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Targeting innate immune pathways for cancer immunotherapy

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Abstract

The innate immune system is critical for inducing durable and protective T cell responses to infection, and has been increasingly recognized as a target for cancer immunotherapy. In this review, we present a framework wherein distinct innate immune signaling pathways activate five key dendritic cell activities that are important for T cell mediated immunity. We discuss molecular pathways that can agonize these activities and highlight that no single pathway can agonize all activities needed for durable immunity. The immunological distinctions between innate immunotherapy administration to the tumor microenvironment versus administration via vaccination are examined, with particular focus on the strategies that enhance dendritic cell migration, interferon expression, and interleukin-1 family cytokine production. In this context, we argue for the importance of appreciating necessity vs sufficiency when considering the impact of innate immune signaling in inflammation and protective immunity, and offer a conceptual guideline for the development of efficacious cancer immunotherapies.

eTOC

Innate immune pathways are commonly discussed targets of cancer immunotherapy. Cao and Kagan review the state of this rapidly advancing field of study. They introduce the concept that five key innate immune activities in dendritic cells are needed to stimulate durable T cell mediated anti-tumor immunity.

Introduction

Cancer immunotherapies represent a notable example of how basic scientific explorations can impact human health. A wealth of fundamental biochemistry and genetic studies have identified modulators of T cell function that impact inflammation and immunity. Examples in this area include investigations of membrane proteins that potentiate or suppress T cell receptor (TCR) signaling activities, such as CD40, CD80 and CD86, which potentiate

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J.C.K consults and holds equity in Corner Therapeutics, Larkspur Biosciences and Neumora Therapeutics. J.C.K. is listed as an inventor on patents filed by Boston Children's Hospital on the use of novel dendritic cell stimuli in a therapeutic setting. None of these relationships influenced this study.

TCR signaling activities, and PD-1 and CTLA4, which suppress TCR functions[1,2]. These proteins are known respectively as costimulatory and coinhibitory molecules, with the latter representing targets of therapies that promote anti-tumor immunity[3–5].

Despite these successes in translating basic science discoveries into clinical treatments of disease, the benefits of T cell directed cancer immunotherapy are not comprehensive. Therapies that target T cell coinhibitory receptors (*e.g.* PD-1 or CTLA4) are effective at treating a minor spectrum of patients with cancer[6]. A contributing factor to immunotherapy unresponsiveness is the paucity of tumor T cell infiltration, characterizing non-inflamed or "cold" tumors. Mechanisms involved in the absence of T cell infiltration include the lack of tumor antigens, defects in antigen presentation, and poor T cell activation and homing into the tumor bed[7]. Therefore, an objective of cancer immunobiology is to identify ways to convert cold tumors to inflammatory T cell enriched "hot" tumors. Innovations towards this goal may derive from the one area of biology where the immune system has been successfully weaponized to provide life-long immunity to disease—infection.

Inquiries of how infectious agents induce durable and protective immunity have been ongoing for many years[8,9]. Yet, the molecular basis of pathogen detection remained elusive long after the molecular descriptions of T cell activation were underway. The descriptions of the pattern recognition receptors (PRRs) of the innate immune system, expertly reviewed in 2002 by Janeway[10], provided a conceptual framework to discuss infection-mediated induction of adaptive immunity. PRRs are a structurally unrelated set of proteins that share the ability to interact with microbial products, typically cell wall components or nucleic acids. Upon microbial detection by PRRs expressed by dendritic cells (DCs), several immunostimulatory activities are triggered that promote T cell mediated immunity. Examples of PRRs include the Toll-like Receptors (TLRs), RIG-I like Receptors (RLRs), nucleotide binding domain leucine rich repeat containing proteins (NLRs), c-type lectin receptors (CLRs), and the enzyme cyclic GMP-AMP synthase (cGAS). The detailed mechanisms by which PRRs sense and respond to microbes and their products has been described in detail elsewhere[11–14]. In this review, we discuss PRRs that control key activities of DCs needed to stimulate T cell mediated immunity, and how PRR-targeted therapies may be utilized to advance the goal of tumor eradication.

Innate immune signaling pathways in DCs that stimulate durable T cell mediated immunity

