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Dendritic cell-based cancer therapeutic vaccines

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Abstract

The past decade has seen tremendous developments in novel cancer therapies, through targeting of tumor cell-intrinsic pathways whose activity is linked to genetic alterations, as well as the targeting of tumor cell-extrinsic factors such as growth factors. Furthermore, immunotherapies are entering the clinic at an unprecedented speed following the demonstration that T cells can efficiently reject tumors and that their anti-tumor activity can be enhanced with antibodies against immune regulatory molecules (checkpoints blockade). Current immunotherapy strategies include monoclonal antibodies against tumor cells or immune regulatory molecules, cell-based therapies such as adoptive transfer of ex vivo activated T cells and natural killer (NK) cells, and cancer vaccines. Herein, we discuss the immunological basis for therapeutic cancer vaccines and how the current understanding of dendritic cell (DC) and T cell biology might enable development of next-generation curative therapies for patients with cancer.

Introduction

Vaccination represents one of the most effective methods to prevent disease (Finn and Edwards, 2009; Nabel, 2013; Subbarao et al., 2006). Preventive vaccines are designed to block the spread of infection and their activity correlates with the induction of specific antibodies and long-lived memory B cells (Pulendran and Ahmed, 2011). Cellular immunity can also be induced, especially with vaccines composed of attenuated microbes (Pulendran and Ahmed, 2011). On the other hand, therapeutic vaccines are designed to eliminate the cause of a given disease, e.g. elimination of cancer cells or virally-infected cells, and to treat the disease. Their activity is mostly dependent on antigen-specific $CD8^+$ T cell educated to generate cytotoxic T lymphocytes (CTLs) that reject cancer or infected cells. Ideally, therapeutic vaccines should both prime naive T cells and modulate existing memory T cells, i.e., induce a transition from non-protective $CD8^+$ T cells to healthy $CD8^+$ T cells able to yield effective CTLs (Figure 1). Indeed, cancer is a chronic disease and as such it is associated with skewed T cell memory, for example, chronically activated $CD8^+$ T cells that express programmed cell death 1 (PD-1) and are anergic (Freeman et al., 2006). In addition, vaccination should lead to generation of long-lived memory $CD8^+$ T cells that will act to prevent relapse (Figure 1).

The numerous clinical studies assessing therapeutic vaccination in cancer during the past two decades have helped us define the desired properties of vaccine-elicited $CD8^+$ T cells associated with rejection of cancer (Appay et al., 2008). These include: i) high T cell receptor (TCR) affinity and high T cell avidity for peptide MHC (pMHC) complexes expressed on tumor cells (Appay et al., 2008); ii) high amounts of granzymes and perforin (Appay et al., 2008); iii) expression of surface molecules that allow T cell trafficking into

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the tumor [e.g. CXCR3 (Mullins et al., 2004)] and persistence in the tumor site [e.g. the integrins CD103 (Le Floc'h et al., 2007) and CD49a (Sandoval et al., 2013a)]; and iv) high expression of costimulatory [e.g. CD137 (Wilcox et al., 2002)] or low expression of inhibitory [e.g. Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4) (Peggs et al., 2009) or PD-1 (Freeman et al., 2006)] molecules. The components of the immune system necessary for the induction of such $CD8^+$ T cells include: i) the presentation of antigen by appropriate antigen presenting cells (APCs) (Joffre et al., 2012; Lizee et al., 2012); and ii) the generation of $CD4^+$ T cells producing cytokines helping $CD8^+$ T cell proliferation and differentiation, for example IL-21 (Spolski and Leonard, 2008) (Figure 2).

Numerous avenues of therapeutic vaccination against cancer are currently pursued (Finn, 2008). Searching the term “cancer vaccines” in clinicaltrials.gov yields 1307 clinical studies (as of July 2013), with 152 in Phase III clinical trials and 591 in Phase II clinical trials, which highlights the clinical activity in the field. A common feature among these studies, and a critical step in vaccination, is the efficient presentation of cancer antigens to T cells (Figure 2). Because DC are the most efficient antigen presenting cells (Banchereau and Steinman, 1998), exploiting their diversity, in terms of subsets as well as plasticity, is likely to yield improved therapeutic vaccines.

DCs are an essential component of vaccination through their capacity to capture, process, and present antigens to T cells (Banchereau and Steinman, 1998). While immature DCs in peripheral tissues efficiently capture antigens (Mellman and Steinman, 2001), antigen presentation usually results in immune tolerance because of the lack of costimulatory molecules (Steinman et al., 2003; Tarbell et al., 2007). Induction of immune tolerance occurs through various mechanisms including T cell deletion and expansion of regulatory T cells (Treg) (Steinman et al., 2003; Tarbell et al., 2007). Activated (mature), antigen-loaded DCs initiate the differentiation of antigen-specific T cells into effector T cells displaying unique functions and cytokine profiles. DC maturation is associated with a wide variety of cellular changes including: i) decreased antigen-capture activity; ii) increased expression of surface MHC class II molecules and costimulatory molecules; iii) acquisition of chemokine receptors e.g.CCR7, which guide their migration (Trombetta and Mellman, 2005); and iv) the ability to secrete different cytokines e.g. interleukin-12 (IL-12) that control T cell differentiation. It is now accepted that vaccine adjuvants act by inducing DC maturation (Steinman and Banchereau, 2007). Vaccines can also reach lymph-node resident DCs directly through the lymphatics (Itano et al., 2003). Recent years brought about an increased understanding of DC biology, the existence of distinct DC subsets with specific functions as well as distinct molecular mechanism that DCs use to regulate the immune response. Hereunder, we will discuss how this progress can be harnessed for improved vaccination against cancer.

