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Stimulating CD27 to quantitatively and qualitatively shape adaptive immunity to cancer

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Abstract

The capacity of the immune system to recognize and respond to tumors has been appreciated for over 100 years. However, clinical success has largely depended on the elucidation of the positive and negative regulators of effector cells after activation via the antigen cell receptor. On the one hand, effector cells upregulate checkpoint molecules that are thought to play a role in limiting immunopathology. On the other, second and third waves of costimulation are often required to promote the expansion, survival and differentiation of effector cells. While it is clear that the immune system can be unleashed by blocking checkpoint molecules, this approach is most effective when preexisting responses exist in patients. Thus, coordinating checkpoint blockade with costimulation could potentially expand the patient population that receives benefit from cancer immunotherapy. This review will discuss how the costimulatory molecule CD27 sculpts immunity and preclinical/clinical data indicating its potential for cancer immunotherapy and its clinical translation.

Introduction

In broad terms, CD27 stimulation has been described to influence three stages of effector cell activity that could be influential with respect to anti-tumor immunity. CD27 stimulation co-operates with CD28 to support the initial activation and expansion of T cells; it perpetuates the expansion and survival of effector cells in the periphery; and it augments cytolytic and cytokine functions of effector cells. The direct and indirect mechanisms that control these contributions are beginning to be elucidated, enhancing the possibility of tailoring elements of effector cell function according to need.

Biology and biochemistry of CD27

CD27 is a member of the TNF-superfamily, which includes both costimulatory and apoptosis-inducing molecules. CD27 is expressed constitutively on naïve and acutely activated effector T cells and NK cells [1]. Expression on B cells is limited to a subset of differentiated cells; as their contribution to tumor immunity is not well characterized, we

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will not discuss B cells further in this review. Acute down-regulation of CD27 occurs by internalization and shedding while transcriptional repression of CD27 occurs in well-differentiated effector cells. In many tumors CD27 remains expressed on infiltrating lymphocytes (TIL) and available to transmit signals to relevant T and NK cells. CD27 signaling generally supports CD28-mediated costimulation ([2] and our observation that CD27 agonistic antibodies are weak adjuvants on their own in a vaccination setting [3••]). However, in instances of infectious inflammation the requirement for CD28 can be overcome by the availability of CD27 stimulation ([4]). The requirement for lead-in CD28 signaling is likely due to the need for NFAT-driven transcription of genes involved in the initiation of T cell cycling and proliferation, while CD27 stimulation supports the survival of proliferating T cells. CD27 stimulation drives TRAF-mediated activation of JNK [5;6] and NIK-dependent activation of the NF κ B pathway [7] and the activation of a PIM-1 kinase pathway [8] (Figure 1). While the basic tenets of CD27 signaling appear to be understood, how these diverse pathways are integrated to influence effector cell survival and differentiation has not been well characterized. Aside from NF κ B, the transcriptional pathways and nodes activated by CD27 signaling are poorly described. CD27 signaling precedes that of other members of the TNF-superfamily, such as 4-1BB (CD137) and OX40 (CD134), but the distinct contributions of these signals to T cell functions and the mechanisms of their integration are not understood.

Expression and regulation of CD70 (CD27L)

The only identified ligand for CD27 is CD70, whose expression is under extensive intrinsic and extrinsic regulation [9•;10]. CD70 expression can be induced on dendritic cells (DC), macrophages and B cells and in the absence of CD70-CD27 stimulation T cell responses to activated DC and many infectious agents are muted [11;12], indicating the critical role of this pathway in promoting T cell responses. CD70 surface expression is initiated by coordinated signals from components of innate (TLR; IFN-1) and adaptive (primarily CD40, but TRANCE has some ability) immunity, and is generally not seen in the absence of CD80/CD86 costimulatory molecules. CD70's expression is regulated both by metalloprotease cleavage and internalization after engaging CD27 [10]. Recent studies have suggested that regulatory T cells can also prune CD70 from DC, defining a novel pathway for reducing DC function in the tumor microenvironment [13•;14•]. Expression of CD70 on human T cells has been frequently described and is considered an activation marker [15;16], but the relative contribution of CD70 expression by antigen presenting cells (APC) compared to T cells in the biology of CD70-mediated stimulation has not been elucidated. Given the importance of CD27 in eliciting and sustaining effector responses, remarkably few studies have assessed the prognostic utility of CD70 expression in the tumor microenvironment or the efficiency by which factors that stimulate DC (such as CD40, PAMPs, DAMPs and IFN-1) elicit CD70 expression on intra-tumoral DC.