Due to their unique ability to stimulate naïve T cells, there has been longstanding interest in targeting DCs using vaccines or cell-based immunotherapies. There are five key activities in DCs that are needed to stimulate new and long-lived antigen-specific T cell responses (Figure 1). These activities include 1) MHC-mediated presentation of protein antigens, 2) T cell costimulatory molecule expression, 3) Effector T cell activating cytokine expression, 4) DC migration to the lymph node that drains the cancerous or infected tissue, and 5) production and release of the memory inducing cytokines interleukin (IL)-1β and type I interferon (IFN). The former cytokine (IL-1β) mediates CD4+ and CD8+ T cell activities[15–17] whereas the latter (IFN) primarily mediates CD8+ T cell activities[18–20]. Each

of these five DC activities is necessary for the differentiation of naïve T cells into robust and durable mediators of anti-infective and anti-tumor immunity. PRRs have attracted much attention in this area, as chemical mimics of microbial cell wall components or nucleic acids can elicit several of these activities from DCs. For example, TLR signaling on DCs promotes antigen capture[21], and loading on MHC-I and MHC-II[22,23]. TLRs also promote the expression of T cell costimulatory molecules, including CD40, CD80 and CD86[24], and the expression of IL-12[25] and type I IFNs[26], which are key cytokines that induce type 1 CD4+ T cell and cytolytic CD8+ T cell effector responses to infection and cancer. RLRs[27] and cGAS[28] also stimulate DCs to drive the above-described T cell activities, and represent particularly potent inducers of type I IFN production (Figure 2). However, it is becoming increasingly appreciated that not all PRRs elicit similar DC activities and distinct subsets of DCs express different repertoires of PRRs[29]. In addition, recent studies have suggested that PRR stimulation is not sufficient to activate all five activities in DCs that are key to stimulate durable lymphocyte responses (Figure 2). For example, robust induction of DC migration does not occur when PRRs are activated. In the case of respiratory syncytia virus (RSV) infections, DC migratory activities from the lung to the draining lymph node were intact in mice lacking MyD88 and MAVS[30], which regulate TLR and RLR signaling respectively[13,27]. In contrast, RSV-induced cytokine and costimulatory molecule expression were ablated in the absence of MyD88 and MAVS[30]. Similarly, while TLR ligand injection into the skin induces some migration of DCs to the draining lymph nodes, this activity is not maximal and can be substantially enhanced by other DC stimulants, as discussed below[17].

Like migratory activities, TLRs and most other PRRs are unable to elicit IL-1β production from DCs, the absence of which results in deficiencies in memory T cell induction and re-activation[16,17,31,32]. Whereas TLRs are robust inducers of pro-IL-1β production, the cleavage and release of this cytokine into the extracellular space is not mediated by TLR, RLR or cGAS signaling alone[33]. Rather, TLR signaling must occur in conjunction with a second signal, which often represents cellular injury or dysfunction, in order for DCs to release bioactive IL-1β into the extracellular space. The cellular injury signals that promote pro-IL-1β cleavage and release are numerous, yet commonly result in the assembly of a protein complex in the DC cytosol called the inflammasome[34]. The inflammasome is one of several supramolecular organizing centers (SMOCs), which represent the signaling organelles of the innate immune system. In the TLR, RLR and cGAS pathways, distinct SMOCs are assembled that activate inflammatory transcription factors such as NF-κB, AP-1 and IFN regulatory factors (IRFs)[35]. Inflammasomes, in contrast, do not stimulate transcription, but rather serve as a subcellular site of inflammatory caspase activation, commonly caspase-1[36]. Caspase-1 can cleave pro-IL-1β into its bioactive state and also cleave the pro-protein gasdermin D (GSDMD), which forms plasma membrane pores[37–41]. These GSDMD pores may serve as conduits for IL-1β secretion or (if unrepaired by the cell) may promote a lytic form of cell death known as pyroptosis[37–41]. As TLRs, RLRs and cGAS are not effective inducers of inflammasome assembly, these PRRs are unable to stimulate production of bioactive IL-1β.

The significance of the role of IL-1β for induction of adaptive immunity dates to the earliest descriptions of this cytokine as a lymphocyte activating factor (LAF)[42–45]. More recently, Paul and colleagues revealed that CD4+ and CD8+ T cell responses to protein antigens

are enhanced when adjuvants are supplemented with recombinant IL-1β[32,46]. Genetic analysis has revealed the requirement of IL-1 receptor signaling on T cells for memory cell generation[16]. In the context of cancer, the use of adjuvants that induce IL-1β release from DCs was effective at inducing long-lived populations of resident memory CD8+ T cells that protect mice from multiple implantable tumor models[17,31]. However, not all inducers of IL-1β production from DCs are capable of stimulating T cell mediated anti-tumor immunity. Stimuli that elicit inflammasome activities that promote DC pyroptosis are robust inducers of IL-1β production, but the death of the DC interferes with all other activities for antigen-specific T cell generation[17,47]. Examples of pyroptosis-inducing inflammasome agonists include aluminum hydroxide and QS-21, both of which agonize the NLRP3 inflammasome and induce pyroptosis[48,49]. These chemicals are used clinically as adjuvants and represent robust inducers of antigen-specific antibody responses[50,51]. However, their utility in generating cytolytic and T helper cell type 1 (TH1) responses is limited, as the death of DCs associated with these stimuli likely undermines the days-long T cell interactions needed to stimulate adaptive immunity[52]. There are distinct NLRP3 agonists that promote inflammasome activities in the absence of pyroptosis. These agonists include a set of oxidized lipids, typified by the chemical PGPC (1-palmitoyl-2-glutaryl-sn-glycero-3-phosphocholine), which are naturally released from damaged cells[53]. When murine DCs are stimulated with TLR ligands and PGPC, IL-1β is added to the repertoire of cytokines these cells can produce while maintaining viability. These DCs also display heightened migratory activities compared to DCs stimulated with TLR ligands or aluminum hydroxide alone[17,54,55] (Figure 2).

