Dendritic cells: versatile controllers of the immune system

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The immune system has multiple pathways for recognizing and responding to microbial components and other disease-related stimuli. The dendritic-cell lineage of white blood cells controls this intricate system (**Fig. 1**). After nearly 35 years of research, there are many perspectives from which to appreciate the powerful influence of dendritic cells within the broad reach of immunology.

From the perspective of natural selection, dendritic cells help the immune system defend against more than a thousand different forms of infection. They capture microbial proteins and lipids, and present them to lymphocytes, thereby launching lymphocyte responses.

From a physiological perspective, resistance to infection is not a single automatic response. Instead, dendritic cells select from a host of rapid, short-lived innate reactions and from the more slowly acquired and longer-lived adaptive responses (**Box 1**).

From a cellular perspective, dendritic cells are best known for their role in initiating T-cell immunity, a role that I will emphasize in this Commentary. Nevertheless, dendritic cells can influence all types of lymphocytes, and, I suspect, they will eventually be found to affect some non-immune cells as well.

From a medical perspective, dendritic cells influence many clinical conditions. In addition to providing resistance to some diseases, dendritic cells can instigate autoimmune inflammation and allergy and transplant rejection, and they can be exploited by several infections and tumors.

Owing to their pervasive role in immune responsiveness[1–5], dendritic cells are emerging as key targets for developing new therapies that are disease specific, whether the goal is to enhance resistance or silence unwanted responses.

What led to the discovery of these cells 35 years ago?

Box 1 Innate and adaptive immune mechanisms

Innate and adaptive immune mechanisms operate through more than a dozen cell types that express more than 300 membrane molecules that are denoted by CD numbers—CD1 through CD300. Genetic deficiencies in these products result in heightened susceptibility to infection or to unwanted immune responses against self.

Innate mechanisms include antimicrobial peptides, phagocytosis by macrophages and granulocytes, the complement system, chemokines, cytokines (interleukins, interferons and other) and natural killer (NK) lymphocytes.

Adaptive mechanisms include antibody-producing B lymphocytes, various kinds of helper T cells, killer T cells and suppressor or regulatory (T_{reg}) T lymphocytes.

Diversity is the spice of life (and of immunology)

A hallmark of the broad scope of the immune system is its capacity to recognize and respond to an infinite diversity of entities termed antigens. T cells specifically recognize antigens in hundreds of infectious agents, dozens of cancers, an expanding array of allergies, many histocompatibility antigens in transplants and increasing numbers of self and environmental antigens during autoimmune diseases. Understanding the diversity of immune recognition was so challenging when I entered the field in 1970 that it was likened to God (for 'Generation of Diversity').

It was MacFarlane Burnet, in his beautiful clonal selection theory, who realized the cellular basis for diversity[6]. Burnet proposed that the immune system was comprised of a repertoire of clones, each with a distinct receptor for antigen. The repertoire of immunocytes, as he called them, contained clones that could recognize a world of antigens, including medically relevant ones. Individual antigens would then cause the specific, relevant clone to multiply and produce its receptor as a secreted antibody. Joshua Lederberg provided a genetic perspective to clonal selection. He proposed that immunocytes would have a somatic mechanism to mutate immunoglobulin genes and produce a diverse repertoire[7]. Susumu Tonegawa's breakthrough was the identification of the somatic mechanism that involved genetic recombination[8]. Michel Nussenzweig and Philip Leder proved that, after a membrane antibody is expressed, it regulates further recombination to endow each clone with a single receptor[9]. As a result of this and other accomplishments in lymphocyte biology, diversity is now understood in cellular and molecular terms.

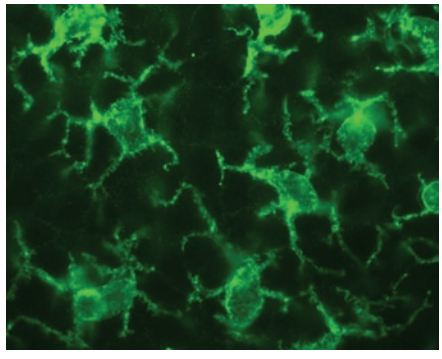

Figure 1 Dendritic cells as they are appear in the skin (and other body surfaces). The stellate cells are stained for a cell-specific marker, Langerin (also known as CD207) in green.

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Figure 2 Zanvil Cohn (left) and Ralph Steinman (right) examining data.