Functional consequences of CD27 stimulation

Effector Activation and expansion

CD27 stimulation contributes in a context-dependent manner to the primary T cell response [11]. Consistent with the notion that CD27-derived signals comprise a major component of the “help” provided to CD8⁺ T cells from CD4⁺T cell activated DC [17–19], CD8⁺ T cells receiving CD27 stimulation increase CXCL10 expression (augmenting recruitment of T cells to DC [20] and have a lower threshold of activation for naïve T cells [21;22] and initiate the expression of EOMES, a critical transcription factor in the development of effector and memory CD8⁺ T cells [3••]. In the context of low inflammation (e.g. peptide/DC priming) the absence of CD27 eliminates primary CD8⁺ T cell responses, and curtails CD4⁺ T cell responses [23]. In highly inflammatory settings (e.g. viral infections), the absence of CD27 stimulation diminishes primary T cell responses but it is not obligatory, suggesting some overlap or compensation with other stimulatory pathways. Thus, CD27-mediated stimulation could augment the activation and expand the repertoire of T cells that can respond to tumor antigens.

Effector Survival and Memory Generation

Post expansion, CD27 stimulation can both augment effector cell expansion and survival and enhance the development of memory CD8⁺ T cells [11]. Various mechanisms have been described that could contribute to these outcomes, and are likely highly context-dependent. CD27 stimulation promotes the expression of IL-2, an obligate survival cytokine, in T cells that take up residence in peripheral tissues [24–27]. However, CD27 stimulation also moderates the influence of IL-12-mediated terminal differentiation [28] and Fas-L-mediated apoptosis of effectors [29]. Bcl_{XL} and PIM-1 expression are induced by CD27 stimulation [8], which may limit mitochondrial dysfunction and apoptosis [30]. Notably, we have determined that CD27 stimulation supports the re-expression of IL-7R and the common γ -chain in activated T cells, which may provide critical survival factors during expansion and contraction phases of the T cell response ([28] and Dong et al, manuscript in preparation). CD27 has also been shown to contribute to the expansion of CD4⁺ T cells, though it likely plays a subdominant role to OX40 [23].

Effector Differentiation and Polarization

The induction of EOMES expression and IL-2 by CD27 stimulation may play instructive roles increasing the expression of IFN γ in CD8⁺ T cells [3••;31;32]. CD27 signaling has been reported to influence the expansion, polarization and subsequent cytokine production by CD4⁺ T cells, though some controversies exist in this area. On the one hand, data from CD27-knockout mice and CD70-transgenics argue that CD27 signaling supports the expansion of CD4⁺ T cells and polarization to a TH1-like phenotype [11;31], while simultaneously suppressing IL-17 production [33••]. The polarizing capabilities of CD27 stimulation has been reported to be either independent [34] or dependent on IL-12 [35;36], perhaps a by-product of increased IL-12R expression [36]. As TH1-immunity constrains tumor outgrowth, it will be important to define whether CD27 stimulation can promote IFN γ production from CD4⁺ T cells independently or needs IL-12 expression in the TME.

Of note, the impact of CD27 stimulation on the subsequent expression of CD40L by CD4⁺ T cells, which plays critical roles in DC activation, has not been explored.

Treg development and function

Seminal studies from the Borst group identified a critical role for CD70 expression within the thymic medulla in the promotion of regulatory T cell (Treg) development [37••]. However, the overall importance of CD70-mediated Treg survival is unclear. On the one hand, CD27 knockout mice have a modest decrease in Tregs (our unpublished data) and don't exhibit overt autoimmunity (though this could be to reduced activation/survival of autoreactive T cells); however, CD70 blockade has been shown to diminish Treg frequency in the tumor microenvironment [38] leading to enhanced control of tumor outgrowth. Consistent with this, we have found that many transplantable tumors do not graft well on CD70 knockout mice (our unpublished data). Taken together, these data indicate that as agonistic antibodies to CD27 are explored clinically, their impact on Treg frequency and function (see below) will need to be carefully examined.