The enhanced migratory and IL-1β production activities of DCs exposed to TLR ligands and PGPC demonstrate that PRR stimulations alone are not sufficient to maximally elicit all five of the key activities needed to stimulate T cell mediated immunity. As such, DCs stimulated with TLR ligands and PGPC are more immunostimulatory than DCs that have been activated with TLR ligands (or aluminum hydroxide) alone[17,56] (Figure 2). In reference to the term “active”, which historically defines TLR stimulated cells, DCs exposed to TLR ligands and PGPC have been termed “hyperactive”. *In vitro* studies have demonstrated that murine type 1 or type 2 DCs (*i.e.* cDC1 or cDC2) can achieve a hyperactive state, and that CD8+ T cell mediated anti-tumor immunity is dependent on cDC1s in mice[57]. Studies in human monocyte-derived DCs demonstrated that similar activation states exist, and hyperactive human cDC2s are associated with an enhanced ability to elicit TH1 and TH17 cell differentiation[58]. Consistent with the idea that hyperactive DCs are more immunostimulatory than other DC activation states, recent work has found that TLR ligand + PGPC-based adjuvants generate CD8+ T cell responses to model tumor antigens to a greater extent than TLR ligands or aluminum hydroxide adjuvants alone[17]. This increased generation of antigen-specific T cells through the use of DC hyperactivating adjuvants is associated with durable protective immunity to implantable tumor models in mice[17].

When considering the above-described data from the perspective of therapeutic development, a critical theme emerges. No single innate immune pathway can elicit all five of the key activities in DCs needed to stimulate durable T cell immunity. Additionally, we consider that much effort in vaccine development has rightfully focused on the identification of cancer-associated (or microbial) antigens. These antigens may serve as guides for

the induction of T cell mediated immunity[59]. However, antigen identification is but one component of the process needed for efficient induction of adaptive immunity. The ability for a vaccine to induce protective immunity is not only dependent on the antigen(s) selected, but also on the DC stimulant used. DC stimulants, *i.e.* adjuvants, that stimulate all key activities in DCs may confer more robust and durable T cell responses to said antigen, and may be the missing puzzle piece that drives the immunogenic conversion of cold tumors to hot tumors. In the following sections, we discuss this concept further by describing current efforts at harnessing innate immune pathways as tools for cancer immunotherapy. In each instance, we discuss the approach in terms of reported efficacy, and how the approach relates to the five key DC activities needed to stimulate T cell mediated immunity. By using this five activity guideline, we aim to explain successes and disappointments in immunotherapy approaches, and potentially to provide a logic-based operating plan for future immunotherapy development.

Using growth factors to increase intra-tumoral DC abundance

Conventional type I (cDC1) and type 2 (cDC2) DCs represent the principal antigen presenting cells that generate new T cell responses to cancer antigens, yet the abundance of these cells in tumors is often low[60–62]. The low abundance of DCs within a cancerous (or infected) tissue is considered a bottleneck for antigen delivery to the lymph node in the context needed for naïve T cell stimulation[63]. To alleviate this bottleneck, efforts have been taken to increase DC abundance through the use of the DC differentiation factor FMS-like tyrosine kinase 3 ligand (FLT3L)[64]. While FLT3L-based immunotherapies have efficacy in several models of cancer, and in some trials in humans, these approaches also demonstrated that new DC generation is not sufficient to confer immunity. FLT3L-based approaches need to be combined with DC stimulatory approaches to ensure the increase in DC abundance correlates with an increase in the types of T cell responses needed for anti-tumor immunity.

FLT3L treatments inhibit the growth of murine solid tumors including colon carcinoma, prostate cancer, Lewis lung carcinoma, melanoma, and lymphoma[65–68]. In addition, adoptive cellular therapy with T cells expressing FLT3L triggered DC proliferation within tumors and lymphoid tissues, enhanced type I IFN pro-inflammatory signatures, and promoted antitumor activity in solid tumor models in mice[69]. Studies that use FLT3L as part of combined therapies have advanced us a step further. For instance, a multipronged approach involving *in situ* immunomodulation with FLT3L along with TLR3 and CD40 co-stimulation (and radiotherapy) enhanced DC-mediated T cell recruitment and triggered regression of multiple orthotopic tumor models in mice[70]. In murine melanoma models, systemic administration of FLT3L followed by intra-tumoral treatment with TLR3 ligands expanded and activated DC progenitors in the tumor proper, sensitized the tumors to antibodies that blocked the interactions between the coinhibitory receptors PD-1 and PD-L1, and protected these mice from tumor re-challenge[62]. Immunostimulatory gene therapy using adenoviruses expressing FLT3L and thymidine kinase promoted antitumor immunity and improved survival in murine model of brainstem glioma, and is currently being tested in the clinic[71]. Finally, in a clinical trial, *in situ* vaccination with a combination of FLT3L, radiotherapy, and a TLR3 agonist induced anti-tumor T cell responses and cancer remission in patients with advanced stage indolent non-Hodgkin's lymphomas[72]. These collective