Human DC subsets

Human DCs in the steady state were first studied in whole blood and skin. Three cell surface markers characterize blood DCs: CD303, expressed on plasmacytoid DCs (pDCs), and CD1c and CD141, both expressed on circulating DCs (Dzionek et al., 2000; Dzionek et al., 2001; MacDonald et al., 2002). Both $CD1c^+$ and $CD141^+$ DCs can produce IL-12, thereby enabling the generation of Interferon-γ (IFN-γ)-secreting type 1 $CD4^+$ T (Th1) cells, and the priming of naive $CD8^+$ T cells (Meixlsperger et al., 2013; Schlitzer et al., 2013). Both $CD1c^+$ and $CD141^+$ DCs, isolated from blood or tissues, are able to cross-present long peptides of melanoma-tissue-derived antigen (MART-1) to T cell lines (Segura et al., 2012) and acquire viral antigens and drive antiviral effector $CD8^+$ T cell responses (Yu et al., 2013). However, they also display unique features. $CD141^+CD1c^-$ DCs, the human counterpart of mouse CD8α+ DCs, produce very large amounts of IFN-α upon recognition

of synthetic double-stranded RNA (dsRNA) (Meixlsperger et al., 2013) and, when activated with poly I:C, efficiently cross-prime $CD8^+$ T cells (Bachem et al., 2010; Crozat et al., 2010; Haniffa et al., 2012; Jongbloed et al., 2010; Lauterbach et al., 2010; Mittag et al., 2011; Poulin et al., 2010). $CD1c^+$ DCs from both blood and lungs are uniquely able to drive the differentiation of $CD103^+CD8^+$ mucosal T cells with high retention capacity in the lung (Yu et al., 2013).

Studies of human cutaneous DCs demonstrated their phenotypic and functional heterogeneity (Klechevsky et al., 2008; Nestle et al., 2009; Joffre et al., 2012). In particular, LCs specialize in priming $CD8^+$ T cell immunity whereas interstitial/dermal ($CD14^+$) DCs promote humoral immunity (Klechevsky et al., 2008). The efficiency of LCs in priming naïve $CD8^+$ T can be partially explained by their ability to produce IL-15 (Banchereau et al., 2012a; Romano et al., 2012) and/or upregulate CD70 (van der Aar et al., 2011). Interstitial DCs can either act directly on B cells (Dubois et al., 1997) or prime $CD4^+$ T cells to differentiate into T follicular helper (Tfh) cells that help B cell differentiation in germinal centers (GCs) (Crotty S., 2011). They induce the differentiation of Tfh through the production of IL-12 (Schmitt et al., 2013). Interstitial DCs can generate type 2 $CD8^+$ T cells (Tc2) producing low amounts of Granzyme A and displaying poor CTL functions, a property that can be inhibited by blocking ILT4 (Banchereau et al., 2012b). Thus, vaccines that target interstitial DCs might raise good antibody responses but poor $CD8^+$ T cell immunity.

DCs express numerous non-clonal pattern recognition receptors (PRRs), which permit sensing and transmission of danger signals to adaptive immunity. PRRs include membrane C-type lectins and Toll-like receptors (TLRs), and cytoplasmic NOD-like receptors (NLRs) and DNA/RNA sensors (Barber, 2011; Desmet and Ishii, 2012). These receptors allow DCs to sense pathogens, apoptotic and necrotic cells, and stressed cell products, for example extruded DNA (Caielli et al., 2012). Herein, we will only discuss a few examples of these recognition mechanisms to illustrate how these DC properties can be harnessed to generate more efficient cancer vaccines. Interested readers can find more in-depth discussion in recent reviews (Coffman et al., 2010; Desmet and Ishii, 2012; Latz et al. 2013).

Nucleic acid detection can lead to the production of protective type I IFN via endosomal or cytoplasmic sensors (Barber, 2011; Desmet and Ishii, 2012; Zhang et al., 2011a; Zhang et al., 2011b). This offers a venue for development of potent vaccine adjuvants generating high levels of type I IFN, such as poly I:C binding TLR3 and cytoplasmic sensors, Imiquimod binding TLR7 and CpG oligonucleotides binding TLR9 (Coffman et al., 2010). Some lectins harbor signaling motifs in their cytoplasmic regions that deliver activation signals when engaged by ligands expressed on necrotic cells (Sancho and Reis e Sousa, 2013). For example, macrophage-inducible C-type lectin (MINCLE) detects nuclear ribonucleoproteins released from damaged cells (Sancho and Reis e Sousa, 2013), whereas CLEC9A, expressed uniquely on $CD141^+$ DCs, detects actin exposed on necrotic cells (Ahrens et al., 2012; Zhang et al., 2012), thereby facilitating cross-presentation of necrotic cell antigens (Sancho et al., 2009). DCs also express inflammasome components that regulate the release of caspase activation-dependent cytokines, including IL-1β, IL-18 and high-mobility group box 1 (HMGB1) (Latz et al., 2013). Inflammasome activation in DCs can occur through recognition of microbial ligands such as flagellin or through indirect mechanisms resulting from the phagocytosis of particles, including alum, uric acid, and biodegradable particles that are currently being tested as vaccine adjuvants (Coffman et al., 2010; Latz et al, 2013). Activation of the inflammasome also plays a very important role in response to cancer therapy via so-called “immunogenic cancer cell death” (Kroemer et al., 2013). There, certain types of anti-cancer chemotherapy drugs such as anthracyclines or oxaliplatin can induce immunogenic cancer cell death, which is characterized by secretion of HMGB1 from dying