When I began my career in 1970, a big gap in clonal selection theory was the 'immunogenicity' problem. Specifically, the injection of antigens often did not lead to detectable clonal selection and immunity. Consequently, it was not clinically feasible to use either antigens from microbes or tumors to induce resistance, or antigens from allergens, transplants and autoimmune tissues to specifically silence (tolerize) immunity.

The discovery of dendritic cells

One idea was that antigens had to be affixed in an intact form to macrophages to facilitate clonal selection[10,11]. During my postdoctoral work with Zanvil Cohn, a leader in macrophage biology[12], we were unable to find persistent intact antigen on macrophages[13,14]. In 1972, I wondered whether the immunogenicity problem might be profitably studied in the mouse spleen, even though this system seemed remote from the pressing medical problems involving the immune system. Robert Mishell and Richard Dutton in 1966 had set an irresistible stage by figuring out how to generate antibody responses to certain antigens from suspensions of mouse spleen cells[15]. It was then discovered that lymphocytes (mixtures of B and T cells), if purified in various ways, would not form antibodies unless 'accessory cells' were added[16]. I thought accessory cells might offer a chance to understand immunogenicity.

Cohn and I (**Fig. 2**) were committed to studying cells directly and examining their subcellular organelles to understand function. We did something that had not been done before: we looked at the accessory cell populations with phase contrast and electron microscopy. We then found that the accessory cells included not only typical macrophages, but also stellate and elongate cells (**Fig. 3**) that did not look or act like any macrophage that had been studied[17,18].

Because of their tree-like shapes, particularly in the living state—in which they continually formed and retracted their processes—we named them dendritic cells (derived from *dendron*, the Greek word for tree). And even though the dendritic cells represented less than 1% of the cells that we could isolate from spleen, their distinctive traits and potential importance in initiating clonal selection spurred a sustained commitment to figure them out.

It took several years to identify independent approaches to enrich dendritic cells and macrophages to test the two cell types in functional assays. It then quickly became evident that dendritic cells were unique and particularly potent inducers of T-cell immunity[19–26]. Whereas others were mixing accessory cells and T cells in a one-to-one ratio to generate immunity, we had to add only one dendritic cell per 100 lymphocytes to induce strong clonal expansion. Observing the potency of dendritic cells provided many eureka moments in the lab that were shared by key scientists, especially Michel Nussenzweig, Kayo Inaba, Wesley van Voorhis, Maggi Pack, Gerold Schuler and Nikolaus Romani (**Fig. 4**). I have summarized elsewhere[27,28] some early events in the discovery of dendritic cells and their powerful capacity to generate immunity.

Dendritic cells control major T-cell activities

Dendritic cells have been found to influence three essential elements of T cell biology: repertoire, recognition and response.

Repertoire. The repertoire of distinct T-cell clones had been predicted by Burnet, as I mentioned above. Dendritic cells help shape this repertoire in the thymus by presenting self antigens and deleting self-reactive T cells, thereby reducing clones that could bring about autoimmune reactions.

Recognition. The way in which T-cell clones recognize antigen (**Fig. 5**) could not have been predicted. After many breakthroughs, some of which were recognized by the Lasker awards given to Rolf Zinkernagel, Peter Doherty, Emil Unanue, Jack Strominger and Don Wiley, it became clear that protein antigens must first be processed and presented as peptide-MHC (major histocompatibility complex) complexes before a specific T-cell clone could be selected[29–31].

Dendritic cells are specialized to capture antigens and select T-cell clones *in vivo*. They have multiple potential receptors to enhance antigen uptake and are efficient at processing these antigens to form peptide-MHC complexes. As dendritic cells localize to body mucosal surfaces, they are ideally positioned to capture antigens[32–34]. The dendritic cells then migrate to lymphoid or immune organs to join a vast dendritic-cell network, all the time probing the local environment by extending and retracting their processes[35]. As T cells circulate continually into and out of the lymphoid organ, the antigen-bearing dendritic cells are positioned to bring about clonal recognition and responses *in vivo*, a process that has now been observed directly in intact lymphoid tissues[36–39].

Response. Selected T cells can follow many pathways after recognizing a peptide-MHC complex (**Fig. 5**). All can be controlled by dendritic cells *in vivo*. When an antigen is selectively delivered to dendritic cells in intact lymphoid organs, the clone expands at a rate of two to three cell divisions per day[40–42]. The dendritic cells also induce the clone to differentiate to acquire function, especially to form $CD8^+$ killer lymphocytes and an expanding array of $CD4^+$ helper cells. The latter include

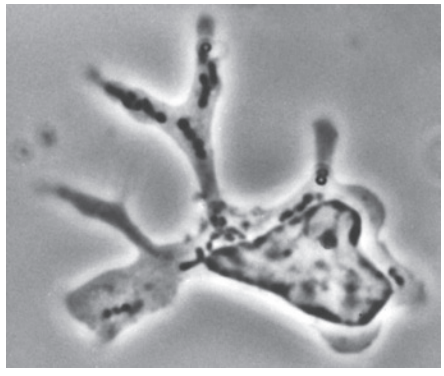

Figure 3 Phase contrast of a splenic dendritic cell. The dense granules are mitochondria.

