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Armed oncolytic viruses: A kick-start for anti-tumor immunity

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ABSTRACT

Oncolytic viruses (OVs), viruses that specifically result in killing tumor cells, represent a promising class of cancer therapy. Recently, the focus in the OV therapy field has shifted from their direct oncolytic effect to their immune stimulatory effect. OV therapy can function as a "kick start" for the antitumor immune response by releasing tumor associated antigens and release of inflammatory signals. Combining OVs with immune modulators could enhance the efficacy of both immune and OV therapies. Additionally, genetic engineering of OVs allows local expression of immune therapeutics, thereby reducing related toxicities. Different options to modify the tumor microenvironment in combination with OV therapy have been explored. The possibilities and obstacles of these combinations will be discussed in this review.

1. Introduction

1.1. The anti-tumor immune response and the immune profile of tumors

The innate and the adaptive immune system work together to detect transformed cells and remove them before they form a tumor [1]. The anti-tumor response starts with the release of tumor associated antigens (TAA) from dying cancer cells and accompanying signal molecules, which attract and activate cells of the innate immune system [2,3]. Whereas NK and γd-T cells can recognize and kill tumor cells directly, antigen presenting cells (APCs), such as DCs and macrophages, take up TAAs to activate the adaptive immune system [4,5]. The maturation of APCs by the accompanying danger signal molecules determines the skewing to a preferred T helper cell (Th) 1 response. These Th1 signals constitute of pro-inflammatory cytokines, such as interleukin (IL)-12, type I interferons (IFNs) and tumor necrosis factor (TNF), and damage-associated molecular pattern molecules (DAMPs), such as nuclear protein HMGB1, heat-shock proteins and ATP, [3]. The Th1 cytokines stimulate the generation of tumor specific cytotoxic CD8+ T cells (CTLs), which are crucial effector cells in the antitumor response [6]. Subsequently, effector T cells, including T helper cells and CTLs, are attracted to the tumor site via a gradient of T cell attracting chemokines, including chemokine (C-C motif) ligand 2 (CCL2), CCL5/RANTES, chemokine (C-X-C motif) ligand 9 (CXCL9), and CXCL10 [7]. At the site, CTLs recognize and kill tumor cells mediated by MHCI-T cell receptor interactions. If the immune system succeeds in destruction of the beginning tumor, the host remains free of cancer.

In some cases, tumor cells are reprogrammed to evade the immune system resulting in an equilibrium between dying tumor cells and tumor cells surviving the immune attack. As a consequence, a selection of immunosuppressive or less immunogenic tumor cell variants is introduced, which cannot be eliminated by the immune system [8]. These tumor cells establish a tumor microenvironment (TME), in which the function of anti-tumor immune cells is attenuated (Fig. 1) [9]. **First of all,** tumor cells and stromal cells (endothelial and epithelial cells and fibroblasts) produce factors such as transforming growth factor-β (TGF-β), prostaglandin E2 (PGE2) and IL-10, that disrupt APC maturation in the TME [3,7,9]. As a result, DCs isolated from the TME often display a partly matured, immune suppressive phenotype and secrete cytokines that induce non-favorable Th2 responses [7]. **Secondly**, tumors inhibit infiltration of effector T cells by repressing the production of T cell attracting chemokines CXCL9/10 and modification of CCL2 [7,10].

Abbreviations: AdV, adenovirus; ATP, adenosine triphosphate; APC, antigen presenting cell; CTLA-4, cytotoxic T lymphocyte antigen 4; CTL, cytotoxic T lymphocyte; CXCL/CCL, C-X-C motif ligands; DAMPs, damage-associated molecular pattern molecules; DC, dendritic cell; GITRL, glucocorticoid-induced TNFR-related protein; GM-CSF, granulocyte-macrophage colony-stimulating factor; HMGB1, high-mobility group protein B1; HPGD, hydroxyprostaglandin dehydrogenase; HSV, Herpes Simplex Virus; IAV, influenza A virus; IDO, indoleamine 2,3-dioxygenase; IFN, interferon; IL, interleukin; LAG-3, lymphocyte-activation gene 3 protein; MDSC, myeloid derived suppressor cell; MHC, major histocompatibility complex; MV, measles virus; MYXV, myxoma virus; NDV, Newcastle diseases virus; NK, natural killer; OV, oncolytic virus; PD-L1, programmed death ligand 1; PGE2, prostaglandin 2; TAA, tumor associated antigen; TGF, transforming growth factor; TIM-3, T cell immunoglobulin domain and mucin domain-3; TME, tumor microenvironment; TNF, tumor necrosis factor; VSV, vesicular stomatitis virus; VV, vaccinia virus

