly immunosuppressive tumor microenvironment. Current strategies to overcome these limitations include the selection of distinct virus platforms, the introduction of an inflammatory cytokine gene and the use of combinatorial therapy. However, clinical efficacy is a delicate balance of forces, between: (i) effective OV replication and virus clearance by the induced antiviral immunity, (ii) antitumor immunity and factors promoting tumor growth, and (iii) immune stimulation and the immunosuppressive nature of the tumor microenvironment. Therefore, altering any one of these parameters may counteract the positive effect of the other parameters and the development of OVs with multi-modal death-inducing activity is the increasingly recognized therapeutic goal.

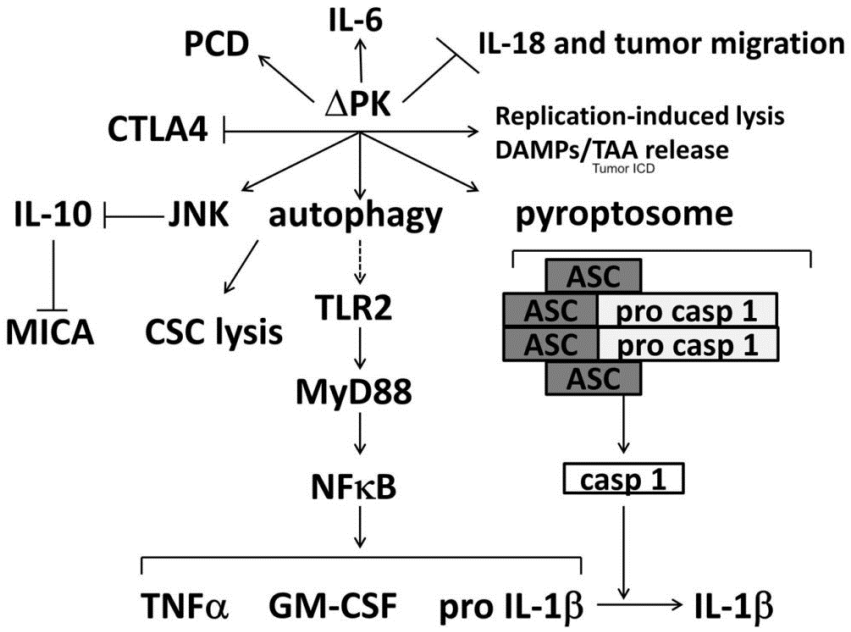

Fig. 1. ΔPK has multi-modal oncolytic activity. ΔPK lyses the tumor cells through virus replication and this results in the release of tumor-associated antigens (TAAs) and damage-associated molecular patterns (DAMPs) that modulate tumor immunity and trigger immunogenic cell death (ICD). It also induces multiple and independent programmed cell death (PCD) pathways including activation of caspase-3, caspase-7, calpain and autophagic cell death, resulting in increased tumor penetration and CSC lysis. Apoptosis is further stimulated by ΔPK-mediated restored expression of the tumor suppressor H11/HspB8, which is inhibited in melanoma. ΔPK-induced ICD includes alteration of the immunosuppressive tumor microenvironment, through: (i) JNK/AP-1-mediated inhibition of the immunosuppressive cytokine IL-10, and (ii) stimulation of the inflammatory cytokines TNF-, GM-CSF, IL-1 and IL-6. TNF- and GM-CSF are upregulated through activation of TLR2/NF-kB pathways; IL-1 through pyroptosis. IL-10 inhibition upregulates MICA, thereby stimulating NK and T cell-mediated tumor cell cytotoxicity. In addition, ΔPK downregulates melanoma cell expression of the negative immune checkpoint regulator CTLA-4, further favoring ICD, and breast cancer cell expression of IL-18, thereby interfering with tumor cell migration.

We developed ΔPK, a Herpes simplex virus type 2 (HSV-2) OV with multi-modal oncolytic activity (Fig. 1) and superior clinical efficacy. Indeed, complete remission was seen in 87.5% of mice bearing human melanoma at 5 months after the last ΔPK injection and survival was 100%. ΔPK is deleted in a protein kinase gene (ICP10PK), which controls both virus growth in normal cells and cell survival, a unique regulatory process which is not conserved in the closely related HSV-1. While ICP10PK deletion reduces virus growth, it also triggers multiple programmed cell death (PCD) pathways (caspases-3,-7, calpain, and autophagic cell death) and restores expression of the tumor suppressor function (H11/HspB8) thereby further stimulating apoptosis. The activated PCD pathways provide distinct and independent cell killing mechanisms, increasing tumor penetration and efficient CSC lysis in both melanoma and breast cancer.

The multi-modal oncolytic activity of ΔPK also includes inhibition of the tumor immunosuppressive microenvironment and ICD. ΔPK inhibits tumor secretion of the immunosuppressive cytokine IL-10 while increasing the secretion of multiple pro-inflammatory cytokines (TNF-a, IL-6, GM-CSF and IL-1b), which counteract immunosuppression. IL-10 down-regulation is through activation of JNK/AP-1 pathways. Its loss blocks recruitment of immune inhibitory T cells (Tregs) and stimulates immune-mediated tumor cell killing through upregulation of MICA, the ligand for the activating receptor NKG2D that is expressed on cytotoxic T and natural killer (NK) cells. TNF-a, IL-6 and GM-CSF upregulation is through the activation of Toll-like receptor factor 2 (TLR2)/NF-kB pathways; IL-1b through pyroptosome-dependent caspase-1 activation. TNF-a and GM-CSF are independently associated with improved efficacy of virotherapy. IL-1b induces robust and durable primary and secondary CD4+ T cell responses and IL-6 enhances cytotoxic T cell responses and therapeutic immunity by counteracting Tregs-mediated immunosuppression. Moreover, ΔPK inhibits expression of the negative T cell function regulator CTLA-4 that is constitutively expressed by melanoma cells in order to maintain immune tolerance. It also inhibits IL-18, a pro-inflammatory cytokine that is expressed by breast cancer cells and is involved in tumor cell migration and escape from immune surveillance (Fig. 1). Significantly, ΔPK was well tolerated in phase I clinical trials in which it was shown to inhibit immunosuppressive CD4+Th2 cells while inducing the overriding CD4+ Th1 cells. The clinical efficacy of ΔPK in other tumor types is currently under investigation.

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