cells, which engages TLR4 on DCs (Kroemer et al., 2013). As DCs simultaneously capture dying cancer cells, this signal facilitates cancer antigen processing and presentation by DC to T cells (Kroemer et al., 2013). This in turn plays an important role in boosting anti-cancer immunity via endogenous vaccination. Indeed, the absence of HMGB1 expression by dying tumor cells compromises DC-dependent T-cell priming by tumor-associated antigens (Yamazaki et al., 2013). Exploiting these unique molecular pathways for antigen delivery and DC activation represents another way of harnessing DCs for vaccination.

Dendritic cell-based vaccines

DCs can be exploited for vaccination against cancer through various means including: 1) non-targeted peptide/protein and nucleic acids-based vaccines captured by DCs *in vivo*, 2) vaccines composed of antigens directly coupled to anti-DC-antibodies, or 3) vaccines composed of ex vivo generated DCs that are loaded with antigens. We will discuss selected examples of current therapeutic vaccination approaches to illustrate these key concepts. All these approaches are assessed in ongoing clinical trials.

Non-targeted vaccines

Vaccines composed of short 9-10 amino-acids (aa) long peptides, with or without adjuvants demonstrated that MHC class I-restricted antigen-specific $CD8^+$ T cell immunity can be mounted in patients with metastatic disease (Boon et al., 2006; Rosenberg et al., 1998; Speiser et al., 2008). The clinical success was however limited (Rosenberg et al., 2005), possibly because of the lack of $CD4^+$ T cell help which we now know is necessary for the generation of potent CTLs and long-lived memory $CD8^+$ T cells (Janssen et al., 2005; Filipazzi et al., 2012). Long synthetic peptides of ~ 25-50aa have the advantage of potentially inducing broad immunity with both $CD8^+$ T cell and $CD4^+$ T cell responses against multiple epitopes (Quakkelaar and Melief, 2012). Vaccination of 20 patients with high-grade vulvar intraepithelial neoplasia with a long peptide covering the two oncogenic proteins E6 and E7 of high-risk human papilloma virus type 16 (HPV16), led to complete regression of all lesions and eradication of virus in 9 individuals (Kenter et al., 2009). A high ratio of vaccine antigen-specific effector T cells to $CD4^+CD25^+Foxp3^+$ Treg cells was predictive of clinical benefit (Welters et al., 2010). Vaccination of patients suffering from recurrent ovarian cancer with long peptides covering p53 led to expansion of p53-specific $CD4^+$ T cells in blood and tumor (Leffers et al., 2009). However, no impact on the clinical course of the disease was observed (Leffers et al., 2009). The lack of clinical responses might be explained by the domination of the immune response to vaccine antigens by $CD4^+$ T cells that secreted type 2 (IL-4 and IL-5) rather then IFN-γ. Indeed, Type 2 $CD4^+$ T cells might not be protective against cancer. Durable expansion of p53-specific type 2 $CD4^+$ T cells was also observed in patients with colorectal cancer (Speetjens et al., 2009). Combining the long p53 peptide vaccine with IFN-α resulted in increased expansion of antigen-specific IFN-γ–secreting $CD4^+$ T cells, though the impact on clinical efficacy remains to be established (Zeestraten et al., 2013). These results further illustrate the challenges that the re-programming of preexisting T cell memory represents, and the need to identify vaccines that will enable priming of a new T cell repertoire.

With the advances of proteomics, vaccines can now be prepared with peptides representing antigens identified from patients' tumors. The peptides are combined with granulocyte-macrophage colony stimulating factor (GM-CSF) to attract and activate DCs, and low dose of cyclophosphamide to control Tregs. This regimen led to immune responses that were associated with clinical responses (Walter et al., 2012). While it is difficult to assess which component of this therapy accounted for good immune and clinical efficacy, shifting from shared tumor antigens common to many patients to patient-specific neo-antigens may enable to efficiently activate an available T cell repertoire against which Tregs might not have

developed. The concept of patient-specific vaccines was initiated more than two decades ago with idiotype vaccines in lymphoma (Kwak et al., 1992) where tumor idiotypic determinants were conjugated to the immune carrier keyhole limpet hemocyanin (KLH) (Kwak et al., 1992). A Phase III trial in patients with lymphoma showed that such a vaccine combined with GM-CSF can lead to significant prolongation of disease-free survival (Schuster et al., 2011).

