Stimulator of interferon genes (STING)

Stress conditions such as UV irradiation, exposure to genotoxic agents, stalled DNA replication, and even tumors trigger the release of cytosolic genomic DNA (cgDNA). Classically, cgDNA induces interferon response via its binding to proteins such as STING.

STING contributes to antiglioma immunity by triggering type I interferon (IFN) induction in glioma microenvironment. Moreover, 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 [1].

Although type I IFNs play critical roles in antiviral and antitumor activity, it remains to be elucidated how type I IFNs are produced in sterile conditions of the tumor microenvironment and directly affect tumor-infiltrating immune cells. Mouse de novo gliomas show increased expression of type I IFN messages, and in mice, CD11b(+) brain-infiltrating leukocytes (BIL) are the main source of type I IFNs that are induced partially in a STING (stimulator of IFN genes)-dependent manner. Consequently, glioma-bearing Sting(Gt) (/Gt) mice showed shorter survival and lower expression levels of Ifns compared with wild-type mice. Furthermore, BILs of Sting(Gt) (/Gt) mice showed increased CD11b(+) Gr-1(+) immature myeloid suppressor and CD25(+) Foxp3(+) regulatory T cells (Treg) and decreased IFNγ-producing CD8(+) T cells. CD4(+) and CD8(+) T cells that received direct type I IFN signals showed lesser degrees of regulatory activity and increased levels of antitumor activity, respectively. Finally, intratumoral administration of a STING agonist (cyclic diguanylate monophosphate; c-di-GMP) improved the survival of glioma-bearing mice associated with enhanced type I IFN signaling, Cxcl10 and CCL5, and T-cell migration into the brain. In combination with subcutaneous OVA peptide vaccination, c-di-GMP increased OVA-specific cytotoxicity of BILs and prolonged their survival. These data demonstrate significant contributions of STING to antitumor immunity via enhancement of type I IFN signaling in the tumor microenvironment and suggest a potential use of STING agonists for the development of effective immunotherapy, such as the combination with antigen-specific vaccinations [2].

Human and mouse breast and lung cancer cells express protocadherin 7 (PCDH7), which promotes the assembly of carcinoma-astrocyte gap junctions composed of connexin 43 (Cx43). Once engaged with the astrocyte gap-junctional network, brain metastatic cancer cells use these channels to transfer the second messenger cGAMP to astrocytes, activating the STING pathway and production of inflammatory cytokines such as interferon-α (IFNα) and tumor necrosis factor (TNF). As paracrine signals, these factors activate the STAT1 and NF-κB pathways in brain metastatic cells, thereby supporting tumour growth and chemoresistance. The orally bioavailable modulators of gap junctions meclofenamate and tonabersat break this paracrine loop, and provide proof-of-principle that these drugs could be used to treat established brain metastasis [3].

1)
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