# Old Meets New: The Interaction Between Innate and Adaptive Immunity

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**The innate immune system is an ancient and diverse collection of defenses, including the recognition of pathogens through the use of germline-encoded pathogen receptors. The adaptive immune system, encompassing T and B cell responses, is a more recent development that utilizes somatically recombined antigen receptor genes to recognize virtually any antigen. The adaptive immune system has the advantage of flexibility and immunologic memory but it is completely dependent upon elements of the innate immune system for the initiation and direction of responses. Appropriate innate and acquired immune system interactions lead to highly efficient recognition and clearance of pathogens, but maladaptive interactions between these two systems can result in harmful immunologic responses including allergy, autoimmunity, and allograft rejection.**

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Immunologic defenses in vertebrates consist of two immunologic subsystems—innate and adaptive. For much of the past 30 years, immunologists and microbiologists have studied innate and adaptive immunity in isolation. Today, these elements of immunity are appreciated as obligate and synergistic parts of the system that mediate successful host responses to infection and tissue injury. The innate immune system encompasses a collection of host defenses that range from the non-specific barrier function of epithelia to the highly selective recognition of pathogens through the use of germline-encoded receptors. A common feature of these diverse elements is a rapid and blunt response to infection or tissue destruction (Janeway and Medzhitov, 2002). In contrast, the adaptive immune system uses somatically rearranged antigen receptor genes to create receptors for virtually any antigen. The adaptive immune response is slower but more flexible and is able to combat infections that have evolved to evade innate responses. The adaptive immune system has the capacity to recognize and respond to virtually any protein or carbohydrate imaginable; yet, without the innate immune system to instruct it—in effect, telling it whether, when, how, and where to respond—it is powerless. The mechanisms by which the innate immune system instructs and directs adaptive immune responses are becoming increasingly clear and what follows is a discussion of this immunologic interface.

## The Innate Immune System: Rapid Response

The innate immune system responds by recognition of conserved motifs in pathogens as well as a number of other indicators of cell stress or death. The cellular components of the innate immune system include dendritic cells, monocytes, macrophages, granulocytes, and natural killer T cells, as well as the skin, pulmonary, and gut epithelial cells that form the interface between an organism and its environment. The non-cellular aspects of the innate system are diverse and range, from the simple barrier function of the stratum corneum to complex pathways such as the complement cascade. These non-cellular elements seek to prevent the entry of pathogens through physical blockade, or once invaded, to destroy pathogens directly or call them to the attention of phagocytes. This review will focus primarily on innate immune elements that are known to interface with the adaptive immune system.

The innate immune system has evolved to recognize molecular patterns common to many classes of pathogens; these elements have been termed pathogen-associated molecular patterns (PAMP). PAMP are diverse and include lipopolysaccharides (LPS), aldehyde-derivatized proteins, mannans, teichoic acids, denatured DNA, and bacterial DNA (Medzhitov and Janeway, 2002). The innate immune system recognizes PAMP using a group of germline-coded, evolutionary conserved proteins termed pathogen-recognition receptors (PRR) (Janeway and Medzhitov, 2002). PRR were initially defined as cell-surface pathogen receptors present on innate immune cells, but this definition has been expanded to include secreted and locally produced molecules that mediate many steps in inflammation including directed phagocytosis, activation of inflammatory signaling pathways, induction of cell death, and activation of the complement or coagulation cascades (Janeway and Medzhitov, 2002).

The Toll-like receptors (TLR) are a particularly important group of pathogen receptors. These molecules are expressed on both innate immune cells and on cells in various tissues including endothelial cells, epithelial cells, and fibroblasts (Schnare *et al*, 2001; Janeway and Medzhitov,

Abbreviations: Ig, immunoglobulin; IL, interleukin; PAMP, pathogen-associated molecular patterns; TLR, Toll-like receptors; Treg, T-regulatory

2002). Ten TLR family members specific for various microbial molecules have been identified in humans. Binding of TLR to their microbial ligands leads to activation of phagocytes and direct killing of pathogens, as well as to the release of pro-inflammatory cytokines and anti-microbial peptides (Takeda *et al*, 2003). In addition, these molecules activate dendritic cells and are therefore important in the initiation of adaptive immune responses, a role that will be discussed more fully below. Binding of ligands to TLR triggers activation of the nuclear factor-κB (NF-κB) signaling pathway (Takeda *et al*, 2003). This signaling pathway is a master switch for the induction of inflammation. In the skin, NF-κB signaling induces the expression of chemokines, cytokines, adhesion molecules, matrix metalloproteases, nitric oxide synthase, and enzymes that regulate prostanoid synthesis, in short, everything needed to instigate an inflammatory response (Medzhitov and Janeway, 1997).

