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Dendritic cells are emerging as a critical cell type that is correlated with basic cancer immunobiology and also be considered as potential targets or at least as key players in any effort intended to generate therapeutic vaccines

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Abstract
Dendritic cells are central to the initiation of primary immune responses. They are the only antigen-presenting cell capable of stimulating naive T cells, and hence they are pivotal in the generation of adaptive immunity. Dendritic cells also interact with and influence the response of cells of the innate immune system. The manner in which dendritic cells influence the responses in cells of both the innate and adaptive immune systems has consequences for the bias of the adaptive response that mediates immunity to infection after vaccination or infection. It also provides an opportunity to intervene and to influence the response, allowing ways of developing appropriate vaccination strategies. Dendritic cells (DC) are responsible for initiating all antigen-specific immune responses. As such, they are the master regulators of the immune response and serve this function by linking the microbial sensing features of the innate immune system to the exquisite specificity of the adaptive response. They are exceptionally efficient at antigen presentation and also adept at generating just the right type of T cells in response to a given pathogen. Importantly, DCs also help guide the immune system to respond to foreign antigens while avoiding the generation of autoimmune responses to self. DCs are thus paradoxically important in cancer, generating both immunity and tolerance. Given their central role in controlling the immune response in patients with cancer, DCs are emerging as a critical cell type that must be considered as we come to understand basic cancer immunobiology. They should also be considered as potential targets or at least as key players in any effort intended to generate therapeutic vaccines.

Keywords: Dendritic cell; antigen-presenting cell, innate immunity, vaccination, MHC Molecule.

Introduction

Dendritic cells are professional antigen processing cells. They have a number of receptors that enhance the uptake of antigens, and they are specialized to convert these antigens into MHC-peptide complexes that can be recognized by lymphocytes. However, the dendritic cells need to do more than present antigens to T cells. They are also potent accessory cells that directly trigger and control responses by T cells and by all other types of lymphocytes.

Some early studies showed that dendritic cells carry on their surface high levels of major histocompatibility complex (MHC) products, which are critically recognized by T-lymphocytes. The high levels of MHC led Steinman to test these cells in the mixed leukocyte reaction (MLR), a well-known clinical assay for identifying the compatibility of tissue transplants between donors and recipients. At the time, this assay was known as mixed "lymphocyte" reaction, because it presumed that the B lymphocytes were presenting MHC products from the organ transplant donor to the recipient's T cells.

Instead, Steinman found that dendritic cells were the major stimulators and were unusually potent. In fact, a dendritic cell to T cell ratio of 1 to 100 sufficed to initiate vigorous and optimal responses. Moreover, the dendritic cells directly activated both the subset of helper T cells as well as the killer T cells. Once activated by dendritic cells, the T cells could also interact vigorously with other antigen presenting B cells and macrophages to produce additional immune responses from these cells.

The term "accessory" has since been replaced by the terms "professional" and "co-stimulatory," but the basic concept is unchanged. Dendritic cells provide the T cells with needed accessory or co-stimulatory substances, in addition to giving them a signal to begin to grow and function. For example, two of these specialized activities include the production of cytokines, like interleukin-12 and interferons, and the expression of a number of needed membrane molecules like CD40, CD70, and CD86.

Dendritic cells also influence the type or quality of the response. A T cell, for example, has to know whether the enemy is a virus that needs to be resisted with its own interferons and cytolytic molecules, or whether the pathogen is a parasite that requires a different set of protective cells to respond with antibodies. Therefore, when dendritic cells migrate to the body's pool of T cells areas in the lymph nodes, they need to orchestrate two fundamental components from the repertoire of lymphocyte functions. First the dendritic cells select the rare specific T cells from the assembled repertoire that recognize the specific peptide information the dendritic cells are carrying. Amazingly, only one in 10,000-100,000 of

the T cells in that repertoire are able to respond to this information. Second, the rare T cells that are selected for expansion then differentiate into helper and killer T cells that have the appropriate functions to eliminate the infection or disease causing stimulus. After these two decisions have been made, the newly activated T cells leave the lymph node to return to the body surface or peripheral organ to eliminate the antigens. For orchestrating these various processes efficiently and precisely, the dendritic cells are considered to be "conductors of the immune orchestra."