NK cells

CD27 expression is strongest on CD56^{hi} NK cells [39;40] which are generally defined as cytokine producing cells. Although CD27 does not appear to be necessary for the development of NK cell subsets and activity [41], several studies have revealed an impact of CD27 stimulation on mature NK cell function. In murine studies, agonistic anti-CD27 enhances proliferation and IFN γ production and cytotoxicity in an IFN γ -dependent manner [42]. Similarly, soluble CD70 augmented IFN γ production, but not cytolysis, from human NK cells [43]. However, CD70-transfected tumor cells can induce NK-mediated rejection [44] and can be more susceptible to NK-mediated lysis [45]. In contrast, blocking CD70 with sCD27 attenuates both cytotoxic activity and cytokine production [46]. Thus, while targeting CD27 will likely increase IFN γ production by NK in the tumor microenvironment [47], it remains possible that optimal CD27 stimulation could also augment cytolytic activity within the cytokine-producing subset.

Therapeutic implementation of targeting CD27

Direct promotion of anti-tumor immunity

Preclinical studies with fully-human agonistic antibodies to CD27 indicated that many facets of murine lymphocyte responses to CD27 stimulation are recapitulated by human lymphocytes in vitro and in vivo [48•;49]. The induction of CD70 expression; directly targeting of CD27 with agonistic antibodies; or enforced expression of CD70 on tumor cells can promote adaptive immunity in a variety of tumors models [32;47;50–54•] and is associated with increased NK and T cell frequency and function. Mechanistically, by mimicking elements of CD4⁺ T cell help (i.e. licensing of DC) CD27 stimulation could prevent tolerance induction [52;55]. Alternatively, CD27 signaling supports the expansion of T cells in response to low avidity peptides, enhancing T cell survival and effector functions, and this may increase the repertoire of tumor infiltrating lymphocytes [32;47;47]. Agonistic anti-CD27 was found to be generally well tolerated and demonstrated evidence of biological activity in a Phase I clinical trial. Several clinical responses were found in heavily pretreated

patients with either solid or hematological malignancies, with some being quite durable. Strikingly, de novo and pre-existing CD8⁺ T cell responses to melanoma antigens expanded in a subset of patients. Furthermore, both CD4⁺ and CD8⁺ T cells expressed activation markers consistent with recently activated T cells, suggesting that CD27 augments immunity in these patients. (Burris et al; manuscript submitted). This ability to expand T cell responses as a monotherapy might suggest that sufficient CD28-mediated signaling is available in tumor draining lymph nodes to support initial T cell proliferation. Interestingly, checkpoint molecules such as PD-1 were still expressed on activated T cells arising after CD27 therapy, and therefore logical combinations with checkpoint blockade antibodies (which have shown efficacy in pre-clinical models [54]) are being tested in ongoing clinical studies (Table 1). Similarly, combinations of CD27 stimulation with tumor irradiation and other approaches to induce tumor inflammation are in clinical trials. As CD27 signaling pathways can operate independently from MAPK and AKT/mTOR there may be opportunities to activate CD27 while simultaneously inhibiting classical oncogenic pathways. One caveat is that chronic stimulation of CD27 can lead to the terminal differentiation of effector T cells [31;56] and reductions in circulating NK cells. Indeed, CD4⁺ T cells in general, and Treg cells in particular, were reduced in Phase 1 study patients receiving CDX1127. The mechanism of Treg loss is currently unclear and could be either antibody dependent cellular cytotoxicity (Treg express the highest level of CD27 in PBMC), or activation induced cell death. However, responses to mitogens (PHA; PMA/ionomycin) and a select panel of pathogen derived peptides (CEF: CMV, EBV, influenza) were not compromised in patients examined in the Phase 1 trial, indicating that chronic CD27 signaling does not lead to tolerance. Careful analysis of the patient data with respect to antigen-specific responses will be needed to understand whether CD27 stimulation promotes deeper/terminal effector differentiation in patients, and this will likely be best achieved in vaccine-based clinical trials where frequent TCR engagement accompanies CD27 stimulation. If chronic stimulation of CD27 under these conditions induces terminal differentiation, the tempo of anti-CD27 infusion, or CD70 induction, will need to be considered in trial design, and a better mechanistic understanding of how CD27 regulates T cell differentiation and the effects of Fas-mediated apoptosis and anti-apoptotic molecules will need to be pursued. The lack of deletion/tolerance in patients treated with agonistic anti-CD27 compared to what might have been predicted from CD70-transgenic mouse model may also be a function of using an antibody that might not fully replicate the strength or intensity of CD70-mediated stimulation. Thus, chronic CD70 induction via CD40 stimulation may be more detrimental to T cell function.