Peptide-protein vaccines are poorly immunogenic by themselves unless adjuvants are added to generate robust anti-tumor immune responses. Many adjuvants are currently under evaluation as constituents of cancer vaccines (Dubensky and Reed, 2010). These include agonists of various TLRs such as TLR3 (poly I:C), TLR4 (monophosphoryl lipid A; MPL), TLR5 (flagellin), TLR7 [Aldara® (Imiquimod)], TLR7-TLR8 (Resiquimod), and TLR9 (CpG) (Dubensky and Reed, 2010). Combinations of adjuvants targeting different pathways might synergize to generate more potent immune responses as their combination can activate DCs in a synergistic fashion (Coffman et al., 2010). A promising candidate is GlaxoSmithKline's (GSK) AS15 adjuvant system, which incorporates monophosphoryl lipid A (MPL) that acts via TLR4, the saponin QS-21, and CpG oligonucleotides that act via TLR9 (Cluff, 2010). Vaccines composed of recombinant MAGE-A3 protein and AS15 elicited specific immune responses and clinical activity in both a Phase II study in patients with metastatic melanoma (NCT00086866) and a Phase II study in patients with resected non-small cell lung cancer (NSCLC) (NCT00290355) (Brichard and Lejeune, 2007). Phase III trial are currently ongoing in two settings: 1) in patients with resectable regionally advanced melanoma (DERMA Phase III trial, NCT00796445) (Kirkwood, 2011); and 2) in patients with MAGE-A3 expressing NSCLC with minimal residual disease post-surgery (NCT00480025). Clearly, a better understanding of DC biology will provide a fertile ground for discovery of novel adjuvants.

DCs are also engaged in response to complex vaccine preparations such as GVAX® tumor cell based vaccines where cancer cells are genetically modified to express GM-CSF which attracts and activates DCs (Le et al., 2010). Such GVAX vaccines have shown some immune and clinical activity in pancreatic cancer (Thomas et al., 2004; Lutz et al., 2011) and other types of solid tumors (Dranoff, 2002). Another vaccine platform is based on recombinant *Listeria monocytogenes*(*Lm*), an intracellular bacterium that targets DCs *in vivo* and utilizes both class I and II antigen-processing pathways (Brockstedt et al., 2004; Le et al., 2012). The live mutant *Lm*-based vaccine that expresses mesothelin elicits mesothelin-specific T cells in mice and humans (Le et al., 2012). Engineered viruses can ferry selected antigens as well as co-stimulation cassettes (Larocca and Schlom, 2011). A randomized Phase II trial with a poxvirus-based vaccine expressing prostate-specific antigen (PSA) (PROSTVAC) and TRICOM (CD54, CD58 and CD80) carried out in men with metastatic prostate cancer showed an improved overall survival (8.5 months) (Kantoff et al., 2010b). Another strategy is based on intratumoral delivery of oncolytic viruses, i.e., viruses that preferentially infect and kill cancer cells. These can be modified to express GM-CSF to attract DCs and lymphocytes at the lysed tumor site (Russell et al., 2012). A phase II study of GM-CSF-oncolytic herpes virus in patients with stage IIIc/IV melanoma indicated durable regression in both injected and non-injected lesions suggesting systemic effect (Senzer et al., 2009). The recent data from randomized prospective phase III clinical trial, showed tumor regression lasting at least 6 months in 16% of patients treated with the recombinant virus. Only 2% of patients treated with GM-CSF in the control arm showed such response (OPTiM, Oncovex Pivotal Trial in Melanoma, Amgen website). A formal analysis of the trial is expected later this year. Viral vectors to deliver antigens to DCs, either directly by encoded genes or indirectly via tumor lysis, is an attractive strategy as it mimics the natural way of infection and generation of protective immunity. Yet, the immunogenicity of these vectors might prevent their efficacy upon boosting, therefore

calling for prime-boost strategies where a second vector is used for boosting the specific immune response. This strategy is currently developed in the context of HIV vaccines (both preventive and therapeutic) and could be applied to cancer in case of success.

Vaccination with ex vivo generated DCs

DC can be generated ex vivo, loaded with different forms of antigens, activated and injected in patients (Palucka and Banchereau, 2012). Clinical studies from the past 15 years have analyzed: i) different DC vaccine preparations; ii) different DC activators; iii) different forms of antigen preparations from short peptides to complex whole tumor cell hybrids; iv) different routes of DC injection. These studies were initially performed as single treatments but combination studies are now being assessed with agents such as systemic adjuvants, for example poly I:C (Aarntzen et al., 2008; Kalinski et al., 2013; Palucka and Banchereau, 2012; Schuler, 2010). These studies concluded that DC-based vaccines are safe and can induce the expansion of circulating $CD4^+$ T cells and $CD8^+$ T cells that are specific for tumor antigens. While objective clinical responses have been observed in certain patients, there is a discrepancy between the blood immune response and the rate of clinical responses, as we will later discuss. The clinical response takes time to build up but remissions can be long-lasting. The US Food and Drug Administration (FDA) has approved, for the treatment of metastatic prostate cancer, Sipuleucel-T, a cellular product composed of enriched blood APC cultured with a fusion protein of prostatic acid phosphatase (PAP) and GM-CSF. Treatment with Sipuleucel-T resulted in a ~4-month-prolonged median survival in patients with prostate cancer (Kantoff et al., 2010a). Another subsets of blood DCs, plasmacytoid DCs, which represent the main source of type I IFN upon viral infection have also been assessed as the basis for cancer vaccines (Liu, 2005; Tel et al., 2013). Some patients with metastatic melanoma, who have been vaccinated with activated pDCs loaded with tumor antigen-peptides, showed antigen-specific $CD4^+$ and $CD8^+$ T cell responses (Tel et al., 2013).