In addition to TLR, other types of tissue factors associated with inflammation can act as danger signals leading to the activation of phagocytes and dendritic cells (Matzinger, 2002; Kapsenberg, 2003). These factors include heat-shock proteins, lectins, cytokines, chemokines, extracellular matrix components, and various cell-surface molecules including lipids from necrotic cells. These danger signals lead to phagocyte activation and destruction of endocytosed pathogens as well as activation of dendritic cells and the resultant initiation of adaptive immune responses.

Anti-microbial proteins and peptides are additional components of the innate immune system. These molecules include large proteins such as lysozyme and cathepsin G as well as smaller anti-microbial peptides including the defensins, cathelicidins, and the skin anti-microbials dermcidin and psoriasin (Madsen *et al*, 1991; Schittek *et al*, 2001; Ganz, 2003). Mice deficient for cathelicidin are susceptible to infections with *Group A Streptococcus*, demonstrating the importance of these molecules (Nizet *et al*, 2001). The defensin family of peptides has anti-microbial effects at physiologic concentrations and is produced by a variety of cell types including neutrophils and epithelial cells of the epidermis, bronchial tree, and genitourinary tract. Defensins kill pathogens directly through cell lysis and can also induce the chemotaxis of monocytes, dendritic cells, and T cells. For example, the defensin hBD-2 binds to the CCR6 chemokine receptor and is chemotactic for both immature dendritic cells and memory T cells (Yang *et al*, 1999). This is a notable example of a molecule, microbicidal in its own right, that also signals to key elements of both the innate and adaptive immune systems.

Anti-microbial peptides have particular clinical relevance in dermatology. It has long been observed that patients with psoriasis, a chronic inflammatory and hyperproliferative skin disorder, suffer from fewer skin infections than would be expected, given the degree of skin barrier disruption. It was recently reported that psoriatic scales contain high levels of anti-microbial peptides including defensins, psoriasin, and additional novel compounds (Harder and Schroder, 2005). The anti-microbial psoriasin, first isolated from psoriatic epidermis (Madsen *et al*, 1991), protects human skin from *Escherichia coli* infection (Glaser *et al*, 2005). The high levels of microbicidal peptides in psoriatic skin may underlie its relative resistance to bacterial superinfection. In contrast, skin affected by atopic dermatitis is notoriously susceptible to infections with Gram-positive bacteria and has also been found to lack expression of the important anti-microbial proteins cathelicidin and the defensin hBD-2 (Ong *et al*, 2002).

## The Adaptive Immune System: Flexible but Dependent

T and B lymphocytes are the cellular elements of the adaptive immune system, a relatively recent evolutionary development dating back to the emergence of vertebrates some 400 million years ago. The hallmarks of the adaptive immune response are flexibility and memory. Flexibility is provided by the unique way in which T and B cells recognize antigens. Unlike cells in the innate system, which use a fixed repertoire of inherited receptors, T and B cells undergo a recombination of antigen receptor genes to create novel and unique antigen receptors capable of recognizing virtually any antigen. B and T cells that have encountered antigen persist over the long term within an organism and provide rapid and specific responses to reinfection, a concept known as immunologic memory.

Antibodies, encoded by heavy and light immunoglobulin (Ig) genes, are the antigen receptors on B cells. Antibodies can be both cell surface bound and secreted and are classified by the isotype of their heavy chains (IgM, IgG, IgE, IgA). Antibodies recognize the tertiary (three dimensional) structure of native proteins and glycoproteins. B cells first produce pentameric IgM but under the influence of T cell cytokines and other factors, B cells undergo additional genetic recombination events leading to isotype switching and production of IgG subtypes, IgE or IgA. Fine tuning of antigen specificity is also accomplished by affinity maturation. This process involves hypermutation of antibody genes combined with competition for antigen within lymphoid follicles, leading to selective survival of B cells with the highest affinity for antigen.

T cell receptors differ from B cell receptors in several fundamental ways. First, they are never secreted, existing instead on the cell surface as heterodimers of αβ or γδ subunits. Second, T cells recognize peptides produced by the proteolytic cleavage of antigens as opposed to the native proteins recognized by B cells. Thus, T cells recognize the primary structure (amino acid sequence), and B cells recognize the tertiary (three-dimensional folded) structure of a protein. Lastly, T cells recognize antigenic peptides only when they are presented on the cell surface bound to class I or class II major histocompatibility (MHC) proteins .

Cellular cross-talk is a hallmark of the adaptive immune system. In order for naïve B cells to proliferate and differentiate in response to most antigens, they must be stimulated by a $CD4^+$ helper T cell that is specific for the same antigen. T cells also require a second signal in order to proliferate and differentiate after encountering antigen. T cells that do not receive this co-signal are likely to be rendered unresponsive, or anergic. Thus, T cells determine what B cell antigens will be recognized, and T cells need another signal in order to proliferate in response to antigen, a signal that can be provided by B cells. B and T cells

therefore engage in a complex dialog during immune responses.