CD27-stimulation as a “Signal 3” molecular adjuvant for vaccines

CD27 stimulation is being developed as part of next-generation, molecularly-defined vaccine platform (“Vaccineering”) for both shared antigen and neo-antigens [57–59]. CD27 stimulation significantly increases the magnitude of T cell responses to peptide or protein antigen in murine models [3••;17;60•] and synergizes with IFN-1 in both the expansion of effector CD8⁺ T cells and the subsequent development of CD8⁺ T cell memory. As the variegated influences of CD27 on effector and memory T cell development become more understood, there may be opportunities select regimens to support central, effector or tissue resident memory cells. The capacity of CD27 stimulation to attenuate polarization to TH17 also needs to be considered, as IL-17 producing T cells have been shown to have potent anti-

tumor activity in a variety of tumor models, as will the influence of CD27 stimulation on B cell differentiation and antibody production. CD27 stimulation in combination with recombinant approaches for NK stimulation (such as IL-15 or recombinant NK-ligands) to augment innate responses to tumors may be an important avenue for development. As CD27 stimulation, or stimulation of other TNF-superfamily members such as CD134 (OX40) and CD137 (4-1BB) does not generally bypass the need for Signal 2, approaches that co-induce CD80/CD86 expression will likely need to be considered. Direct targeting of CD28 with agonistic antibodies has been intractable to date due to extreme toxicity [61], suggesting that activation of DC, macrophages or B cells will be necessary to achieve CD28-CD27 synergy. Thus, inclusion of TLR agonists or delivering antigen as immune-complexes or as part of recombinant FcR molecules may be an attractive option.

Augmentation of cellular therapies

Given the impact of CD27 on T cell viability, a logical opportunity will be to implement CD27 stimulation during either expansion of T cells from surgical resections for adoptive transfer protocols, as described for the related molecule 41BB [62]. The timing and influence of CD27 on effector/memory differentiation could be exploited to enhance the expansion/differentiation of TIL for either acute anti-tumor function or long-term engraftment [63]. Additionally, engraftment of either expanded TIL, transgenic PBMC or even CAR-T could be enhanced by carefully engaging CD27 costimulation during the infusion, or even using synthetic biology approaches to engraft CD27 intracellular domains to CAR [64]. Due to the varied effects of CD27, the timing and tempo of stimulation will need to be carefully assessed in the clinical setting.

Conclusion

Given its safety profile, targeting CD27 may offer significant opportunities to augment tumor immunotherapies across a variety of platforms. As we understand the biology and mechanistic activity, and modifiers thereof, of CD27 stimulation in different contexts, it is anticipated that this pathway may be exploited to substantially increase the proportion of patients who could receive benefit from cancer immunotherapy.

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Highlights

CD27 is a critical link from activated Dendritic Cells to T cells and NK cells, and can be constrained by Treg pruning of its ligand, CD70.

CD27 stimulation promotes both NK and T cell survival and effector functions

Greater understanding of how CD27-associated signaling pathways are integrated or regulate distinct facets of CD27 biology are needed

CD27 stimulation provides opportunities to sculpt the qualities of the immune response to a variety of therapeutic platforms

Figure 1. Interactivity and stimulatory pathways for CD70-CD27

Dendritic cells upregulate CD70 expression after receiving signals from CD40 and pathogen receptors, providing costimulation via CD27 for NK and Treg and conventional T cells. CD27 signals are transmitted vis TRAF2 and TRAF5, involving the NIK, JNK and PIM1 kinases. Functional consequences of CD27 stimulation on T cells include modulation of cytokine expression, transcription factors that promote expansion and differentiation, and anti-apoptotic proteins.

Table 1

Current cancer immunotherapy trials involving CD27 stimulation

Approach	Agent	Disease	Trial #
Checkpoint Combinations	Ipilimumab (anti-CTLA4)	Melanoma	NCT02413827
	Nivolumab (anti-PD1)	Select solid malignancies	NCT02335918
	Atezolimumab (anti-PDL1)	Select solid/Renal	NCT02543645
Conventional/targeted combinations	Sunitinib	Renal	NCT0238611
	Stereotactic Irradiation	Prostate	NCT02284971
	Glembatumumab (tox in conjugated anti-gpNMB)	Melanoma	NCT02302339
Vaccines	DEC205-NYESO/polyICLC	Melanoma	NCT02413827
	ONT-10 (MUC1/LipidA)	Ovarian/Breast	NCT02270372
	IMA950 (IDH1)	Low grade glioma	NCT02924038