While considerable progresses have been made over the years, additional studies are required to fully reveal the potential immunotherapeutic impact of ex vivo generated DCs. Most studies have been performed in late stage patients who display strong immunosuppression mechanisms, for example Tregs that counteract the induction of effective immunity to vaccine antigens. Nevertheless, there are two ongoing phase III trials assessing in comparative studies clinical efficacy of monocyte-derived ex vivo generated DC vaccines. One trial is testing DC vaccine in patients with newly diagnosed brain tumor (glioblastoma) following surgery as add-on to the standard of care combining radiation and chemotherapy (NCT00045968; Northwest Therapeutics). The DCs are loaded with autologous tumor lysate. The second trial is testing DC vaccine in patients with advanced kidney cancer (renal carcinoma) as add-on to targeted therapy with Sunitinib, a receptor tyrosine kinase inhibitor (NCT01582672; ADAPT trial, Argos Therapeutics). The DCs are loaded with autologous tumor RNA. The three common features of these two trials are 1. Vaccination of patients with resected tumors, and thus lower tumor burden, 2. Vaccination in combination with other therapy; and 3. Loading DCs with autologous tumor preparations. Time will show whether the promising phase II data observed with these vaccines will be confirmed in phase III.

In vivo DC targeting

Pioneering studies from Ralph Steinman and Michel Nussenzweig demonstrated the principle of targeting antigens to DCs in vivo through the coupling of antigens to antibodies specific to DC surface receptors such as DEC205 or DCIR (Bonifaz et al., 2002; Hawiger et al., 2001; Soares et al., 2007a). Importantly, in the absence of adjuvants, targeting antigens to $DEC205^+$ DCs *in vivo* induces antigen-specific tolerance (Hawiger et al., 2001), which

can be used as treatment against autoimmune diseases such as type I diabetes (Steinman, 2012). Administration of these complex vaccines with DC-activators such as TLR3, TLR7-8, or CD40 agonists enables the maturation of DCs and thus the establishment of immunity rather than tolerance (Steinman, 2012). The induced immunity was shown to be protective in a number of diseases including various infections (malaria, HIV) and cancer (Steinman, 2012; Tacken and Figdor, 2011). DC targeting-based vaccination studies in non-human primates demonstrated robust T cell immunity in prime-boost design with HIV gag-DEC205 targeting vaccine (Flynn et al., 2011).

Currently, numerous in vitro and *in vivo* studies in human and mice are focused on developing DC-targeting vaccines. For example, targeting antigens through the DC surface lectinss DCIR (Klechevsky et al., 2010; Meyer-Wentrup et al., 2009), DC-SIGN (Dakappagari et al., 2006), Dectin 1 (Ni et al. 2010), CLEC9A (Sancho et al., 2008) and Langerin (Flacher et al., 2009), results in humoral and cellular responses including both $CD4^+$ and $CD8^+$ T cells. As observed in the original studies with DEC205, the presence or absence of adjuvants has profound impact on immune responses. Thus, in the absence of adjuvants, injection of antigens coupled to antibodies against CLEC9A results in strong antibody responses, which are linked to the generation of Tfh cells (Caminschi et al., 2012). It also results in priming of Tregs (Joffre et al., 2010) but not $CD8^+$ T cell immunity despite the capture and the cross-presentation of targeted antigens by $CD8\alpha^+$ DCs (Sancho et al., 2008). This can be skewed by the addition of adjuvants, for example poly I:C, at which point targeting of antigen to DCs via CLEC9A results in potent and robust anti-tumor $CD4^+$ and $CD8^+$ T cell immunity (Sancho et al., 2008; Joffre et al., 2010). In vivo studies in mice comparing immunogenicity of HIV antigens linked with antibodies to Langerin/CD207, DEC205/CD205, and CLEC9A receptors, along with anti-CD40 antibody to induce DC activation induced comparable levels of gag-specific Th1 and $CD8^+$ T cells (Idoyaga et al., 2011). These target molecules are expressed by $CD8\alpha^+$ DCs and the responses were more robust than those obtained by targeting gag to $CD8\alpha^-$ DCs via DCIR (Idoyaga et al., 2011). Thus, when the appropriate DC subset is targeted with a vaccine antigen with appropriate adjuvants, several different receptors expressed by that subset are able to initiate T cell immunity.

However, different DC receptors can deliver different signals to the same DC leading to distinct types of immune responses. For example, targeting antigens to DC-ASGPR, in the absence of adjuvants, favors the generation of antigen-specific IL-10 secreting $CD4^+$ T cells with regulatory properties both in vitro in the human and in vivo in non-human primates (Li et al., 2012). Targeting the same DC population with antibodies to LOX-1 results in Th1 responses (Li 2012). Furthermore, targeting different human DC receptors revealed the importance of the antigen internalization into either early or late endosomes (Chatterjee et al., 2012). Thus, in human $BDCA1^+$ and monocyte-derived DCs, antibodies to CD40 and mannose receptor targeted antigens to early endosomes, whereas antibodies to DEC205 targeted antigens primarily to late compartments. The receptor that was least efficient at internalization, CD40, turns out to be the most efficient at cross-presentation because it promotes limited intra-endosomal degradation (Chatterjee et al., 2012). Similarly, the targeting of different DC receptors generates quantitatively and qualitatively different T cell responses in vivo in mice (Dudziak et al., 2007; Soares et al., 2007b). There, unlike $CD8\alpha^+$ DCs that express DEC205, $CD8\alpha^-$ DCs, which express 33D1 antigen, are specialized for presentation of targeted antigen on major histocompatibility complex (MHC) class II. This difference in antigen processing was shown to be intrinsic to the DC subsets and associated with increased expression of proteins involved in MHC processing (Dudziak et al., 2007). Thus, it will be essential to refine the understanding of DC biology to guide the processing of targeted antigen and subsequent presentation resulting in $CD8^+$ T cell immunity.