studies support the idea that innate immune cell numbers are key to enhance anti-tumor immunity, but that increasing DC abundance is not sufficient for protection. Innate immune activities within these DCs are required to extract the benefit of FLT3L-based therapies.

Using DC stimulants (*i.e.* adjuvants) to increase T cell stimulatory cytokine production

Stimuli of PRRs, including TLRs and cGAS, have been explored as means to increase inflammatory DC activities and enhance anti-tumor immunity[73,74]. These efforts can be grouped into two categories: direct immunostimulation via injection of PRR ligands into the tumor microenvironment (TME) or indirect immunostimulation through the use of PRR ligands as adjuvants in cancer vaccines. A distinction between these approaches is the tissue in which the immunotherapy is delivered. In the case of cancer vaccines, the therapy is typically delivered via injection into a healthy region of the body distal to the diseased (*i.e.* cancerous) tissue. Injection into the healthy skin, for example, may stimulate cells other than DCs. Local macrophage, fibroblast or endothelial cell responses that exist at the site of injection may result in reactogenicity (swelling, pain), but these symptoms are usually resolved without consequence[75]. The stimulated DCs at the injection site, in contrast, migrate to the lymph node that drains the injection site and represent the key agents of T cell stimulation. The exposure of non-DCs to innate immune agonists at the site of vaccine injection may therefore have a temporary impact, in terms of local reactogenicity, but the long-term effects of the vaccine are largely mediated by other cell types. This statement may not apply when considering injections of innate immune stimuli into the TME. In the TME, innate immune agonists may impact cancer, stroma, and immune cells in ways that could either potentiate or undermine anti-tumor immune responses. Furthermore, as discussed in the accompanying review by Pittet and colleages[76], complex environmental conditioning cues result in significant DC heterogeneity within the TME. DC subsets have differential and overlapping capacity to capture, traffic, and present tumor antigens to naïve T cells in tumor draining lymph nodes[77]. There is also accumulating evidence of impactful intra-tumoral DC-T cell crosstalk during the development of anti-tumor immunity. For instance, there are subsets of tumor resident DCs that express chemokines and costimulatory signals that facilitate homing and differentiation of immature T cells into antigen-specific effector T cells within the tumor proper[78,79]. Intra-tumoral DCs are also thought to be important in re-stimulating previously activated effector T cells. Therefore, DC-subset specificity and compartmentalization sculpt T-cell immunity. Importantly, this idea means that the variable nature of the TME, between patients as well as throughout the disease course in an individual, translates into unpredictability in response to intra-tumoral therapeutic delivery of innate immune stimuli (compared to vaccination approaches). In the following section, we discuss examples of beneficial and potentially non-beneficial effects of intra-tumoral delivery of innate immune stimuli.

Within the TME, normal or cancerous cells are abundant, as are cell death events. The factors released by damaged cells in the TME can stimulate TLRs, cGAS and likely other PRRs. Examples of such factors include heat shock proteins, ATP, nucleic acids, uric acid, calcium regulatory protein S100 family, and nuclear protein high mobility group box 1[80].

Activation of TLRs by this diverse repertoire of damage associated molecular patterns (DAMPs) modulates signaling pathways in a cell and context-specific manner. For instance, TLR stimulation in DCs is pivotal for priming antigen presentation and inducing cytotoxic T cell responses. In macrophages, TLR stimulation promotes M2 to M1 phenotypic switching, expression of costimulatory molecules and immunostimulatory cytokines, and consequently antitumor immunity[81]. Furthermore, TLR activation facilitates differentiation of myeloid-derived suppressor cells (MDSC) towards an M1 phenotype and enhances tumor regression in mice[82]. TLR ligation on T and B cells may promote their survival, as well as cytokine, antibody, costimulatory molecule expression, and effector functions[83,84]. Interestingly, in tumor cells, TLR signaling can have conflicting functions. TLRs may facilitate interactions with immune cells to reverse immune suppression[85] and promote tumor apoptosis[86]. However, TLRs on tumor cells can also promote tumor stemness, resistance to cytotoxic lymphocyte attack, and tumor cell proliferation and metastasis[87].