T cells can be divided into a number of distinctive subsets based on their migration patterns and functional abilities. Naïve T cells recirculate primarily between the blood and lymph nodes, a pattern aided by their expression of the homing receptors L-selectin and CCR7 (Mackay *et al*, 1990; Sallusto *et al*, 1999). This allows them to sample the environments of lymph nodes from different tissue types, increasing their chances of encountering specific antigen. Memory T cells can be further divided into central memory and effector memory cells (Sallusto *et al*, 2004). Central memory T cells primarily migrate between blood and lymph nodes in a pattern similar to that of naïve T cells, although recent evidence suggests that these cells may also enter peripheral tissues (Campbell *et al*, 2001). Central memory T cells serve primarily as long-lived reservoirs of immunologic memory. When stimulated with antigen, these cells give rise to additional central memory cells as well as effector memory T cells. Effector memory T cells are shorter lived and aggressive, specialized for migration into target tissues and neutralization of pathogens (Sallusto *et al*, 2004).

Memory T cells can also be characterized based on what peripheral tissues they enter. The body can be subdivided into different immunologic zones, and T cells that encounter antigen first in a particular tissue tend to recirculate through that tissue in the future (Campbell and Butcher, 2002; Kupper and Fuhlbrigge, 2004). This tissue-specific migration is controlled by the expression of specific molecules, termed homing receptors, on the surface of memory T cells. Expression of the homing receptor cutaneous lymphocyte antigen guides T cells to the skin, and expression of the integrin $\alpha_4\beta_7$ sends T cells specifically to the gut (Picker *et al*, 1990; Butcher *et al*, 1999). This selective recirculation to the sites of prior antigen exposure allows T cells to focus their attention on sites where this antigen is most likely to be encountered in the future.

Lastly, $CD4^+$ T helper cells can be functionally divided into Th1-, Th2-, and T-regulatory (Treg) cells. Th1 cells secrete Th1 cytokines including IFN-$\gamma$ and TNF-$\beta$ and are efficient at activating macrophages and stimulating cytotoxic T cells, thereby inducing what is termed cell-mediated immunity. Th2 T cells secrete Th2 cytokines such as interleukin (IL)-4, IL-5, and IL-13, and are efficient at stimulating B cells to make antibodies, in particular IgE, inducing what is called the humoral immune response (Mosmann and Coffman, 1989). The immune response to a pathogen can be primarily cellular or humoral, based on the particular response of an individual. In general, Th1 cytokines encourage cellular immunity and can suppress Th2 responses. A notable exception is the finding that the Th1 cytokine IFN-$\gamma$ acts to induce B cell production of IgG2a antibodies, a subtype implicated in Th2 autoimmune diseases including lupus (Gavalchin *et al*, 1987; Snapper and Paul, 1987). Similarly, Th2 cytokines activate humoral responses and can act to suppress cellular responses. Treg cells are a recently recognized family of $CD4^+$ T cells that act to suppress the responses of other T cells. These cells play a role in regulating self-tolerance but may also interfere with immunity to tumors (Sakaguchi *et al*, 2001).

In summary, T cells can be considered to be "polarized" in a number of different ways. Memory T cells are spatially polarized in that they migrate to specific tissues based on where they first encountered antigen. Secondly, helper T cells are functionally polarized in that they encourage different types of immunity: cellular immunity, humoral immunity, or no immunity (tolerance). Lastly, memory T cells are both spatially and functionally polarized by whether they migrate primarily to lymph nodes and promote memory responses (central memory T cells) or migrate to peripheral tissues and promote destruction of pathogens (effector memory T cells). These T cell polarization states help to fine tune and regulate the adaptive immune response. Most, if not all, of these polarization states are the direct result of signaling from the innate immune system through its intermediate cell, the dendritic cell.

## Dendritic Cells: The Bridge Between Old and New

Dendritic cells are members of the innate immune system that are particularly efficient at stimulating T cells to respond to antigen (Banchereau and Steinman, 1998). Dendritic cells are the only cells capable of activating naïve T cells, and they can load endocytosed antigenic peptides on both MHC class I and MHC class II molecules, allowing presentation to both CD8 and CD4 T cells (Rescigno *et al*, 1998; Guermonprez *et al*, 2003). Dendritic cells develop in the bone marrow and migrate to the tissues in an immature form. Immature dendritic cells efficiently take up antigens from the environment but they do not provide T cell co-stimulatory signals and are therefore poor activators of T cells. Dendritic cells undergo maturation when they are exposed to a number of danger signals including the PAMP described above as well as various cytokines and tissue factors (Chain, 2003). Upregulation of co-stimulatory molecules occurs during maturation with the result that mature dendritic cells are extremely potent activators of T cell responses.

