Protective role of STING against gliomagenesis: Rational use of STING agonist in anti-glioma immunotherapy

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Introduction

Glioma accounts for approximately 40% of all primary brain tumors and are responsible for approximately 13,000 cancer-related deaths in the US each year, representing a large unmet medical need. We have previously demonstrated the protective role of type I interferon (IFN) signaling against glioma progression using a clinically relevant de novo mouse glioma model, and identified single nucleotide polymorphisms (SNPs) in human IFNA genes associated with the prognosis of glioma patients.1 However, it remained elusive how type I IFNs were induced in the glioma microenvironment. We have recently demonstrated that type I IFNs are induced in de novo glioma tissues and directly impact on functions of immune cells.2 Glioma-bearing brain tissues showed higher levels of type I IFNs than non-tumor-bearing brains. Using a type I IFN-reporter mice (tdTomato mice), type I IFN signaling was detected in a variety of glioma-infiltrating immune cell populations. Especially, type I IFN signaling downregulated Foxp3 and Tgfb1 expression levels and immuno-suppressive activity in CD4+ T cells, while upregulated Tbx21 and Ifnreg expression levels and cytotoxic activity in CD8+ T cells, suggesting that type I IFN signaling directly enhances antitumor activity of T cells in the glioma-microenvironment.

We next focused on the signaling mechanism responsible for the type I IFN production in the glioma microenvironment. STING (stimulator of IFN genes) plays a critical role as one of the adaptors for cytosolic DNA sensing thereby triggering type I IFN production.3 Due to the presence of apoptotic or necrotic cells in the tumor microenvironment, we hypothesized that double strand DNA (dsDNA) such as genomic DNA (gDNA) from the dead cells would induce type I IFN signaling through STING. Using wild type (WT) and STING-deficient (StingGt/Gt) mouse-derived macrophages, we demonstrated in vitro that gDNA upregulated type I IFN mRNA levels at least partially in a STING-dependent manner. Also, in the glioma microenvironment compared with WT mice, these observations suggest that STING is at least partially responsible for spontaneous type I IFN production in glioma and positively affects the activity of immune cells in the glioma microenvironment (Fig. 1).

On the basis of these observations, we attempted to evaluate if administration of STING agonist would enhance the anti-glioma immunity. Intratumoral administration of STING agonist improved the efficacy of peptide vaccination in a mouse glioma model, suggesting the rational use of STING agonists in the immunotherapy of brain tumor.
enhances antiglioma immunity by enhancing the recruitment of T cells into the brain tumor site. Moreover, administration of c-di-GMP significantly enhanced the efficacy of peptide vaccinations targeting a tumor-specific antigen by recruiting peptide-specific CD8+ T cells in the tumor site. This strongly supports the development of combination strategy with vaccine and a STING agonist. Although we selected c-di-GMP as a STING ligand in this study due to its commercial availability, there are more agonists for STING such as c-di-AMP, cGMP-AMP (2’3’cGAMP or 3’3’cGAMP), or 10-carboxymethyl-9-acridanone (CMA).4,5 Moreover, while activities of bacterium-derived c-di-GMP can be dependent upon SNPs in human STING, metazoan-derived 2’3’cGAMP stimulate STING regardless of the SNP status.6 These observations warrant inclusion of 2’3’cGAMP in our studies evaluating STING agonists as adjuvants in cancer immunotherapy.7 On the basis of our current study, early-phase clinical studies are warranted to evaluate the safety and efficacy for intratumoral administration of a STING agonist in patients with glioma as well as other tumors.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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