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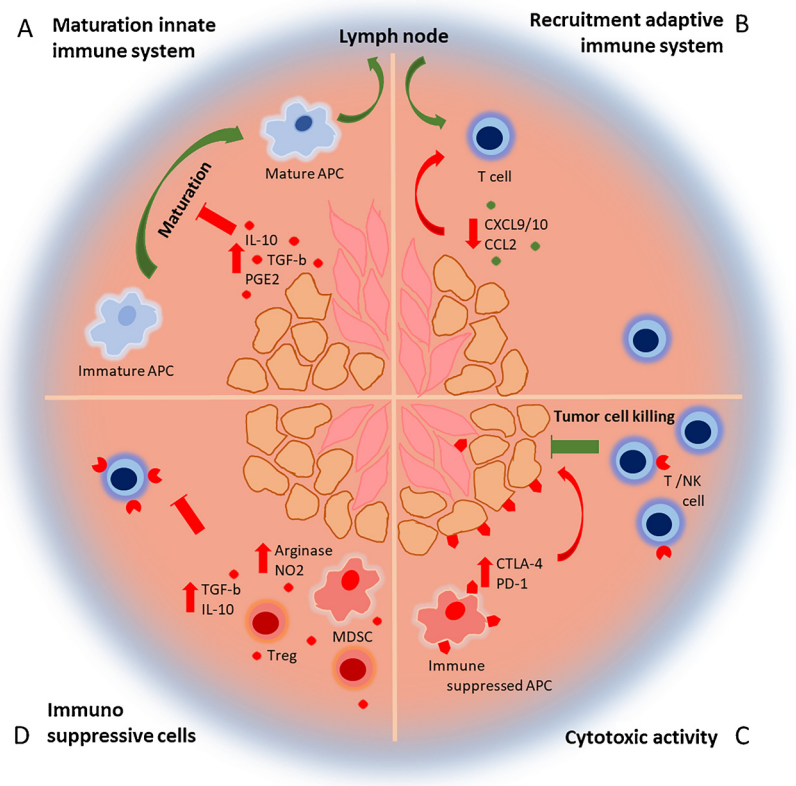

Fig. 1. The immunosuppressive tumor micro environment. (A) Tumor cells (orange) and stromal cells (pink) secrete immune suppressive molecules, which inhibit the maturation of APCs. Maturated APCs migrate to the lymph node to activate the adaptive immune system. (B) As a result, activated T cells migrate to the tumor driven by a chemokine gradient. However, the secretion of chemokines is lowered in the tumor resulting in reduced T cell infiltration. (C) T cells that enter the TME to target the tumor cells are inhibited by immune suppressive receptors expressed by the tumor, stromal cell, but also immune suppressed APCs. (D) Tregs and MDSCs are recruited to the TME, which secrete more immune suppressive molecules and inhibit the T cell response even further.

Thirdly, effector T cells that can infiltrate the tumor are attenuated by expression of several immunosuppressive molecules and persistent exposure to tumor antigens. As a result, T helper cells and CTLs isolated from the TME often present an exhausted phenotype, characterized by high level expression of immune checkpoint receptors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) [10]. Ligation of these receptors with their ligands expressed on tumor and stromal cells, but also immunosuppressed APCs, leads to inhibition of the tumor specific T cell response. **Fourthly**, regulatory immune cells such as CD4+ regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) are recruited to the tumor site. Similar to tumor cells, Tregs secrete IL-10, Indoleamine 2,3-dioxygenase (IDO) and TGF-β, leading to further attenuation of the T cell response [7,11]. Furthermore, Tregs consume IL-2, which is indispensable for T cell activation [7]. MDSCs contribute to the suppression of effector T cells through production of arginase and nitric oxide, which deprives T cells from amino acids necessary for proliferation [12].

Despite all these evasion mechanisms, CTLs and Th1 T helper cells are still considered to be the most crucial effector cells in anti-tumor immunity and their infiltration into the TME is associated with good prognosis in various types of cancer [13]. Proper activation of these cells is key for an effective antitumor response and the abundance of mechanisms used by tumors to suppress these cells offers many targets for cancer immunotherapy strategies.

At the moment, multiple strategies to target the TME are being explored. Recent successes have led to the FDA approval of checkpoint inhibitors anti-CTLA-4 (clinical responses in 10–15% of treated patients) and anti-PD1 (clinical responses in 30–40% of patients) for treatment of melanoma [14,15]. Clinical trials have shown that dual, synergistic blockage improved antitumor responses against melanoma, indicating that it might take more than one approach to induce powerful and long lasting anti-tumor immunity [16,17]. However, systemic administration of these checkpoint inhibitors, as well as other immunotherapies, often coincides with severe immune-related adverse effects similar to autoimmune diseases [16,17]. A promising treatment option to potentially overcome this obstacle is oncolytic virotherapy.

1.2. Oncolytic viral therapy

Oncolytic virotherapy is an approach that uses oncolytic viruses (OVs), either with natural tropism for neoplastic cells or genetically modified to enhance selectivity for tumor cells [18,19]. Tumor cells often lack an adequate antiviral response, making them more susceptible to OV infection than healthy cells. The viral infection leads to tumor regression through two distinct mechanisms: direct killing of tumor cells by replication dependent induced cell death and promotion of an antitumor response towards all tumor cells, including non-infected cells, by inducing immunogenic cell death. Types of immunogenic cell death, such as immunogenic apoptosis, necrosis and autophagic cell death, are characterized by the release of TAAs in combination with DAMPs and viral pathogen associated molecular patterns (PAMPs) [19]. Following the secretion of DAMPs and cytokines, more innate immune cells, such as macrophages, DCs, NK cells and neutrophils infiltrate the tumor environment. The immune stimulating cytokine secretion leads to maturation of APCs and hence presentation of TAAs and viral antigens to activate the adaptive immune system in the lymph nodes. Cytotoxic T cells will start infiltrating the tumor again and specifically eliminate cancer cells. Simultaneously, memory T cells are formed, which improves protection against new tumor challenges in mouse models [20,21]. Therefore, it is evident that OV therapy can function as a ‘kick start’ for the antitumor immune response by providing TAAs in an immunogenic manner and inducing infiltration of immune cells.

Recently, the focus in the oncolytic virotherapy field has shifted from their oncolytic effect to their immune stimulatory effect. Recombinant OVs armed with immune modulators further enhance the activation of the immune system and overcome the immunosuppressive TME [18]. The first armed OV approved by the FDA is oncolytic Herpes-Simplex-Virus (HSV)-1 expressing GM-CSF showing improvement of