Dendritic cells detect danger signals within the tissues and transmit this information to T cells. Pathogens and tissue insults of many kinds are translated into a common result—activation and maturation of dendritic cells through the NF-$\kappa$B signaling pathway. It is now becoming recognized that dendritic cells pass on a remarkable amount of information to T cells about the type of insult that prompted their maturation (Kapsenberg, 2003). This information affects whether a T cell will respond to antigen, how it will respond, and likely where it will go to respond. The signals that mediate this rich communication are only partially established, and the discussion below will focus on what is currently known about this process.

Dendritic cells provide a number of sequential signals to responding T cells. The first signal consists of the interaction of the T cell receptor with specific antigen and MHC on the surface of the dendritic cell and determines the antigen specificity of the response. The second signal provides the co-signaling that T cells need in order to respond to antigen. This co-signaling can be either positive (co-stimulation) or negative (co-inhibition) and can be provided by a growing

family of molecules including CD80 (B7-1), CD86 (B7-2), CD28, and CTLA-4 (Baxter and Hodgkin, 2002; Chen, 2004). In the absence of a second signal or in the presence of a co-inhibitory signal, T cells fail to respond to antigen and may in fact be rendered unresponsive to this antigen in the future (Fig 1*A*). Thus, the second signal answers the question "will I respond?" The third signal delivered by the dendritic cell stimulates $CD4^+$ T cells to develop into Th1, Th2, or Treg T cells (Fig 1*B*). This third signal determines the functional polarization of these cells and answers the question "how will I respond?" Lastly, T cells receive poorly characterized signals from either dendritic cells or their environment, which stimulate them to produce homing receptors that will direct them to migrate through tissues similar to those in which they first encountered antigen (Campbell and Butcher, 2002) (Fig 1*C*). This fourth signal determines spatial polarization and answers the question "where do I go to respond?" As our knowledge about the complexities of lymphocyte behavior expands, additional signals that fine tune T cell responses will likely be discovered.

Co-signaling (the second signal) is delivered by dendritic cells that have undergone activation and maturation in response to the detection of danger signals in the environment. These signals, described above, are diverse but generally have activation of the NF-κB pathway in common (Bonizzi and Karin, 2004). In most cases, activation of dendritic cells leads to maturation but there are certain immunosuppressive drugs and microbial compounds that arrest dendritic cells in an immature state, preventing them from expressing co-stimulatory molecules. These dendritic cells are unable to stimulate lymphocytes fully and may in fact induce tolerance through anergy or production of Treg cells (Kapsenberg, 2003). For example, *Plasmodium falciparum* infects red blood cells and these infected cells paralyze dendritic cells by binding to CD36 and CD52 (Urban and Roberts, 2002). Thus, although the innate immune system is efficient at perceiving a variety of danger signals and translating these into T cell responses via dendritic cell maturation, there are a number of pathogens that have evolved to evade this response.

Functional polarization of T cells by dendritic cells (the third signal) is a remarkable story that continues to unfold. Different PAMP and danger signals appear to polarize dendritic cells functionally into Th1-, Th2-, or Treg-type cells, imprinting them with the ability to produce cytokines and to induce T cells to differentiate selectively into Th1, Th2, or Treg cells. PAMP and other danger signals can thus be divided into type 1, type 2, and regulatory-type PAMP that induce the formation of Th1, Th2, and Treg cells, respectively. Dendritic cells subsets appear to be flexible in that they can adopt any polarization state, although rare subtypes may be hardwired to produce Treg cells (Bilsborough *et al*, 2003). Thus, dendritic cells tell T cells not only *to respond* but also *how to respond*, tipping them off as to the type of immune response that should be initiated.

Type 1 PAMP have been most fully studied and include many but not all of the TLR. For example, double-stranded RNA binds to the TLR3 (Alexopoulou *et al*, 2001) and induces the maturation of dendritic cells that strongly support the formation of Th1 T cells (Cella *et al*, 1999; de Jong *et al*, 2002). LPS binding to TLR4 induces IL-12 production in dendritic cells as well as the ability to induce a Th1 phenotype in T cells in both mice and humans (Langenkamp *et al*, 2000; Boonstra *et al*, 2003). But not all TLR-associated signals produce type 1 dendritic cells. *Mycoplasma*-derived lipopeptide 2 binding to TLR2–TLR6 heterodimers induces dendritic cells to secrete IL-10, not IL-12, and these dendritic cells induce unpolarized T cell responses (Weigt *et al*, 2003). Moreover, TLR2 triggering by the lysophosphatidylserine from the parasite *Schistosoma mansoni* actually stimulates dendritic cells to secrete the regulatory cytokine IL-10 and induces T cells to adopt a Treg phenotype (van der Kleij *et al*, 2002).