T_H1, T_H2 and T_H17 T cells that resist various categories of infection, and $Foxp3^+$ and interleukin (IL)-10^+ T cells that silence immunity to harmless self and environmental antigens. When misdirected or dysfunctional, these forms of $CD4^+$ helper cells also cause different forms of inflammatory disease. Importantly, T cells acquire memory; the clone expands in size and function so that immunity is more vigorous and effective upon reexposure to antigen. Dendritic cells have only recently been shown to be involved in memory[43–46].

A vital aspect of a competent immune response is tolerance, the need to silence clones having reactivity to self and thereby avoiding the development of autoimmune diseases. Tolerance develops both in the thymus and elsewhere in the body (peripheral tolerance). Tolerance, much like immunogenicity, is hard to bring about by simply administering protein antigens. The induction of peripheral tolerance is now becoming feasible by using dendritic cells to present the relevant antigen[40–42,47,48]. Importantly, dendritic cells can expand and induce antigen-specific T cells that express Foxp3 and actively suppress autoimmunity[49,50]. By using dendritic cells, relatively small amounts of antigen are required to specifically silence immunity, whereas previously large amounts were needed.

Gaining better antigen-specific control of immunity through dendritic cells

The most gratifying discoveries of dendritic-cell biologists have been the mechanisms that these cells use to play such pervasive roles in immunology.

Metabolic activities of dendritic cells are beginning to be explored. For example, recent studies have revealed that dendritic cells convert vitamin A to retinoic acid, which then is able to induce $Foxp3^+$ T cells to suppress inflammation[51,52]. The induction of antigen-specific suppressor T cells through dendritic cells should be an ideal way to silence unwanted immune responses, including those leading to juvenile diabetes, numerous allergies and transplant rejection.

Dendritic cells have a distinct endocytic system that allows for efficient capture, processing and presentation of antigens[5,53]. In an approach that may guide the future study of dendritic cells *in situ*, antigens are engineered into antibodies to dendritic-cell receptors. When the hybrid antibodies are injected, antigen presentation is enhanced more than 100-fold[40,45,54,55]. This includes cross-presentation[56,57], whereby endocytosed proteins gain access to the proteasome in the cytoplasm and are efficiently presented on MHC class I products[58,59]. Understanding the still mysterious cross-presentation pathway in dendritic cells should enable the development of protein-based vaccines that induce a strong killer T-cell response against infections and tumors.

Dendritic cells rapidly differentiate when they encounter a range of stimuli including microbes, endogenous 'alarmins' and other lymphocytes[60,61]. These stimuli trigger an innate response that consists of numerous cytokines and chemokines. It is still a mystery how dendritic cells react so vigorously and how their rapid innate responses can be turned into more prolonged adaptive responses, including memory. A future research direction will explore the events that take place after dendritic cells and T cells begin to interact, when dendritic cells start to express cytokines and use other molecules such as CD40 and CD70 to generate strong adaptive resistance[54,62].