As evidenced above, the predominant effect of TLR simulation on the diverse population of cells in the TME is anti-tumorigenic, prompting TLR agonists to be studied as immunotherapies. For instance, the TLR2 agonists Pam3Cys and SMP-105 are under investigation in bladder cancer[88]. The TLR3 agonists polyI:C and ARNAX have been shown to enhance effector T cell responses and tumor suppression[89–91]. The TLR4 activators AS04, MPLA, and GLA-SE have been tested in experimental and clinical trials to treat cervical cancer and lymphoma[92]. Flagellin, an agonist of TLR5 and multiple NAIPs in the NLR family, has been studied in the context of head/neck and prostate cancers[93,94]. The TLR7 agonist imiquimod has been tested in several gynecologic cancers. Finally, several variations of CpG oligodeoxynucleotides have been tested as TLR9 agonists in the treatment of a range of tumors[95]. A central feature of all TLR-based immunotherapies is their ability to induce several key activities described in Figure 1. These activities include the induction of antigen-presentation, T cell co-stimulation, T effector cell cytokines, and type I IFNs from responding DCs (and macrophages). The impact of type I IFNs is notable here, as these cytokines are key drivers of cytolytic T cell activities in the TME, as well as analogous Natural Killer (NK) cell activities[96]. As such, type I IFN production has emerged as a functional biomarker of an effective intra-tumor innate immunotherapy. This need for a robust type I IFN response in the TME even extends to chemotherapies, where IFN gene expression profiles are associated with protective immunity[97].

Based on the emerging importance of type I IFNs as a key aspect of intra-tumoral protective immunity, non-TLR pathways that drive IFN responses have attracted attention. Notable examples include the pathways activated by cGAS and its downstream effector protein (which is also a PRR) STING. These proteins induce inflammatory responses typified by type I IFNs to double stranded DNA. Under normal circumstances, DNA is sequestered from the cytosolic space. However, tumor cells are prone to leak DNA into the cytosol, due to a combination of genomic instability, oxidative stress, and metabolism dysregulation[74]. This leaked DNA may be detected by cGAS, which consequently activates its latent enzymatic activity to produce a cyclic dinucleotide (CDN) known as cyclic 2’3’ GMP-AMP (cGAMP). cGAMP, as well as other CDNs, represent ligands for STING that activate inflammatory and IFN responses that are key to stimulate cytolytic and inflammatory T and NK cell responses to cancer. cGAS or STING activation and type I

IFN release from DCs have been shown to augment DC maturation, antigen processing and presentation, migration, tumor antigen-specific T cell priming and activation, and maintenance of cytotoxic T cell stemness[98–102]. In addition, cGAS-STING activation in tumor cells can be anti-tumorigenic by inducing apoptosis[103,104]. STING activation has beneficial effects in several preclinical cancer models[105–108], leading to strong clinical interest in the development of cGAS and STING agonists.

Several *in vitro* and murine tumor models have supported the benefits of natural CDNs that activate STING-induced type I IFN responses in controlling tumor growth and prolonging survival[109–111]. CDNs have also been tested as a cancer vaccine adjuvant and shown antitumor effects in murine models of colon, pancreatic, and upper airway squamous cell carcinoma[112]. The use of these agonists has been limited however, by their instability and low bioavailability. New strategies have explored how to overcome these limitations, including optimizing delivery of CDNs (*e.g.* in biopolymer implants or liposomal nanoparticles)[113,114], as well as structurally modifying the molecules to enhance their stability and potency[115]. Non-CDN STING agonists are also being researched. For instance, a CDN analogue called lavone-8-acetic acid derivative 5,6-dimethylxanthenone-4-acetic acid (DMXAA) suppresses the growth of many mouse models of cancer, including B16 melanoma, in a STING dependent manner[115]. Unfortunately, DMXAA clinical trials have been limited because its interaction is restricted to mouse STING. Therefore, recent studies are exploring DMXAA analogues that may be more efficient at activating human STING[116]. There is also a growing body of research that supports the use of STING agonists as adjuvants with chemotherapy and radiotherapy[110,117]. In addition, STING agonists have been shown in preclinical tumor models to increase the efficacy of T cell directed immunotherapies, such as those targeting coinhibitory receptors[118–120]. However, as was discussed for TLRs, emerging evidence has revealed that cGAS-STING signaling may have pro-tumorigenic functions. This pathway can contribute to a immune-suppressive tumor environment by mobilizing regulatory T cells and myeloid derived suppressor cells (MDSCs), some of the most important suppressors of anti-tumor immunity[121]. In addition, STING signaling is reported to promote tumor cell metastasis by activating noncanonical NF-kB signaling and epithelial-to-mesenchymal transition[122].