Th2-biased host responses are often involved in the effective control of infections with parasitic worms. This Th2 bias may arise from the ability of parasitic antigens to induce the formation of type 2 dendritic cells. ES-62, a glycoprotein isolated from the filarial nematode *Acanthocheilonema viteae*, induces the formation of type 2 dendritic cells that support the selective development of Th2 T cells (Whelan *et al*, 2000). Soluble extracts from the eggs of *S. mansoni* induce the development of type 2 dendritic cells that support Th2 T cell development both *in vitro* and *in vivo* (MacDonald *et al*, 2001; de Jong *et al*, 2002). PRR that can mediate induction of type 2 dendritic cells have yet to be identified, although there is some evidence for the contribution of TLR4 signaling through a pathway independent of myeloid differentiation factor 88 (Kaisho *et al*, 2002).

An increasing number of pathogens are being identified that can induce the formation of regulatory dendritic cells, which in turn support the development of regulatory T cells. Priming with the filamentous hemagglutinin of *Bordatella pertussis* and lysophosphatidylserine from *S. mansoni*, both ligands for the TLR2, induces the formation of regulatory dendritic cells that impose a T-regulatory phenotype on interacting T cells (McGuirk *et al*, 2002; van der Kleij *et al*, 2002).

The mechanisms for the spatial polarization of T cells (the fourth signal) are only beginning to be identified. When T cells are primed by dendritic cells located in the gut-associated lymph nodes, these cells upregulate gut-homing adhesion molecules that will preferentially send them back to this tissue in the future (Campbell and Butcher, 2002). This spatial imprinting was recently shown to be the result of retinoic acid production by gut-associated dendritic cells during T cell priming (Iwata *et al*, 2004). Moreover, only gut-associated dendritic cells produce retinoic acid; skin-associated dendritic cells must use a different signal to imprint T cells with skin-homing ability. Deciphering these molecular signals is particularly important for the development of vaccines that will send T cells specifically to the tissues most at risk for infection.

In summary, dendritic cells provide at least three additional signals to T cells that allow them to fine tune their responses. Information is given on whether or not to respond, how to respond (Th1, Th2, and Treg) and where to respond (selective homing). The innate immune system therefore plays a very active role in supporting T cell responses. Additional signals are likely to be discovered as these interactions are explored more fully.

The innate immune system also has the ability to modify the tolerance of T cells to antigen. Most self-reactive T cells are deleted in the thymus during T cell development but

