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Cytotoxic and immunogenic mechanisms of recombinant oncolytic poliovirus

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An oncolytic virus (OV) based on poliovirus (PV), the highly attenuated polio/rhinovirus recombinant PVSRIPO, may deliver targeted inflammatory cancer cell killing; a principle that is showing promise in clinical trials for recurrent glioblastoma (GBM). The two decisive factors in PVSRIPO anti-tumor efficacy are selective cytotoxicity and its *in situ* immunogenic imprint. While our work is focused on what constitutes PVSRIPO cancer cytotoxicity, we are also studying how this engenders host immune responses that are vital to tumor regression. We hypothesize that PVSRIPO cytotoxicity and immunogenicity are inextricably linked in essential, complimentary roles that define the anti-neoplastic response. Herein we delineate mechanisms we unraveled to decipher the basis for PVSRIPO cytotoxicity and its immunotherapeutic potential.

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Introduction

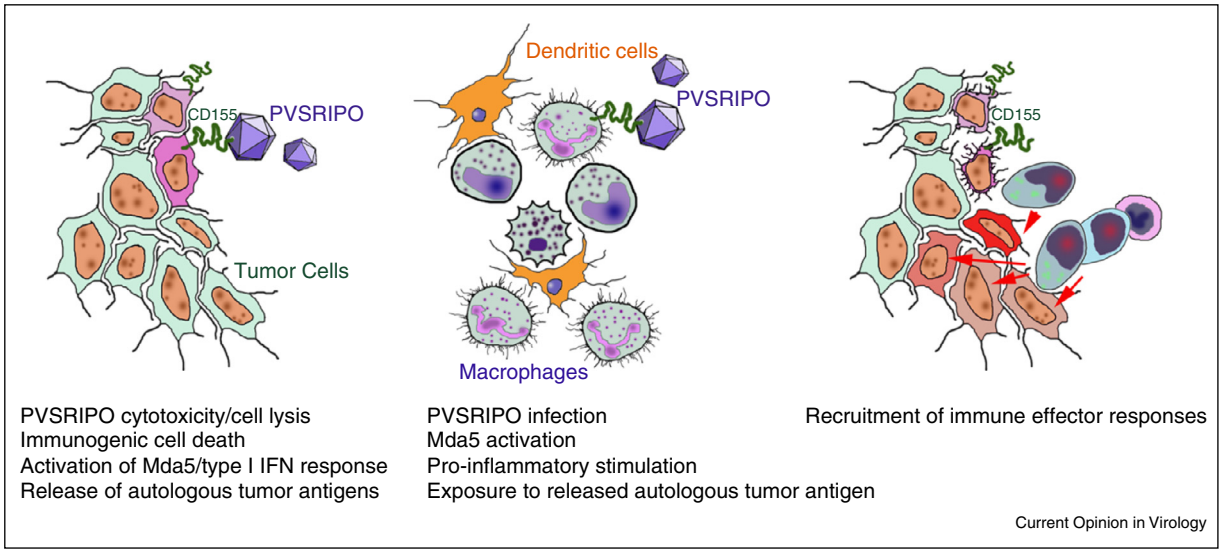
Immunotherapy approaches that bolster immune effector responses against cancer have gained traction after demonstrating significant clinical responses in several indications [1]. These therapies reverse tumor-induced blockades that skew inflammatory responses to favor tumor expansion and persistence and thereby unmask the tumor to the host immune system. Efficacious immunotherapy approaches rely upon the immune system's ability to recognize and react to the distress ligands and neo-antigens present in all cancer cells. Viruses offer a unique advantage for immunologically 'revealing' tumors, having co-evolved with mammalian immune systems for millennia and training our immune system to recognize and kill infected and/or damaged cells.

OVs may recruit immune effector responses through a two-pronged mechanism: infecting and directly lysing cancer cells while simultaneously activating inflammatory anti-viral pathways (Figure 1). Among the major requisite attributes for OVs is documented affinity and specificity for malignant tissue in patients. Our group has developed an attenuated recombinant oncolytic PV that relies on a confluence of many factors to deliver inflammatory cytotoxicity specifically to cancer cells (Figure 1). This strategy was inspired by founding work, demonstrating that replacement of the cognate PV internal ribosomal entry site (IRES), essential for driving translation initiation at the PV RNA genome, with that of the human rhinovirus 2 (HRV2) completely abolishes the inherent, grim neurovirulence of PV [2]. The recombinant, called PVSRIPO for PV (Sabin)-Rhinovirus IRES PV Open reading frame, is derived from the (Sabin) live-attenuated type 1 vaccine strain of PV [3]. PVSRIPO is currently being evaluated in a Phase-I clinical trial against recurrent GBM, where it has shown durable complete radiographic and clinical responses in several patients [4]. Critical mediators of PVSRIPO's clinical efficacy are its uniquely simple, swift and violent cytotoxicity and its unique relation to Mda5, an intriguing cytosolic pattern recognition receptor (PRR) with a powerful immunogenic range [5] (Figure 1). We are working fervently to identify mechanisms mediating both of these aspects of PVSRIPO oncolytic immunotherapy, as they will likely open opportunities to broaden and enhance clinical application.

