pressed on various organs would allow the suppression of activated autoreactive B cells at the target site without the need for T cell involvement. This would be sufficient to prevent the subsequent differentiation of these B cells into plasma cells (Fig. 2).

In summary, there are two types of B cells that appear to be regulated in a T-independent manner. B1 cells, well known for their unique surface markers, have distinct pathways for their activation and migration. The physiological importance of B1 cells in maintenance of the homeostasis at the mucosal surface is clearly demonstrated. The other T-independent B cells, MZ B cells, also appear to have distinct activation and migration pathways. In addition, studies on BLyS, PD-1, and several other molecules have started to elucidate the molecular mechanisms of positive and negative regulation of T-independent immune response. Thus, B cells appear to "have their own kingdom"; they are not always subordinate to T cells. These new aspects of B cell biology will not only affect strategies of immune therapy but also the conceptual framework of evolutional immunology.

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28. We thank N. Minato, T. Tsubata, K. Ikuta, H. Nishimura, and T. Okazaki for their valuable comments and suggestions. Supported by Center of Excellence program from the Ministry of Education, Science, Sports and Culture of Japan.

REVIEW

Dynamics of T Lymphocyte Responses: Intermediates, Effectors, and Memory Cells

Antonio Lanzavecchia and Federica Sallusto

The immune response is initiated in organized lymphoid tissues where antigen-loaded dendritic cells (DCs) encounter antigen-specific T cells. DCs function as packets of information that must be decoded by the T cell before an appropriate immune response can be mounted. We discuss how the dynamics of DC–T cell encounter and the mechanism of T cell differentiation make the decoding of this information stochastic rather than determinate. This results in the generation of both terminally differentiated effector cells and intermediates that play distinctive roles in protection, immunoregulation, and immunological memory.

T lymphocytes recognize antigens by engaging the T cell receptor (TCR) with peptide-MHC (major histocompatibility complex) displayed on the surface of antigen-presenting cells (APCs) (*1*, *2*). Triggering of TCRs results in T cell proliferation and differentiation into a variety of cell fates that determine the class of immune response. $CD4^+$ T lymphocytes can polarize toward T helper 1 (T_H1) or T_H2 cells, which produce different sets of cytokines [interferon-γ (IFN-γ) or interleukin-4 (IL-4), IL-5, and IL-13, respectively] and mediate protection from intracellular or extracellular pathogens (*3*, *4*). $CD8^+$ T lymphocytes differentiate into cytotoxic T cells capable of killing virus-infected cells (*5*). T lymphocytes can also differentiate into regulatory cells, for example, helper cells that migrate to the B cell areas to initiate T cell–dependent antibody responses or suppressor T cells that down-regulate immune responses by secreting inhibitory cytokines (*6*). Some T cells generated during the primary response survive for years as memory cells, which can confer immediate protection and generate more rapid and effective responses upon reencounter with antigen (*7*–*9*).

T cell responses are initiated in the T cell areas of secondary lymphoid organs where naïve T cells encounter antigen-loaded dendritic cells (DCs), a professional type of APC (*10*). There is growing evidence that the information needed to generate different classes of immune response is carried by DCs. Here we focus on the dynamics of DC–T cell interaction. First, we discuss how DCs classify pathogens and assemble packets of information that are delivered to T cells. Then, we consider how T cells decode this information—generating, along a linear differentiation pathway, different types of T cell fates (intermediates as well as effectors). In conclusion, we propose a unified model for DC control of T cell responses.

Dendritic Cells: Packets of Information for T Lymphocytes

DCs are scattered throughout all nonlymphoid tissues where they reside in a resting, so-called immature, state. In response to "danger" signals such as pathogens, inflammatory cytokines, or necrotic cells, DCs migrate to the T cell areas of secondary lymphoid organs and switch from an antigen-capturing to an antigen-presenting and T cell–stimulating mode (*10*, *11*). During this process, defined as DC maturation, the cells assemble peptide–MHC complexes, up-regulate costimulatory molecules, and elaborate cytokines. This results in the formation of packets of information that are delivered to T cells in the draining lymph node (Fig. 1).