Targeting CCR7 to direct DC migration to lymph nodes

After activation, DCs must traffic to the tumor draining lymph nodes, rich in T cells, to initiate adaptive immune responses. The CCR7-CCL19/CCL21 axis guides DCs to their lymph node destination. CCR7 is a G protein-coupled chemokine receptor that can be upregulated by PRRs on DCs and activated by PRR-induced lymph node-homing chemokines CCL19 and CCL21[123]. PRR-induced expression of CCR7 ligands throughout the lymphatic system establishes a gradient that facilitates directional movement of DCs toward their cognate T cells within lymph nodes[124,125]. CCR7 oligomerization and stimulation results in downstream phosphorylation by Src and activation of a variety of molecular pathways including P13K/AKT, MAPK/NF-kB, and HIF-1a signaling[126–128]. The molecular targets of many of these pathways in the regulation of immune cell migration remain elusive, but likely regulate actin cytoskeleton rearrangement, metabolic

reprogramming, as well as protein and epigenetic modifications that collectively influence the migration of DCs toward their destination[129–133].

Aside from DCs, CCR7 can be expressed by cancer cells and potentiate metastasis. In the setting of this dichotomy, studies on the role of CCR7 in tumorigenesis have led to discrepant results[134]. CCR7 expression in lung cancer seems to correlate with better survival prognosis[135], whereas in other circumstances (breast, pancreatic, gastric, colorectal) correlate with metastasis and poor survival prognosis[136–140]. Therefore, CCR7 and its ligands play two important but conflicting roles in tumorigenesis; whether targeting CCR7 using agonists or antagonists is more appropriate for cancer intervention remains debatable. Subsets of pre-clinical studies have shown that CCR7 agonism using intra-tumoral administration of CCL21 or CCL19 ligands potentiate DC and T cell influx into the tumor proper, and antitumor immune response[141,142]. Direct delivery of chemokines, however, has been challenging due to system toxicities. Therefore, recent studies have focused on targeted and controlled delivery of these chemokines using nanoparticles, gene modification, and incorporation into CAR T cell therapy. For instance, a vault nanoparticle encapsulating CCL21 has been developed with promising *in vitro* and *in vivo* results[143]. Murine B16-BL6 melanoma cells transfected to express CCL19 had a slower rate of growth after transplantation, as compared with control counterparts[144]. *In vivo* transfection of CCL19 or CCL21 via intra-tumoral injection of adenoviral vectors encoding these chemokines into murine B16-BL6 melanoma and colon carcinoma reduced tumor growth[145,146]. Co-expression of CCL19 in CAR T cells reduced growth of solid tumors and prolonged survival in mice[147]. Finally, DCs transfected *in vitro* to express CCR7 demonstrated enhanced ability to migrate to draining lymph nodes, and to mediate an anti-tumor response in melanoma and lung cancer models[148–150]. Clinical relevance of this approach was assessed in a phase I trial involving intra-tumoral injection of CCL21-gene modified DCs into patients with lung cancer, which resulted in an enhanced tumor-specific CD8 T cell response[151]. These are just a few of many examples illustrating the clinical potential of exploiting CCR7 in immunotherapy.

Targeting IL-1 signaling to stimulate memory T cells

While TLR and STING agonists are becoming increasingly sophisticated in therapeutic use, a fundamental aspect of immune system function may undermine the utility of these PRR ligands as agents of immunotherapy. This aspect relates to the aforementioned inability of TLR or cGAS-STING agonists alone to induce IL-1β production (Figure 2). IL-1β is a cytokine that has the potential to act both as a general inflammatory agonist in the TME and to maximize memory T cell responses to cancer antigens[31,32]. The receptor for IL-1β is a heterodimer of IL-1R1 and IL-1RacP, which is referred hereafter as IL-1R. IL-1R is expressed by a variety of cell types, including cancer cells, T and B cells, fibroblasts and endothelial cells. IL-1R signaling via its downstream adaptor protein MyD88 is essential to generate memory CD4+ or CD8+ T cells[152]. Past studies have hinted at the potential anti-tumor benefits of IL-1β. For instance, enhanced IL-1β production in mice vaccinated with irradiated melanoma or with *ex vivo* matured/antigen-loaded DCs is associated with enhanced antigen presentation by DCs, antigen-specific T cell activity, and ultimately control of tumor growth[153,154]. Chemotherapy activates NLRP3 inflammasome in DCs,

IL-1β release, and cytotoxic T cell responses that suppress tumor growth[155]. Based on this evidence, vaccination approaches that seek to stimulate long-lived T cell responses would likely benefit from the use of DC hyperactivators as adjuvants to potentiate IL-1β production. In the TME, agonists of IL-1β production may also be beneficial, as IL-1R signaling on memory T cells is key to reactivating their effector functions, including TH1, TH2 and TH17 cells[16]. Consistent with this idea, supplementing T cell therapy with IL-1β improves anti-tumor responses, such as in adoptive T cell therapy of a murine melanoma model[156].