CD8+ T cell immunity

Therapeutic vaccination aims at expanding high avidity $CD8^+$ T cells that can differentiate into CTLs able to kill cancer cells, and can generate long-lived memory CD8+T cells. This could be accomplished either through the priming of naïve T cells or the re-programming of memory T cells that differentiated earlier in an environment not conducive to the generation of potent cytotoxic T cells (Figure 1). Naïve $CD8^+$ T cells differentiate into CTLs in lymphoid organs upon encounter with DCs presenting tumor-derived peptides (Bousso and Robey, 2003) (Figure 2) in the context of co-stimulation through CD80 (Chen et al., 1992), CD70 and 4-1BB (Shuford et al., 1997) as well as DC-derived cytokines such as IL-12 and IL-15 (Araki et al., 2010; Waldmann, 2006; Zhang and Bevan, 2011). The priming of the new repertoire of T cells might be critical for clinical success. Studies with adoptive T cell transfer showed that effector cells derived from naive $CD8^+$ T cells expressed higher CD27 and retained longer telomeres, suggesting a greater proliferative potential (Hinrichs et al., 2011; Klebanoff et al., 2012).

Circulating memory $CD8^+$ T cells include both central memory and effector cells that circulate between secondary lymphoid organs and peripheral tissues. A third category i.e., tissue-resident memory T cells has been recently identified (Jiang et al., 2012; Mueller et al., 2012) and shown to be superior to circulating memory T cells at providing rapid long-term protection against re-infection (Gebhardt et al., 2009; Jiang et al., 2012). CD103 (αE7) integrin allows peripheral $CD8^+$ T cell retention in epithelial compartments (Sheridan and Lefrancois, 2011). In the context of cancer, the expression CD103 by CTLs facilitate their adherence to cancer cells expressing E-cadherin eventually leading to tumor cell lysis and rejection (Le Floc'h et al., 2007). Indeed, for mucosal cancer vaccines, the homing to and retention of $CD8^+$ T cells in the mucosa is critical for efficacy (Sandoval et al., 2013b). In this context, the growth of orthotopic head and neck or lung cancers can be inhibited by a cancer vaccine provided it is administered by the intranasal mucosal route but not the intramuscular route (Sandoval et al., 2013b). This is explained by the induction through intranasal vaccination of mucosal CD8+ T cells expressing the mucosal integrin CD49a, the expression of which is essential for cancer vaccine efficacy (Sandoval et al., 2013b). The critical role of tissue DCs in imprinting the trafficking patterns of elicited T cells explains the critical role of the route of immunization (Mullins et al., 2003; Sheasley-O'neill S et al., 2007) (Mora et al., 2003). The current challenge is to find out how to control T cell differentiation and trafficking in patients.

Designing tomorrow's therapeutic cancer vaccines

The challenge for next generation vaccines is to resolve the discrepancy between the immune and clinical efficacy measured by the rate of cancer rejection. We will summarize herein the three key aspects which, when combined, can bring the resolution to this challenge: 1. The quality of vaccine-elicited $CD8^+$ T cell immunity; 2. The quality of vaccine-elicited $CD4^+$ T cells; and 3. The barriers that vaccine-elicited $CD8^+$ T cells must confront to access and reject cancer.

As discussed at the beginning of this review, adoptive T cell transfer and cancer vaccine studies yielded a better understanding of what constitutes a potent anti-tumor $CD8^+$ T cell immunity. Thus, next generation DC vaccines need to be based on those DC subsets that are best equipped to elicit $CD8^+$ T cells that fulfill these criteria. For example, targeting cancer antigens to $CD141^+$ DCs would allow generation of highly potent CTLs. On the other hand, targeting the antigen to $CD1c^+$ DCs would allow expansion of $CD103^+CD8^+$ T memory T cells able to reside in the tissue.

$CD4^+$ T cells regulate $CD8^+$ T cell immunity both in the priming and effector phase. For example, Tregs can inhibit the effector functions of $CD8^+$ T cells thereby preventing tumor rejection (Tanchot et al., 2012). However, Tregs also play a critical role during the priming by promoting the selection of high avidity $CD8^+$ T cells (Pace et al., 2012). Although mostly helping tumor rejection, Th1 cells might contribute to tumor escape via secretion of IFNγ that triggers expression of PDL-1 in tissues, thus providing an off-signal to effector $CD8^+$ T cells (Sharpe et al., 2007). Th17 cells (Dong, 2008) exert either pro- or anti-tumor activity depending on the tissue environment in which they reside (reviewed in (Wei et al., 2012)). Indeed, IL-17 can synergize with IFNγ to induce tumor cells to secrete CXCL9 and CXCL10, which attract cytotoxic $CD8^+$ T cells (Wei et al., 2012). Thus, it will be now critically important to unravel molecular factors governing $CD4^+$ T cell programming and differentiation and DC molecules that can control such factors. Again, the functional specialization amongst human DC subsets can be harnessed here. Indeed, as we discussed above $CD14^+$ DCs are able to prime Tfh. Meanwhile, LCs prime Th2 cells (Klechevsky et al., 2008); and $CD1c^+$ but not $CD141^+$ DCs are molecularly equipped to generate Th17 responses in human (Schlitzer A, et al. 2013). This knowledge can be applied to design of next generation vaccines to direct the differentiation of antigen-specific $CD4^+$ T cells to a desired phenotype and function.