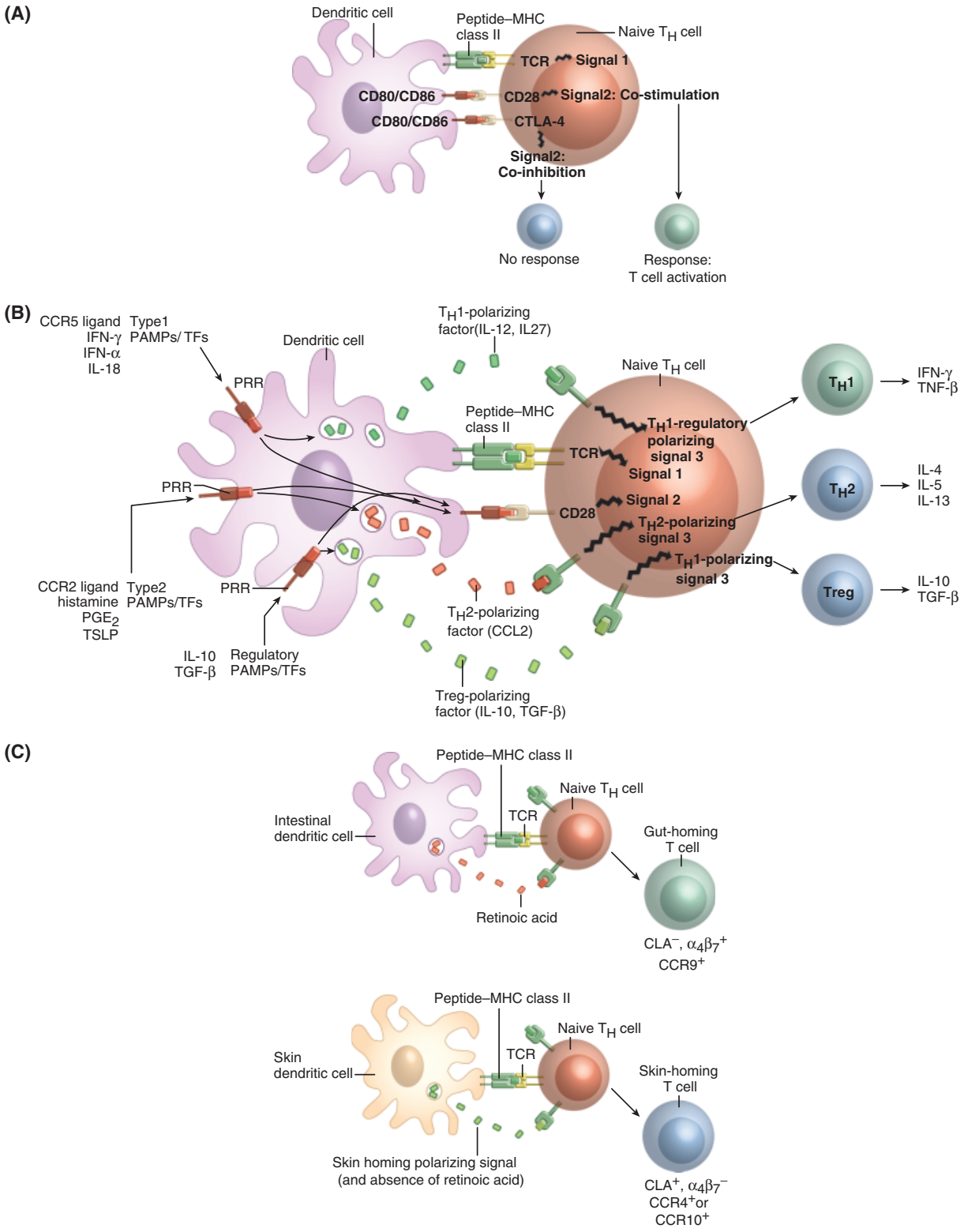


**Figure 1**
**T cell stimulation and polarization require four signals from dendritic cells.** (*A*) Signal one determines antigen specificity and consists of interaction of the T cell receptor (TCR) with peptides loaded onto dendritic cell major histocompatibility (MHC) molecules. Signal two consists of co-signaling and can be either positive, leading to cell activation (co-stimulation) or negative, leading to no response (co-inhibition). Co-signaling molecules, including CD80 and CD86, are upregulated on dendritic cells after binding of pathogen-associated molecular patterns (PAMP) to their cognate receptors. (*B*) Signal three involves the polarization of CD4 T cells into either Th1, Th2, or regulatory T cells. Immature dendritic cells are polarized by the binding of type 1, type 2, or regulatory PAMP and differentiate into mature dendritic cells that induce the formation of Th1, Th2, or T regulatory T cells, respectively. In general, viral-associated PAMP give rise to Th1 responses, and PAMP from parasitic organisms favor Th2 responses. (*C*) Signal four leads to spatial imprinting of T cells, leading to the acquisition of homing receptors that induce selective recirculation through the tissue in which antigen was first encountered. Dendritic cells from the intestine uniquely produce retinoic acid, inducing T cells to upregulate the T cell gut-homing receptors $\alpha_4\beta_7$ and CCR9 and suppress expression of the skin-homing receptor cutaneous lymphocyte antigen (CLA). Signals that polarize T cells to migrate to other sites, including the skin, brain, and pulmonary epithelia, have yet to be identified.