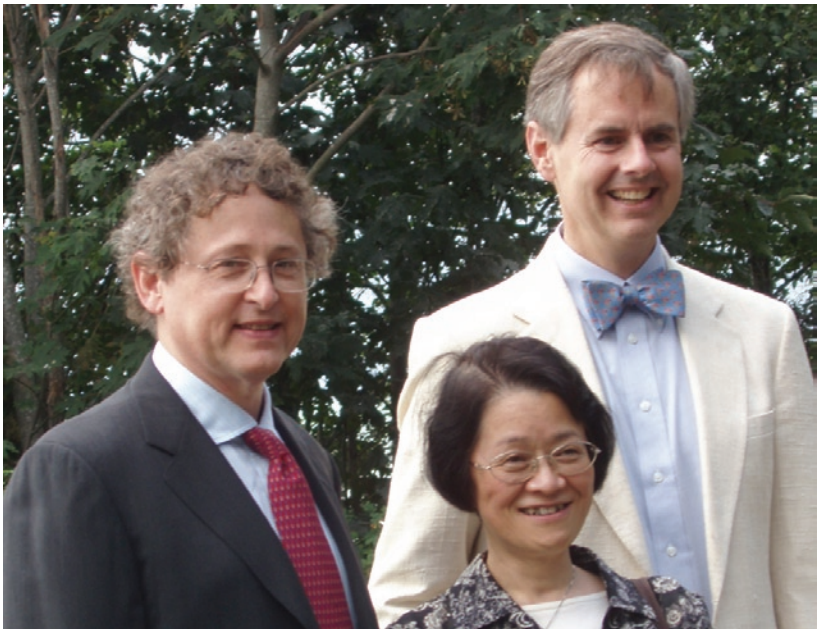

Figure 4 Michel Nussenzweig, Kayo Inaba and Wesley van Voorhis (left to right), who first used dendritic cells to present antigens to T cells.

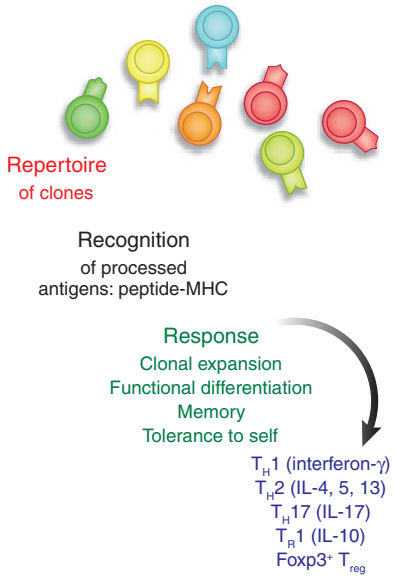

Figure 5 Three elemental R's of T-cell biology: repertoire, recognition, response.

Dendritic cells comprise several different forms or subsets, each having distinct receptors for antigen uptake and signaling, different pathways for antigen processing[55,63] and different functional outcomes[52]. Research in this area may determine that dendritic-cell subsets have evolved to handle select categories of infections and other antigens.

Bringing dendritic cells into medicine

The vision of Mary Lasker was to urge the government to sponsor basic research to understand and treat disease. Her vision remains critical to meet ongoing challenges to the scientific enterprise. One challenge is our declining ability to support independent scientists. I probably could not have carried out my research under the current funding environment for basic research, because many of my grant applications only ranked in the top quartile, whereas funding by the US National Institutes of Health is currently only sufficient for less than 10% of basic proposals.

A second challenge is to energize discovery-oriented research with patients. In the field of immunology, major meetings and journals invariably have too few examples of research performed with human subjects, even though immunology is so central to many areas of medicine. So, government support for patient-

based investigation and for the training of physician scientists should become a priority. The following are some examples where dendritic-cell biology is ripe for patient-based research:

In autoimmunity, research with humans (not mice) has determined that excessive production of cytokines accompanies many diseases. Blocking these cytokines can significantly ameliorate autoimmunity[64]. One culprit is the cytokine-producing dendritic cell. It is now important to identify and silence the driving forces for dendritic-cell production of, for example, tumor necrosis factor in psoriasis[65] and interferons in lupus erythematosus[66,67].

In the field of allergy, research with humans could pursue the lead that allergens can enhance proallergic dendritic-cell functions by triggering a maturation cytokine called thymic stromal lymphopoietin[68] or by blocking IL-12 (ref. 69).

In the field of infectious diseases, immunologists need to contribute to the design of successful vaccines. The biology of dendritic cells suggests several ways to improve the immune response that is elicited by vaccines in humans, particularly in infectious diseases where standard microbial approaches to vaccination do not seem feasible[45,54,70].

The frustratingly high mortality from cancer also needs to be addressed with immunological research in patients, as immune cells and antibodies can provide a broad-based attack on tumors in a specific and nontoxic manner[71,72]. Dendritic cells, targeted with appropriate antigens and stimulated to mature along lines that generate appropriate helper and killer T cells, need to be studied for their potential to elicit immune reactions for cancer treatment and prevention.

Knowing many of the scientists who have helped to explain the pervasive roles of dendritic cells makes me feel like George Palade who said "For a scientist, it is a unique experience to live through a period in which his field of endeavor comes to bloom—to be witness to those rare moments when the dawn of understanding finally descends upon what appeared to be confusion only a while ago—to listen to the sound of darkness crumbling"[73]. The biology of dendritic cells will help to unravel the driving forces for illness and to identify specific strategies to prevent and treat disease.

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COMPETING INTERESTS STATEMENT

The author declares competing financial interests: details accompany the full-text HTML version of the paper at http://www.nature.com/naturemedicine/.

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