Last but not least, once elicited, $CD8^+$ T cells must confront numerous barriers including: i) intrinsic regulators for example CD28-CTLA-4, PD1-PDL1, and ILTs (Pardoll, 2012) as well as extrinsic regulators cells such as Tregs (Fehervari and Sakaguchi, 2004) or myeloid-derived suppressor cells (MDSCs) (Gabrilovich and Nagaraj, 2009); ii) a corrupted tumor microenvironment with pro-tumor inflammation (Coussens et al., 2013; Klebanoff et al., 2011); iii) antigen loss and immune evasion of tumor targets (Klebanoff et al., 2011); and iv) tissue specific alterations such as fatty cells in breast cancer or desmofibrosis in pancreatic cancer stroma (Figure 3). Defining strategies to bypass these obstacles is the object of intense studies to improve the clinical efficacy of vaccination via DCs. A logical approach to address these issues is in the combination of DC vaccine candidates with agents that target different pathways. For example, checkpoint inhibitors such as antagonists to CTLA-4 or PD-1 might offset inhibitor signals (Figure 3) (see companion article by Topalian and Pardoll). The combination of GVAX with anti-CTLA4 antibody (Ipilimumab) has proven to be safe (van den Eertwegh et al., 2012) and pre-clinical models show increased effector $CD8^+$ T cells and enhanced tumor-antigen directed CTL function (Wada et al., 2013).

We foresee tomorrow's vaccines as based on anti-DC antibodies which, thanks to progresses in antibody engineering, can be made into polyvalent vaccines targeting distinct yet specific DC subsets to trigger an ideal composite anti-cancer immune response. Such vaccines will also carry DC activators as well as immunomodulatory molecules to neutralize inhibitory signals as for example anti-PDL-1. This will keep us busy for a while.

Conclusions

We have come a long way since the first clinical trial with ex vivo DCs that was launched in 1996 (Hsu et al, 1996) in our understanding of the main problem: what is needed to elicit therapeutic immunity when cancer escapes the natural barrier of protective immunity. The considerable progress made in the understanding of the biology of DCs and effector and regulatory T cells open avenues for the development of new and novel vaccine strategies. Progresses in “omics” will enable linking genetic alterations with the type of immune response. Novel protocols will be tailored to the patient-specific mutation (Schreiber et al., 2011) and immune alterations the patients display. Thus, there has never been a more exciting time for working on cancer vaccines.

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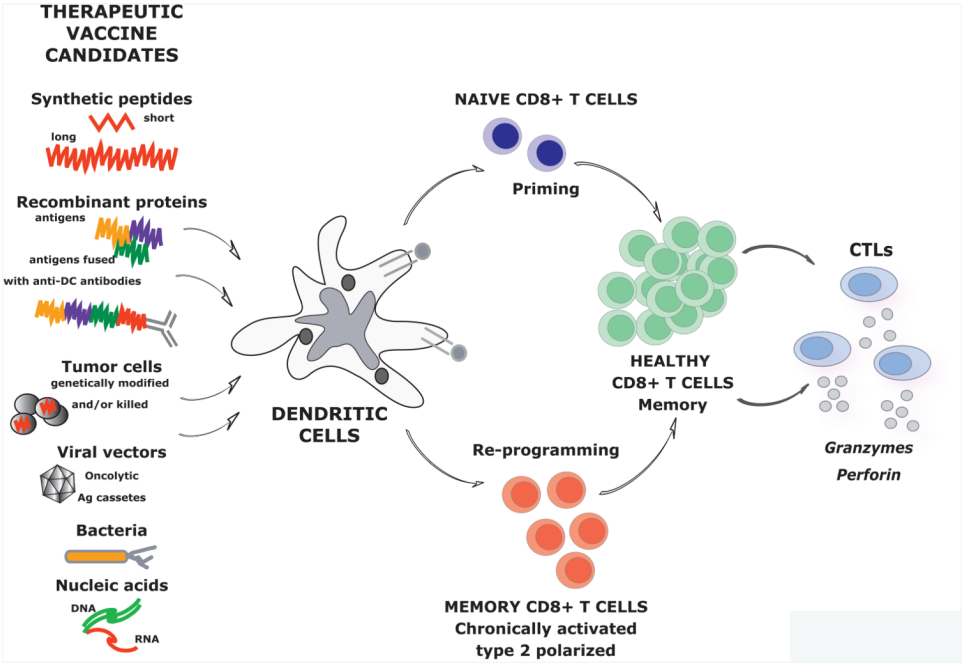

Figure 1. Therapeutic vaccines act via dendritic cells to generate protective CD8$^+$T cell immunity

Therapeutic vaccines are designed to elicit cellular immunity. In this goal, they are expected to prime new T cells as well as induce a transition from chronically activated non-protective CD8$^+$ T cells to healthy CD8$^+$ T cells able to i) generate cytotoxic T lymphocytes (CTLs) that reject cancer and ii) provide long-lived memory CD8$^+$ T cells able to rapidly generate new effector T cells secreting cytotoxic molecules thereby preventing relapse. Numerous approaches to therapeutic vaccines that are being pursued are illustrated. Their common denominator is the action via DCs either randomly or specific targeting.

