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Review

Rationale for stimulator of interferon genes–targeted cancer immunotherapy

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Abstract The efficacy of checkpoint inhibitor therapy illustrates that cancer immunotherapy, which aims to foster the host immune response against cancer to achieve durable anticancer responses, can be successfully implemented in a routine clinical practice. However, a substantial proportion of patients does not benefit from this treatment, underscoring the need to identify alternative strategies to defeat cancer. Despite the demonstration in the 1990's that the detection of danger signals, including the nucleic acids DNA and RNA, by dendritic cells (DCs) in a cancer setting is essential for eliciting host defence, the molecular sensors responsible for recognising these danger signals and eliciting anticancer immune responses remain incompletely characterised, possibly explaining the disappointing results obtained so far upon the clinical implementation of DC-based cancer vaccines. In 2008, STING (stimulator of interferon genes), was identified as a protein that is indispensable for the recognition of cytosolic DNA. The central role of STING in controlling anticancer immune responses was exemplified by observations that spontaneous and radiation-induced adaptive anticancer immunity was reduced in the absence of STING, illustrating the potential of STING-targeting for cancer immunotherapy. Here, we will discuss the relevance of manipulating the STING signalling pathway for cancer treatment and integrating STING-targeting based strategies into combinatorial therapies to obtain long-lasting anticancer immune responses.

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1. Introduction

Immunologists have long considered that the primary function of the immune system is to distinguish between self and non-self. However, the idea that the immune system only reacts to foreign organisms and is tolerant to self was difficult to reconcile with observations that individuals could feature antibodies to self-antigens, including DNA. In 1994, Polly Matzinger challenged the so-called self non-self theory and proposed instead that the driving force that makes the immune system effective lies on its ability to recognise danger [1]. Among the immune cell types able to detect danger, dendritic cells (DCs) are of central importance because of their ability to capture, process and present antigens to T cells [2]. The detection of danger by DCs relies on their expression of pattern recognition receptors (PRRs), which permit sensing, integration and transmission of danger signals to induce adaptive immunity. PRRs include membrane C-type lectins, toll-like receptors (TLRs), cytoplasmic nucleotide binding oligomerization domain (NOD)-like receptors and DNA/RNA sensors [3,4]. These receptors allow DCs to sense pathogens as well as endogenous danger signals released from dying cells such as DNA [5,6]. These recognition mechanisms in DCs can be harnessed to generate more efficient cancer vaccines. For instance, immunogenicity of peptide-protein vaccines can be enhanced by the addition of adjuvants. These include agonists of various TLRs such as TLR3 (poly I:C), TLR4 (monophosphoryl lipid A), and TLR9 [cytosine phospho guanosine (CpG)] [7–12].

The functional properties of DCs prompted their use as a tool in cancer immunotherapy with the aim of inducing anticancer immune responses. Initially, the use of non-targeted short peptides captured by DCs *in vivo* demonstrated that major histocompatibilty complex (MHC) class I-restricted antigen-specific $CD8^+$ T cell immunity could be mounted in patients with metastatic disease [13–15]. The clinical successes were yet limited, possibly because of the lack of $CD4^+$ T cell help necessary for the generation of potent cytotoxic T lymphocytes and long-lived memory $CD8^+$ T cells [16–18]. While the clinical ineffectiveness of dendritic cell-based vaccines is attributable to the immunosuppressive cancer microenvironment that curtails the induction of anticancer immune responses [19,20], the impressive successes of checkpoint inhibitor therapies, which result in 20–40% complete responses in some metastatic cancers, illustrate that cancer-induced immunosuppression can be pharmacologically overcome and anticancer immunity restored [21,22]. This altogether suggests that a better knowledge of DC biology is required to design DC vaccines able to reverse tumour-induced immunosuppression and elicit long-term anticancer responses.

DNA is a potent immune stimulatory molecule widely used as vaccine adjuvant to drive immunity [4,23]. Initially, TLR9 was identified as the sensor for DNA. TLR9 recognises pathogen derived CpG DNA to trigger innate immune signalling predominantly in plasmacytoid dendritic cells [24]. TLR9 was also shown to be responsible for the detection of self-DNA, leading to autoimmunity [25,26]. While TLR9 was promoting immune signalling following its interaction with DNA in endosomes, the mechanisms responsible for the detection of cytosolic DNA were unclear until the characterisation of STING (stimulator of interferon genes).

In 2008, STING was described as a transmembrane component of the endoplasmic reticulum essential for the production of type I interferon (IFN) in fibroblasts, macrophages and DCs in response to cytoplasmic double-stranded DNA (dsDNA) as well as select DNA viruses and intracellular bacteria [27,28]. Interestingly, STING does not share homology with any known immunosensor and seems to represent a novel category of proteins involved in immune signalling in the context of cytosolic DNA presence, with an ability to link the majority of DNA sensors to immune signalling [29,30]. The detection of DNA indeed relies on a variety of cytoplasmic DNA sensors, including the cyclic GMP-AMP synthase (cGAS) [31]. The discovery of cGAS in 2013 actually represented a significant advance in our understanding of the signalling mechanisms underpinning innate DNA sensing. After binding to cytosolic DNA species from viruses, bacteria or self-DNA from the nucleus or mitochondria, cGAS catalyses the production of a type of cyclic dinucleotide (CDN) named cGAMP (cyclic GMP–AMP) [32,33]. Following binding to CDNs, STING activation leads to the phosphorylation of interferon regulatory factor 3 (IRF3) and nuclear factor-κB and the subsequent induction of cytokines and proteins, such as the type I IFN that exert anti-pathogen activities [28,34]. STING was proposed to be activated by other cytoplasmic DNA sensors, including DAI, DHX9, DHX36, IFI204 (IFI16), DDX41, DXX60, Pol III, LRRFIP1, DNA-PK, cGAS and the DNA repair protein Mre11 [35], that bind DNA directly and act upstream of STING to induce type I IFNs [30]. This together defines STING as an adaptor protein that is essential for immune signalling following pathogen DNA detection by cytoplasmic DNA sensors (reviewed in Ref. [36]). Recent reports have also indicated that potent activators of the STING pathway may also include self-DNA that has leaked from the nucleus of the host cell, perhaps following cell division or as a consequence of DNA damage [37]. STING is thus central to the induction of immune responses following DNA detection.

In this review, we discuss recent findings illustrating the links between STING signalling in immune and cancer cells and cancer progression. We also describe emerging strategies that exploit the STING signalling pathway to enhance anticancer immune responses. We