Dendritic cells (DC) maturation

DCs derive their efficiency at antigen presentation and T-cell stimulation from a series of specializations that enhance their overall function. Yet, these specializations do not appear to involve the expression of many, or even any, DC-specific gene products in the fashion of B cells uniquely expressing immunoglobulin receptors or T cells expressing T-cell receptors. Rather, DCs seem to excel by carefully optimizing and regulating an array of properties they share with a variety of cells in the immune system. Although this has classically made DCs difficult to study and to differentiate from other cells, detailed investigation of their function and lineage has proved DCs to represent a distinct if heterogeneous cell type [1].

A key DC specialization is their ability to exist in two functionally distinct states: immature and mature [2]. Immature DCs are generally found in peripheral tissues where they patrol for invading pathogens and dying host cells. As immature DCs are highly adept at endocytosis, particularly macropinocytosis and phagocytosis, they can accumulate large quantities of soluble and cell-bound antigens. A hallmark of immature DCs is their relative inability to present the antigens they accumulate to T cells. Although they synthesize both MHC class I and class II molecules, immature DCs are relatively inefficient at generating peptide-MHC complexes at the plasma membrane. Lysosomal protease activity is attenuated, reducing the formation of antigenic peptides. In addition, MHC class II molecules are actively diverted to lysosomes during their biogenesis due at least in part to ubiquitination, further limiting the accumulation of peptide-loaded complexes at the surface. Immature DCs also secrete very few immunostimulatory cytokines and poorly express ligands for costimulatory molecules.

Upon encountering pathogen-derived TLR ligands, ligands for intracellular sensors, or proinflammatory molecules, immature DCs are triggered to mature, which converts them in 12 to 24 hours from cells adept at antigen accumulation to cells now specialized for T-cell stimulation. After a transient upregulation (presumably to increase the opportunity to capture the newly arrived pathogen), endocytosis is dramatically down regulated. Lysosomes and the antigen-processing machinery are activated, enhancing the efficiency of peptide-MHC production. Ubiquitination of MHC class II and other molecules ceases, allowing peptide-MHC complexes to remain at the cell surface. Next, they are induced to migrate from tissues to lymphoid organs, in part by upregulating chemokine receptors such as CCR7, begin to efficiently generate peptides that can be loaded stably onto MHC molecules, and upregulate the production of costimulatory ligands and immunostimulatory cytokines. They enter T-cell–rich regions of lymph nodes and begin to stimulate antigen-specific memory or naïve T-cell responses [3, 4].

Although the basic features of maturation that enhance the DC's antigen-presentation capacity are fairly well understood, the maturation program itself is more sophisticated. Depending upon the type of pathogen encountered, and therefore the types of TLR ligands and other maturation signals received, DCs can exhibit qualitatively different maturation pathways that will result in qualitatively different T-cell outcomes. In other words, DCs not only stimulate T cells but can polarize the nature of the T-cell response (e.g., T_H1 vs. T_H2 T-cell production) depending on immunologic need (e.g., *Toxoplasma* vs. *Schistosoma* infections, respectively. DCs thus interrogate, interpret, and then transmit the nature of the pathogenic stimulus to guide the immune response. In addition, it seems increasingly likely that some form of maturation signal can be received even in the absence of overt infection, i.e., at the steady state. Such signals may enhance the DC's ability to present self-antigen to promote tolerance and elicit the production of Tregs; alternatively, unstimulated, immature DCs may carry out this function. The mechanisms underlying these events are currently under active investigation as they will likely prove keys to understanding how DCs may act to restrict protective T-cell responses in cancer, and also how they might be mobilized for therapeutic benefit. In this context, it is worth emphasizing that “adjuvants” used during any vaccination procedure are little more than DC maturation signals.