Immature DCs efficiently capture exogenous antigens (*12*) and, upon maturation, load the antigenic peptides on preformed empty, as well as newly synthesized, MHC class II molecules (*13*–*16*). While maturing DCs shut off antigen capture and class II synthesis, the newly formed complexes accumulate on the cell surface and acquire extremely long half-lives, exceeding 100 hours. This mechanism allows DCs to retain peptide–class II complexes for several days once they have been assembled, thereby maximizing presentation of those antigens associated with the infec-

Institute for Research in Biomedicine, Via Vincenzo Vela 6, CH-6500 Bellinzona, Switzerland.

E-mail: lanzavecchia@irb.unisi.ch, federica.sallusto@irb.unisi.ch

tious organisms that triggered the maturation process. DCs process and present on MHC class I molecules viral proteins that are either synthesized within the cell or are taken up from apoptotic cells (*17*, *18*). Peptide–class I complexes have short half-lives (~10 hours), and their presentation must therefore be sustained by continuous synthesis of class I molecules and loading from internal sources of antigen. It is possible that some antigens (and pathogens) may reach lymph nodes either directly, via afferent lymph, or via migrating DCs such that they are released when the DC dies. In both cases, the antigen will be taken up and subsequently processed and presented by DCs that are resident within the lymph node that have different properties than migrating DCs (*19*, *20*).

Upon maturation, DCs rapidly up-regulate B7.1 and B7.2 (*16*, *21*, *22*). By engaging CD28 on naïve T cells, these molecules amplify TCR signaling and facilitate the initial phase of T cell activation (*23–25*). At a later stage, B7.1 and B7.2 may modulate T_H1/T_H2 differentiation (*26*) and down-regulate T cell responses either directly, by engaging CTLA-4 (*24*), or by promoting the generation of regulatory T cells (*27–29*). Mature DCs also express 4-1BBL, which costimulates $CD8^+$ T cells (*30*, *31*), and upon CD40 ligation, DCs up-regulate OX40L, which specifically promotes T_H cell differentiation (*32*). ICOS, a receptor expressed by activated T cells, costimulates IL-10 production (*33*), but it is not clear whether ICOS ligands are up-regulated by specific stimuli in maturing DCs.

DCs are probably the most relevant source of IL-12, the principal cytokine that drives T_H1 polarization (*34*, *35*). In DCs, IL-12 production is controlled by the nature of the maturation stimulus, by environmental factors, and by feedback signals from T cells (*36*). Thus, lipopolysaccharide, poly(I:C), bacteria, and viruses induce IL-12, whereas tumor necrosis factor–α, IL-1, and cholera toxin do not. Furthermore, IL-12 production is enhanced by IFN-γ and inhibited by PGE2. Finally, in maturing DCs that reach the T cell areas, IL-12 production can be potently boosted by activated, memory T cells by CD40L (*37*). Recent evidence indicates that IL-12 production is also subject to a tight kinetic regulation. DCs produce IL-12 only within a narrow time frame, between 8 and 14 hours after appropriate stimulation, and become unresponsive to further stimulation at later time points (*38*). In addition to IL-12, DCs produce IL-18 and IFN-α, which promote T_H1 development and, in same cases, IL-4, which promotes T_H2 development (*17*, *39*). DCs can also produce IL-10, which down-regulates their own function as well as T cell responses (*40*). Although these latter cytokines have been reported to influence T cell differentiation, it is not clear whether they are regulated by maturation stimuli.

Mature DCs have a finite life expectancy, which affects their capacity to stimulate T cells. There is evidence that once they have reached the lymph node, DCs survive for only few days and disappear within 48 hours after interacting with antigen-specific naïve T cells (*41*, *42*). However, it has been shown that activated T cells, expressing RANK ligand, can trigger RANK on DCs, thereby enhancing their viability (*43*, *44*). The life-span of DCs during ongoing responses is a critical aspect that needs to be addressed. In addition, it is worth considering that antigen presentation can be carried out by other cell types including B cells, activated T cells, macrophages, and even fibroblasts. These cells may contribute to the expansion of already primed T cells, thus amplifying and possibly modulating T cell responses (*45*).