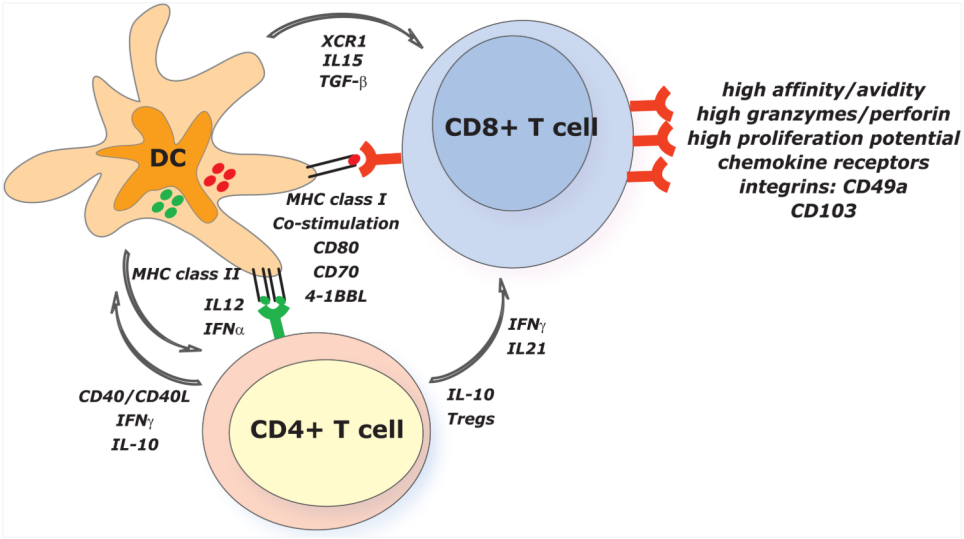

Figure 2. Dendritic cells play a central role in vaccination

The desired properties of vaccine-elicited $CD8^+$ T cells include: i) high TCR affinity and high T cell avidity; ii) high levels of granzymes and perforin; iii) trafficking into the tumor and persistence in the tumor site; and iv) high proliferation potential. Naïve $CD8^+$ T cells initiate a CTL differentiation program upon encounter with DCs presenting tumor-derived peptides via MHC class I. This is supported by co-stimulation mediated by CD80, CD70 and 4-1BB and by DC-derived cytokines such IL-15. XCR1 chemokine secreted by DCs facilitates the interaction with naïve $CD8^+$ T cells. TGFβ expressed by DCs is critical for $CD8^+$ T cells to express CD103 and acquire mucosal phenotype. $CD8^+$ T cell differentiation, especially generation of memory, is dependent on the quality of $CD4^+$ T cell help. The latter one is partially dependent on the IL-12 secreted by DCs. $CD4^+$ T cells producing IFNγ and/or IL-21 can help $CD8^+$ T cell expansion and differentiation. Tregs might play a critical role during the selection of high-avidity $CD8^+$ T cells. This might be ascribed to the cross-talk between DCs and $CD4^+$ T cells where $CD4^+$ T cells control DC functions. There, Tregs can suppress DCs via IL-10 production and also regulate the production of chemokines, thereby limiting the interactions between DCs and low-avidity T cells. $CD4^+$ T cells can also provide DC maturation signals via CD40.

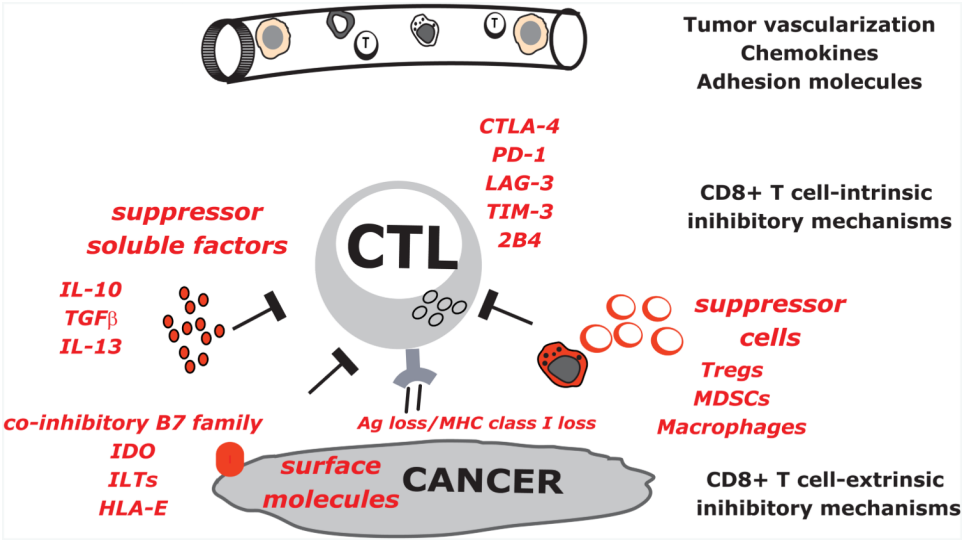

Figure 3. The barriers for CD8$^+$ T cell-mediated tumor rejection

The next generation vaccines must confront and address numerous barriers that CD8$^+$ T cells face including: i) T cells access to the tumor site; ii) T cell intrinsic regulators, for example CD28-CTLA-4, PD1-PDL1; iii) T cell extrinsic regulators such as suppressor cells: Tregs, MDSCs or pro-tumor macrophages; tumor secreted suppressive factors including IL-10; and suppressive surface molecules including co-inhibitory molecules from B7 family.