Antigen processing and presentation by DCs

DCs are exceptional with respect to their ability to capture even small amounts of antigen for presentation. This is particularly true for “cross presentation”, whereby antigens captured from the extracellular space can be converted into peptides loaded onto MHC class I molecules; classically, MHC class I is associated with the presentation of peptides derived from antigens synthesized endogenously (e.g., viral antigens presented by MHC class I on the surface of infected cells). Again, DCs likely derive their efficiency from a series of specializations that primarily reflect the optimization of cell biologic processes that are widely distributed among a variety of cell types.

The basic pathways of antigen processing are well understood, although many important details remain poorly described. MHC class II pathway is most commonly associated with the presentation of antigens derived from extracellular sources. Antigens such as bacteria, protozoans, allergens, or dead cells are internalized by endocytosis and delivered to one or more populations of endosomes and lysosomes where they encounter environments of progressively decreasing pH and increasing hydrolytic activity. In DCs, especially immature DCs, MHC class II molecules are delivered to most of the same compartments. Here, the antigens are denatured and partially cleaved revealing domains capable of binding to MHC class II. Unbound regions of these protein antigens are then removed by exo-proteases leaving a 10-15-mer peptide bound to the MHC class II binding cleft. Upon maturation, these peptide–MHC complexes are transferred to the surface, or are routed there constitutively if formed after maturation.

As mentioned above, the MHC class I pathway is typically associated with the presentation of peptides derived from endogenously synthesized components, such as viral proteins

made in the cytoplasm of infected cells. In this example, a fraction of newly synthesized viral proteins are ubiquitinated, cleaved by the proteasome, and the resulting peptides translocated into the ER via the TAP1/TAP2 ATP-dependent peptide transporter for loading on to MHC class I molecules in the ER lumen. Peptide loading completes the folding process, rendering the MHC class I-peptide complexes competent for transport from the ER to the Golgi complex and finally to the plasma membrane. DCs are peculiarly capable of a variation of this process that allows extracellular antigens also to enter the endogenous MHC class I pathway. This variation, cross presentation, allows antigens internalized by endocytosis to escape across the endosomal, phagosomal, or lysosomal membrane and to become substrates for the cytosolic processing machinery (there is some evidence that the relevant population of MHC class I molecules used for loading may be in endosomal compartments in addition to the ER. How antigen escapes endosomes is unclear, but may simply reflect a controlled rupture of the endosomal-phagosomal membrane. DCs could excel in cross presentation relative to other cells by enhancing the rate of rupture or by attenuating the rate at which internalized antigens are destroyed before reaching the cytosol; there is evidence that both mechanisms are at work.

Importantly, antigens presented by both the MHC class I and class II systems play a role in generating immunity and maintaining tolerance depending on the maturation or activating state of the DCs engaged in presentation.

DCs exist as multiple populations

While most or all DCs may share the phenotypic features associated with maturation and antigen presentation, it is also clear that they exist as multiple subpopulations both in human and in mouse [1]. The relationships among these various subsets are just being worked out based on detailed lineage analysis. Most DCs are directly or indirectly derived from bone marrow precursors, with tissue (including lymphoid organ) residents and circulating DCs being derived from common early progenitors while new DCs recruited from the blood especially in response to inflammation can be differentiated by cytokines (e.g., GM-CSF and IL-4) from monocytes. Langerhans cells, the DCs of the epidermis, may expand by local proliferation or derive from progenitors housed in the hair follicle. Plasmacytoid DCs (pDC) represent another distinctive subset as compared with "conventional" DCs (cDC) that share myeloid or monocytic progenitors. pDCs diverge from cDCs at an early stage of development and are quite distinct in their ability to react to virus infection by the production of prolific amounts of type I interferons. Like other DCs, though, they do retain at least some capacity for antigen presentation.