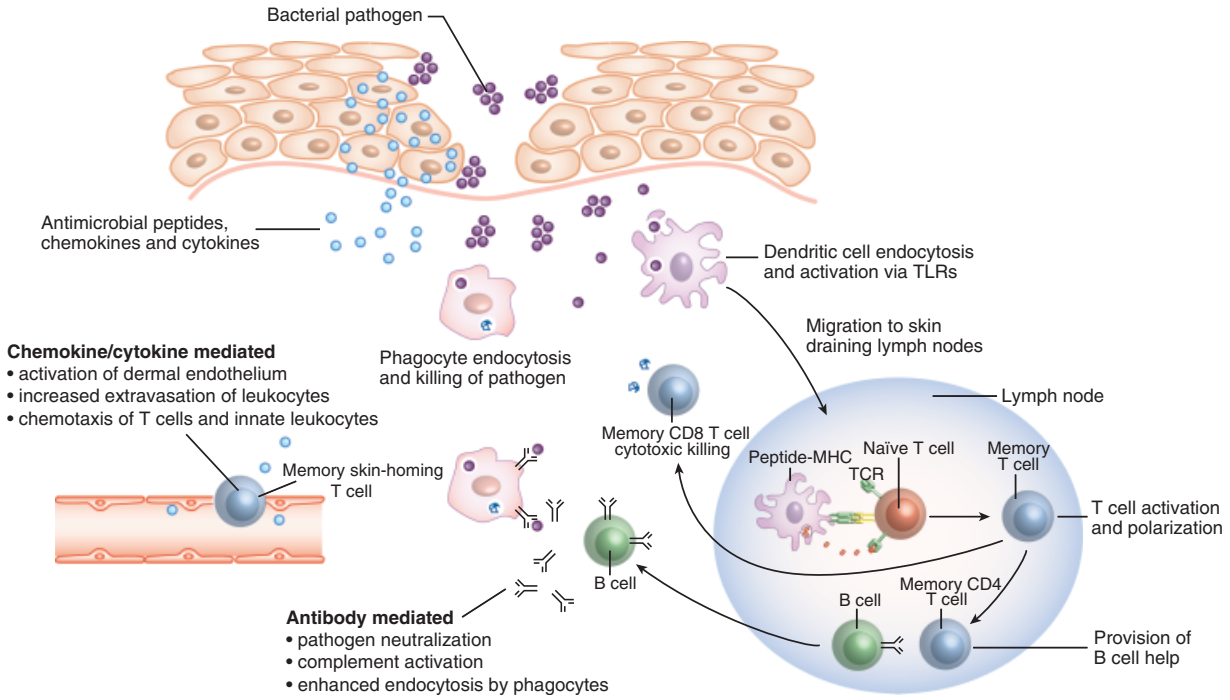


**Figure 2**
**Interactions between the innate and acquired immune systems in response to bacterial infection of the skin.** In response to bacteria that have breached the epithelial barrier, keratinocytes synthesize anti-microbial peptides, chemokines, and cytokines. These factors lead to activation of the dermal endothelium, inducing the migration of innate leukocytes and memory T cells into the skin and additionally guiding these cells via chemotactic gradients. These factors and bacterial antigens activate innate phagocytes to kill ingested organisms and activate dendritic cells to migrate to the skin-homing lymph nodes. In the lymph nodes, dendritic cells present bacterial antigens to naïve and central memory T cells, leading to stimulation of pathogen-specific cells. Effector CD8 cells exit the lymph node, home to inflamed skin and kill pathogens. Helper CD4 T cells provide help to B cells, inducing the production of antibodies that directly neutralize pathogens and lead to additional targeting of innate responses. Antibody-directed phagocytosis by innate cells leads to enhanced antigen presentation, further enhancing acquired responses.

some survive and enter the peripheral circulation. These auto-reactive T cells are controlled by a number of mechanisms that are together termed peripheral tolerance. The innate immune system influences peripheral tolerance at several points. First, dendritic cells that have not received a danger signal present antigen to T cells in the absence of co-signaling molecules. In the absence of co-stimulation or in the presence of co-inhibition, T cells can be functionally silenced and rendered unresponsive to antigens in the future (Baxter and Hodgkin, 2002; Chen, 2004). Second, dendritic cells can induce the formation of Treg cells that can suppress other T cell responses, as discussed above. Lastly, the innate immune system can function to inhibit tolerance by overruling the action of established Treg cells. Dendritic cells triggered by particular TLR can produce IL-6 and other cytokines that render T helper cells resistant to suppression by Treg cells (Kaisho *et al*, 2001; Pasare and Medzhitov, 2003). The innate immune system can therefore function to both induce and suppress tolerance.

Dendritic cells are the main envoys between the innate and adaptive immune system but there are situations when other elements of the innate response signal directly to T cells. For example, some anti-microbial peptides and proteins, including the defensin hBD-2, are chemotactic for T cells (Yang *et al*, 1999). Interestingly, several platelet chemokines, including CXCL4 (PF-4), CCL5 (RANTES), and CTAP-3, also have anti-microbial activity, suggesting that the anti-microbial peptide and chemokine families may functionally overlap (Durr and Peschel, 2002; Tang *et al*, 2002).

Dialogue between the innate and adaptive immune systems is not one sided. Elements of the adaptive response also support the function of the innate immune system. For example, antibodies secreted by B cells bind to macrophages and other phagocytes by interaction with Fc receptors on these cells. Phagocytes can efficiently recognize, internalize, and destroy pathogens using these borrowed antibodies. Moreover, this selective internalization enhances the ability of these cells to internalize and present these antigens to T cells, thereby boosting acquired responses.

## Immunity in the Skin: Adaptive and Maladaptive

To examine the interactions of the innate and acquired immune systems in the context of cutaneous immunity, it is helpful to consider clinical situations that highlight both the positive and negative effects of these systems.

First, we will consider a response of the skin to infection with a bacterial pathogen. As illustrated in Fig 2, bacteria gain access to the body through a break in the skin, thereby overcoming the innate system's first line of defense: an intact stratum corneum. In response to this invasion, keratinocytes produce increased levels of cytokines, chemokines, and microbicidal peptides, including the chemotactic defensins. These peptides have four key effects. First, they help to control the infection by direct killing of the pathogen. Second, they are chemotactic for the cellular elements of