However, as was the case of TLR and cGAS-STING agonists, IL-1R signaling in the TME may also have pro-tumor functions. For instance, IL-1β can enhance recruitment of MDSCs and stimulate IL-17 production by CD4+ T cells that in turn promote tumor growth[155,157–159]. IL-1β can also promote endothelial cell activities that enhance angiogenesis, leading to metastasis[160]. These potential pro-tumor functions of IL-1β have led to speculation that neutralization of this cytokine would promote anti-tumor immunity. Suggestive clinical data to support this theory was offered by a clinical trial initially designed to study Canakinumab (an IL-1β neutralizing antibody) in heart disease. In this trial, circumstantial evidence suggested the ability of the drug to lower lung cancer incidence and mortality[161]. However, a trial to formally assess Canakinumab as an anti-tumor therapy did not yield promising results[162]. This lack of clinical efficacy may be explained by the need for IL-1R signaling to promote T cell responses in cancer. Immunotherapies that promote IL-1 mediated T cell responses may be required to further explore this possibility. Ultimately, the complex role of IL-1 signaling in tumor immunity is likely reflected by its diverse function in a background of heterogenetic tumor environments.

Concluding Remarks

Strategies of inducing anti-tumor immunity are diverse, yet all derive from the focal point of how our body responds to infectious agents. Here we have focused on distinct innate immune agonists and signaling pathways, and how they may be used as agents of cancer immunotherapy. We discussed datasets illustrating that not all innate immune pathways and DC activation states are equivalent. Different DC agonists (and tissues of agonism) may impact the effectiveness of an immunotherapy. Much of what we discussed can be considered prophetic, as we have far more pre-clinical data to interpret than clinical data for innate immunotherapies. Despite this prophetic nature, the lessons learned on how one can use our basic understanding of DC and T cell biology to create new cancer therapies will likely guide the future of innate immunity. As our knowledge of innate immune pathways increases, so will therapeutic opportunities. Importantly, this knowledge will not only inform the future, but will also help explain the past. For example, the paradigm of the five key DC activities needed for T cell immunity (Figure 1) may explain the successes and disappointments of prior approaches to host defense.

In considering immunotherapy approaches of the past, a central point of consideration is that there exists a fundamental distinction between pathways that are necessary and pathways that are sufficient to induce protective immunity. Several pathways have been described as necessary for inflammatory activities in diverse contexts of disease.

Inhibition of any necessary pathway will result in immunosuppression and represents a potential treatment for autoimmune or autoinflammatory disease. For example, TNFα, IL-1R and IL-23 inhibition all offer protection (to varying extents) against autoimmune or autoinflammatory diseases in mice and humans. However, while a pathway may be necessary for inflammation, it may not be sufficient to induce protective immunity. This concept may explain why single target immunotherapies are more effective as tools of immunosuppression than immunostimulation. For example, strategies that target individual molecules and pathways among the five key DC activities have been used clinically as a means of immunostimulation. IL-12R agonists (using recombinant IL-12p70), costimulatory molecule agonists (using CD40 antibodies, recombinant CD40 ligand, or OX40 antibodies), and inducers of type I IFNs have all been attempted for use in a therapeutic setting against cancer, as have individual PRR agonists[163–165]. None of these approaches would be expected to elicit all five of the key DC activities needed to orchestrate robust T cell mediated immunity. In considering the future, approaches that directly agonize all five of the key DC pathways may prove useful. Yet much remains to be learned. We do not yet know the therapeutic potential of distinct DC activation states for most murine models of cancer, particularly in genetically engineered and spontaneous models which may better represent human disease. We also have not fully appreciated the complexity of the DC-T cell crosstalk during tumorigenesis, and how this translates into potential differences in the efficacy and side-effect profile of intra-tumoral versus vaccination approaches of delivering different innate immunostimulants. Another unknown is whether immune responses against leukemia depend on these five key dendritic cell activities to the same extent as solid tumors, especially given the disseminated nature of the disease and lack of an obvious tumor draining lymph node. DCs play an important role in the elimination of leukemic cells[166], and research has explored the use of TLR and STING agonists in the treatment of leukemia[105,167]. However, clinical trials testing DC stimulants in the treatment of blood cancers is only in the preliminary phases (NCT01842139, NCT01834248). Finally, as Pittet and colleagues discuss in their accompanying review[76], we do not know the degree of T cell clonality resulting from DC agonistic treatment, and the relationship between innate and adaptive immunotherapies. Addressing these unknowns will require time, and an increased investment in the basic understanding of immune system functions is necessary. The value of such an investment cannot be overstated, as the impact of human health may be felt for generations to come.

