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Mini Review

Oncolytic virotherapy improves immunotherapies targeting cancer stemness in glioblastoma

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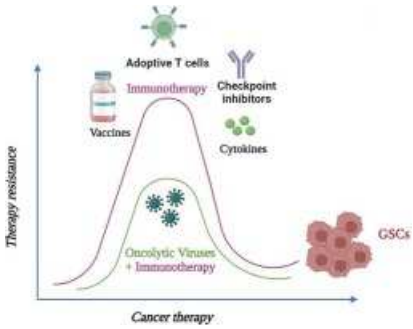
Highlights

- OVs have potency in selecting and killing tumor cells, recruiting effector immune cells to tumor sites.
- OVs mediating targeting of the GSCs niche can reprogram TME of GBM.
- Targeting cancer stemness through engineered OVs improves antitumoral responses.
- The combination of OVs and immunotherapies significantly improved outcomes in the GBM model.

Abstract

Despite advances in cancer therapies, glioblastoma (GBM) remains the most resistant and recurrent tumor in the central nervous system. GBM tumor microenvironment (TME) is a highly dynamic landscape consistent with alteration in tumor infiltration cells, playing a critical role in tumor progression and invasion. In addition, glioma stem cells (GSCs) with self-renewal capability promote tumor recurrence and induce therapy resistance, which all have complicated eradication of GBM with existing therapies. Oncolytic virotherapy is a promising field of therapy that can kill tumor cells in a targeted manner. Manipulated oncolytic viruses (OVs) improve cancer immunotherapy by directly lysis tumor cells, infiltrating antitumor cells, inducing immunogenic cell death, and sensitizing immune-resistant TME to an immune-responsive hot state. Importantly, OVs can target stemness–driven GBM progression. In this review, we will discuss how OVs as a therapeutic option target GBM, especially the GSC subpopulation, and induce immunogenicity to remodel the TME, which subsequently enhances immunotherapies' efficiency.

Graphical abstract



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Introduction

Glioblastoma (GBM) is the most aggressive tumor in the central nervous with a poor prognosis and survival rate of almost 15 months. GBM affects 3.2 per 100,000 people and causes ~200,000 death toll annually [1]. Despite current standard therapies for newly diagnosed GBM (i.e., tumor resection, alkylating antineoplastic agent temozolomide (TMZ), radiation, and combination therapies), the survival rate has reached 20 months with high recurring [2]. Although immune checkpoint blockade (ICB) therapy is promising in various cancers, it has shown limited efficacy in GBM [3].

Tumor heterogeneity has been considered a top hallmark of advanced solid cancers, in particular GBM, and is used as a framework for predicting progression and therapeutic responses [4]. Moreover, poor immune infiltration, low expression of checkpoint molecules (i.e., PD-1, PD-L1, and CTLA-4), genetic mutations, and local and systemic immunosuppression are other major reasons that intensify therapy resistance in GBM [5].

Glioblastoma stem cell (GSC) is the leading player in this framework that begin tumor-initiating cell populations and refractories to treatment [6]. Many studies have shown that GSCs have high plasticity and can proliferate through self-renewal and differentiation, thereby contributing to intratumoral cellular heterogeneity in GBM [7,8]. To prevail in the therapeutic resistance mechanisms of GSCs, it is crucial to have a comprehensive insight into resistance mechanisms and the surrounding niche of GSCs to increase targeted therapy's efficacy. Because of their unique properties, targeting GSCs may provide an unprecedented opportunity for GBM therapy [9]. In this regard, investigation for refining standard treatments to improve

poor disease outcomes is essential.

Oncolytic virotherapy is a promising immunotherapy approach that selectively infects and lyses malignant cells [10,11]. OVs induce releasing pathogen−/damage-associated molecular patterns (PAMP/DAMP) to prepare tumor niches for antitumor responses [12]. Recently, a phase 2 clinical trial of G47Δ (an oHSV) for recurrent glioblastoma has shown that intratumoral administration of G47Δ led to increasing tumor-infiltrating CD4+/CD8+ lymphocytes and reduced level of regulatory cells, thereby stable the disease progression for two years [13]. Up to now, several studies have shown the effectiveness of the zika virus (ZIKV) and herpesvirus (HSV) against GSCs [14]. Here, we will review strategies to exploit oncolytic viruses (OVs) as therapeutic tools and targets in GBM therapy, including how engineering OVs can target GSCs, strategies to reshape and activate immunosuppress microenvironment to overcome GBM immune resistance.

Section snippets

GSCs or stemness drive GBM resistance to immunotherapy

GSCs represent a rare population of cells in the tumor environment with high potency in self-renewal, drug resistance, and cancer relapse. According to previous studies, resistance to standard therapies can be divided into three categories i) radiotherapy (RT), ii) chemotherapy, and iii) immunotherapy [15]. DNA damage following RT is the most prevalent phenomenon that causes DNA double-strand breaks (DSB). ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related) axis and two…

OVs target GBM resistance to immunotherapy CAR production

OVs, defined as the third leg of cancer immunotherapy, mainly target and kill tumor cells and mediate anticancer effects by inflaming the tumor, recruiting antigen-presenting cells in TME, and boosting the activity of anticancer agents [23,24]. Historically, for the first time (in 1896) a 42 years old woman suffering from leukemia presented remission after getting a natural influenza infection [25]. OVs-mediated tumor cell destruction involves two main mechanisms including direct lysis of…

OVs targeting GSCs or stemness to overcome GBM immune resistance

GSCs are a self-renewable population of tumor bulk that can differentiate and contribute to tumor expansion, resistance, recurrence, and metastasis [27]. As noted above, to overcome GBM resistance, it is necessary to have deep insight into inherent mechanisms and surrounding niches of GSCs for targeted therapy [27]. Different factors, including the high capacity of DNA repair, hypoxic niche, and intrinsic signaling pathways, closely correlate with GSCs resistance and can be used as targets for…

Conclusion and future direction

Increasing evidence suggests that four major microenvironments niches (inflammation, hypoxia, perivascular, and infiltrative/invasive front) surrounding GBM tumors create a challenging situation to treat [86]. OVs with incredible potency in selecting and killing tumor cells, recruiting cellular components, and changing the paradigm in TME of GBM. Multiple studies have reported the pivotal role of inflammation in the pathogenesis and evolution of GBM [87,88]. In fact, aberrations in the…

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CRediT authorship contribution statement

Mohsen Keshavarz: Writing – original draft, Visualization, Supervision, Investigation, Conceptualization. **Hassan Dianat-Moghadam:** Writing – review & editing, Visualization, Project administration, Conceptualization. **Seyedeh Sara Ghorbanhosseini:** Writing – original draft, Investigation. **Behrang Sarshari:** Writing – original draft, Investigation, Data curation....

Declaration of competing interest

The authors declare that the research was conducted without any commercial or financial relationships that could be construed as a potential conflict of interest....

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