The PV receptor CD155 in cancer

To be successful, OVs must have tropism for tumor tissue and/or stromal components, usually determined by host cell surface entities (receptors) participating in virus attachment and entry functions. PV tropism is exceedingly simple, because all attachment and entry events are mediated by a single molecule, necessary and sufficient for PV host cell entry, the Ig-superfamily cell adhesion molecule CD155 (a.k.a. PVR, Necl5) [6]. Although the physiologic roles of CD155 remain poorly defined, its arguably most intriguing attribute is near-universal ectopic upregulation in solid neoplasia [7]. This is certainly true for GBM [8], as demonstrated in immunoblots from a panel of primary patient explant GBM xenotransplantation lines with diverse molecular signatures (e.g. with regard to PTEN and AKT status; Figure 2). CD155 has been shown to enhance cancer cell motility and invasiveness [9], regulate NK cell activity [10], and become transcriptionally up-regulated during DNA damage signaling [11]. It is plausible that near-ubiquitous CD155

Figure 1



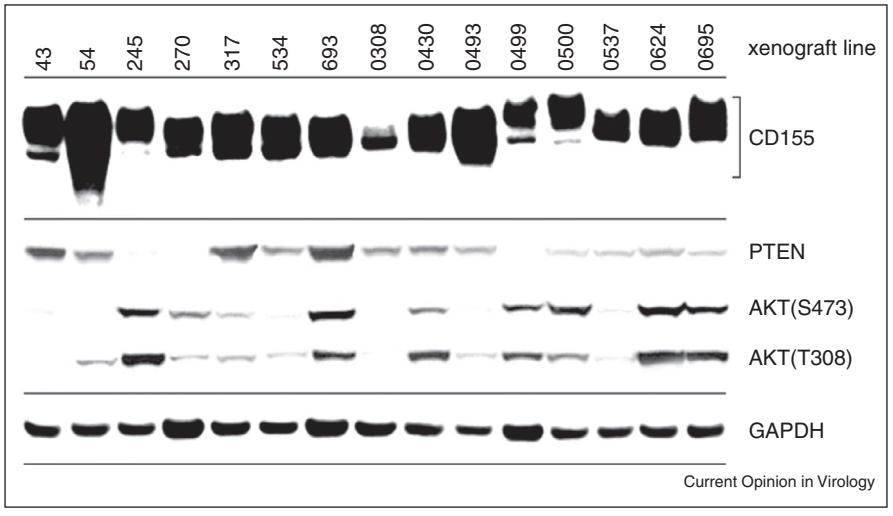
Hypothetical model of PVSRIPO oncolytic immunotherapy mechanisms. A combination of (left) direct viral tumor cytotoxicity and engagement of Mda5/the anti-viral IFN response; and (middle) PVSRIPO non-lethal infection and pro-inflammatory stimulation of tumor-associated macrophages (TAM) and/or dendritic cells; (right) recruits immune effector responses directed against tumor neo-antigens.

expression in cancer is due to selective pressure from one or more of these functions.

Of interest, for example, in the context of GBM where macrophages and myeloid-derived suppressor cells (MDSCs) comprise a significant portion of tumors, CD155 is also expressed on antigen-presenting cells (APCs; explaining its designation as a cluster of differentiation molecule [12,13]; Figure 1). Wild-type PV infection of these cells leads to their pro-inflammatory activation and facilitates antigen presentation/immune effector functions [13]. We confirmed these findings for PVSRIPO and are working to assess how APC infection by PVSRIPO may contribute to antitumor efficacy in murine models.

Upon binding CD155, the PV capsid undergoes a conformational expansion, extruding the myristoylated capsid protein VP4 and externalizing the N-terminus of VP1.

Figure 2



CD155 expression is common in GBM. Primary patient explant GBM xenografts (passaged exclusively in mice) were harvested and lysed for immunoblot analysis. CD155 (variable electrophoretic mobility is due to distinct glycosylation patterns), PTEN, p-AKT(S473) and (T308), and GAPDH were analyzed by immunoblot.