the innate immune system, including phagocytes and dendritic cells. Third, these peptides signal directly to the adaptive immune response by causing chemotaxis of memory T cells. Lastly, these factors lead to activation of the dermal endothelium and increased expression of E-selectin and other vascular adhesion molecules. This leads to increased entry of both innate immune cells and skin-homing memory T cells into the inflamed area of skin. Phagocytes and dendritic cells next arrive and begin to engulf the pathogens. Activation of innate system phagocytes leads to triggering of the respiratory burst and killing of engulfed organisms, whereas activation of dendritic cells induces them to flee the scene, carrying with them the antigenic peptides they have collected. Dendritic cells enter the draining lymph nodes and present the antigens they have acquired to naïve and central memory T cells. During this crucial transfer of information, T cells are tipped off as to the type of immune response to initiate (Th1 *vs* Th2 *vs* Treg) and where to initiate it (acquisition of addressins leading to selective homing). T cells specific for pathogen-associated antigens then proliferate, giving rise to $CD4^+$ T helper cells and $CD8^+$ cytotoxic killer T cells. $CD8^+$ T cells enter the circulation, home to the inflamed skin, and directly destroy pathogens. Meanwhile, pathogen-specific $CD4^+$ cells within lymph nodes provide and to B cells, inducing the production of pathogen-specific antibodies. These antibodies can directly neutralize the pathogen by binding to its surface but can also destroy pathogens via two key interactions with the innate immune system. Firstly, antibodies bound to pathogens can initiate the complement cascade, leading to lysis of the pathogen and further enhanced phagocytosis of the organism by the deposition of complement-derived opsonins. Secondly, antibodies can bind to innate system phagocytes via interaction with Fc receptors. This leads to one of the most daunting collaborations of the innate and acquired immune systems, a phagocyte loaded with microbicidal enzymes and bristling with pathogen-specific antibodies. In addition to direct killing of pathogens, these borrowed antibodies lead to enhanced phagocytosis and highly efficient antigen presentation to T cells, leading to increased adaptive T cell responses. These collaborations of the innate and acquired immune systems lead to multiple levels of defense, ideally leading to clearance of the pathogen.

Adaptive immune responses provide the key elements of specificity and memory but they also carry a risk of inducing maladaptive immune responses including autoimmunity, allergy, and allograft rejection. These conditions occur when the immune system responds to non-pathogenic antigens as if they were infectious. Invertebrates and plants, which lack adaptive immune systems, show no evidence of these maladaptive immune responses (Janeway and Medzhitov, 2002). Interactions between the innate and adaptive immune systems are crucial for these processes; innate elements are responsible for labeling a particular antigen as "dangerous" and passing this information on to the adaptive immune response. T and B cells then initiate a full but misdirected immune response, leading to harmful inflammation. Examples include the immune responses against pancreatic beta cells in diabetes and against melanocytes in vitiligo.

Atopic diseases, including atopic dermatitis, asthma, and seasonal rhinitis, are also the products of maladaptive innate and adaptive immune interactions. Genetic polymorphisms in genes involved in innate immune activation have been associated with an increased incidence of atopic diseases. Allelic forms of CD14, which serves as a receptor for bacterial cell wall components including endotoxin and LPS, have been associated with altered susceptibilities to atopic diseases. The −159 C to T polymorphism correlates with increased levels of serum IgE in atopic children (Baldini *et al*, 1999). Interestingly, this polymorphism correlates with early-onset atopy only during the childhood years, and a second study has confirmed that this polymorphism is not associated with asthma in an adult population (O'Donnell *et al*, 2004; Kedda *et al*, 2005). This CD14 polymorphism is also associated with an increased risk of non-atopic asthma and food allergies (Woo *et al*, 2003). Polymorphisms in the TLR may also contribute to atopy. Polymorphisms in TLR2 are associated with an increased incidence of asthma, allergic rhinitis, and atopic sensitization among children living on farms, and variations in TLR4 correlate with the severity of asthma (Eder *et al*, 2004). Lastly, polymorphisms in the cytokines macrophage migration-inhibitory factor and monocyte chemoattractant protein 1 as well as the intracellular LPS receptor caspase recruitment domain containing protein 15 are all associated with an increased susceptibility to atopic diseases (Kabesch *et al*, 2003; Hizawa *et al*, 2004; Yao *et al*, 2004). In addition to their participation in atopy, autoimmunity, and transplant rejection, exaggerated innate immune responses associated with high levels of inflammatory cytokines can lead acutely to hyperthermia and organ failure, and chronic exposure can lead to the formation of chronic inflammatory states (Kobayashi and Flavell, 2004).

## Conclusions

Recent advances in understanding of the innate and adaptive immune responses have shown that these two systems, previously studied in isolation, are intricately intertwined. Dendritic cells form the chief interface between the innate and adaptive immune systems. These cells convey at least four signals to T cells that lead to modifications of adaptive immune responses. As information continues to emerge about the interdependence of these two systems, it seems somewhat artificial to consider them as separate entities. These two elements may be better visualized as two mutually supportive subsystems, each providing information and assistance to the other. Although imperfect, it is a system that provides a remarkable degree of flexibility and responsiveness, providing the best possible defense against a changing world.

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