Although interesting, the origin and development of diverse DC subsets is less important than their functional implications. Indeed, there is increasing evidence that different populations found even within a single peripheral organ (skin, gut, lung) can have decidedly different functions in inflammation, generating polarized T-cell responses, or the regulation of immunity [4]. These differences likely reflect divergence of DCs at late stages development, or even at the stage of maturation. They are not likely to reflect the existence of distinct cell types with fundamentally different or hard-wired properties. Unfortunately, DC subsets are generally defined on the basis of surface markers that have little if anything at all to do with their functions, making them difficult to study or to understand at the molecular level.

One of the most intriguing properties of subsets concern variations in their capacity for cross presentation on MHC class I. In the mouse, cDCs expressing CD8α in the spleen and lymph nodes are rare populations that both *in vivo* and *in vitro* are more efficient at cross presentation than their more numerous CD8α-negative counterparts. Development of these cells seems to be under the control of the Batf and IRF8 transcription factors. However, no unique transcripts have yet been identified that explain their enhanced capacity for cross presentation; rather, the increased efficiency may reflect a series of small as yet incompletely identified optimizations. In contrast, the CD8α-negative population may be relatively more adept at presentation on MHC class II, although *in vitro* and likely *in vivo* under conditions of antigen excess, both populations can mediate both forms of antigen presentation. In humans, the BDCA3-positive subset (relative to the more numerous BDCA1 subset) has been associated with greater cross presentation capacity, but again as in the mouse, this is a question of degree and not of absolute ability [5].

DCs, cancer, and cancer immunotherapy

The fact that many patients with cancer make objective T-cell responses to their tumors indicates that at some point DCs must have successfully presented one or more tumor-associated antigens to naïve T cells. On the other hand, due to the similarity of many tumor antigens (including proteins bearing point mutations) to normally occurring self-proteins as well as to their chronic exposure to DCs under non inflammatory conditions, antigen presentation by tumor-exposed DCs may just as easily serve to induce tolerance, likely by the generation of Tregs. Furthermore, as a tumor progresses, potent mechanisms of immunosuppression can develop that potently inhibit the function of effector T cells. Some of these can be induced in DCs by factors in the tumor microenvironment, perhaps derived from other infiltrating myeloid cells. Such mechanisms can include the expression of PD-L1 and PD-L2 (ligands for T-cell checkpoint receptor Programmed-Death-1 (PD-1), which induces T-cell "exhaustion"), TGFβ (favors Treg production), and cytosolic enzymes such as indoleamine-2, 3-dioxygenase and arginase (that generate immunosuppressive metabolites). Although as yet poorly characterized mechanistically, it is becoming clear that tumors help ensure their resistance to immune recognition by limiting both T-cell and DC function.

The suppression of DC activity, especially in the absence of optimal adjuvants and antigen delivery systems, helps explain why vaccine therapies in cancer have not yet proved efficacious [6]. Moreover, even if antitumor T cells had been produced as a consequence of vaccination, their activities would likely be subverted by immunosuppression in the tumor bed. In contrast, therapies that target T-cell checkpoints or nodes of immune suppression (anti-CTLA4, anti-PD-1, anti-PD-L1) have exhibited exciting activity, in the first instance by rescuing pre-existing T-cell responses. Used in conjunction with such immunomodulators, the prospects for cancer vaccines as adding to a combination regimen of immunotherapy appear both biologically rational and therapeutically tractable. Such approaches will require not only careful attention paid to the problem of antigen selection, but also, and most importantly from the vantage point of this

brief review, to the issue of adjuvants: what DC maturation signals will facilitate the generation of activated DCs most capable of eliciting anti-tumor T-cell responses? The optimal adjuvant should favor the production of cytotoxic $CD8^+$ T cells. Therefore, it seems reasonable to imagine that adjuvants derived from pathogens that do this in nature (e.g., viruses) might accomplish this task in the therapeutic setting. Alternatively, even synthetic adjuvants that upregulate DC surface proteins known to favor polarization to $CD8^+$ T cells (e.g., CD70) might also suffice.

Conclusion

Such kind of extensive study about the basic biology of DCs, we become substantially better informed as to the steps we can or should take in the therapeutic setting to recruit their participation in enhancing the type of durable responses to cancer we can now expect from successful immunotherapies.

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