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Highlights

1. Lessons from infection-induced immunity inform cancer immunotherapy development
2. Five key dendritic cell (DC) activities stimulate long-lived anti-tumor T cells
3. No single innate immune pathway stimulates all five protective DC activities
4. Next-generation cancer vaccines and intra-tumoral immunizations are in development

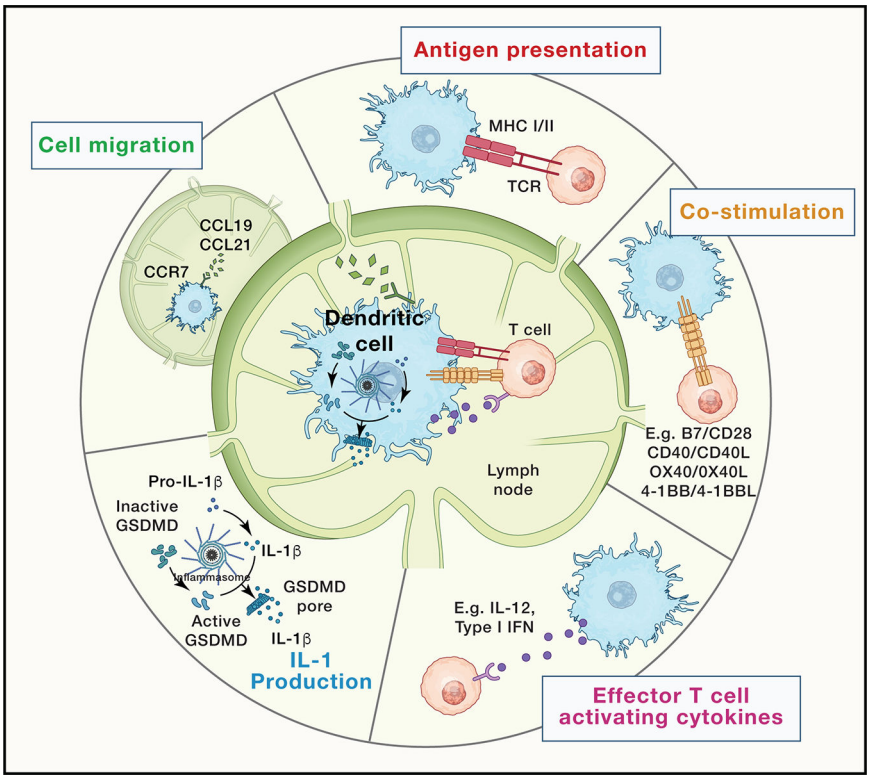

Figure 1. Five key activities in DCs that are needed to stimulate new and long-lived antigen-specific T cell responses.

A generalized, color-coded depiction of these key activities (antigen presentation, co-stimulation, immunostimulatory cytokine production, IL-1 production, cell migration) is provided at the center of the figure and elaborated at the periphery.

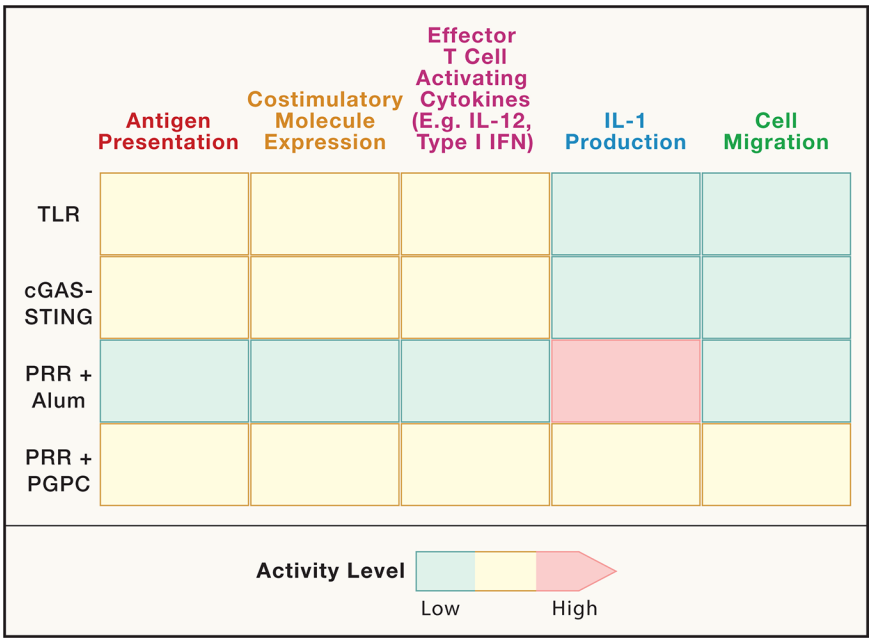

Figure 2. The effect of various innate immune stimuli on the key DC activities.

Relative capacity for different innate immune agonists (TLR, cGAS, with and without adjuvants aluminum hydroxide (alum) or PGPC) to stimulate the key DC activities that are important for eliciting optimal T cell mediated immunity. We note that not all innate immune agonists are shown (*e.g.* ligands for CLRs) and not all have been examined in the same studies. As such, the relative intensity of innate immune activities depicted should be considered speculative and may be context dependent.