In summary, migrating DCs can be viewed as disposable cells that function as discrete packets of information, conveying to the T cell areas of lymph nodes, for the duration of their life-span, details concerning antigen specificity and quantity, costimulatory molecule identity and concentration, and cytokine identity and concentration (Fig. 1). Thus, by virtue of the pattern of information they carry, DCs encode a specific T cell differentiation fate. Below we discuss how T cells decode this information.

T Cell Activation and Differentiation Programs

The TCR is a complex signaling machine that allows T cells to monitor the continuous presence of antigen. Signaling in T cells is sustained, through a serial TCR triggering process, for as long as T cells are in contact with APC but ceases immediately when antigen is removed (*46*, *47*). The duration of TCR stimulation represents the driving force for T cell activation, differentiation, and ultimately death (*48*). Naïve T cells require stimulation for ~20 hours in order to be committed to proliferate (*49*). This high activation threshold is due to an inefficiently coupled signaling machinery (*50–55*). In naïve T cells, CD28 engagement recruits membrane microdomains containing kinases and adapters to the triggered TCR, thereby amplifying the signal transduction process and allowing the activation threshold to be reached more rapidly and at lower doses of antigen than would be required in its absence (*25*, *49*). In contrast to naïve T cells, primed, effector T cells have a low activation threshold, because their signaling machinery is fully coupled (*50–55*). A short TCR stimulation (~30 min) in the absence of CD28 engagement is sufficient to trigger proliferation and IFN-γ production in T_H1 cells, whereas an even shorter stimulation triggers cytotoxicity by $CD8^+$ T cell clones (*56*, *57*). A prolonged stimulation of activated T cells leads, however, to activation-induced cell death, an end-stage result that can be prevented to some extent by CD28 engagement, through Bcl-XL up-regulation (*49*, *58*, *59*).

After completion of the first round of mitosis, activated T cells divide every ~10 hours, giving rise to large numbers of cells. As they divide under continuous TCR and cytokine stimulation, T cells progressively differentiate and acquire the capacity to produce effector cytokines (*60*, *61*). Polarization to T_H1 or T_H2 is promoted by IL-12 and IL-4, respectively (*34*, *62–64*), as well as by the strength and duration of TCR stimulation (*65–67*). T cell polarization involves the expression of specific transcription factors (*68–*

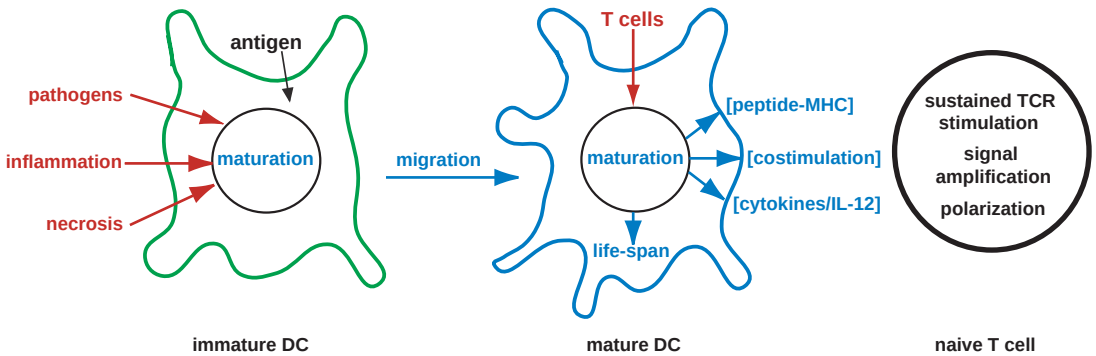

Fig. 1. Mature DCs function as packets of information for naïve T cells. The maturation process is triggered in tissue-resident immature DCs by stimuli (in red) such as pathogens, inflammatory cytokines, or necrotic cells and results in migration to lymph nodes where the maturation process can be reinforced by activated T cells. Maturation (in blue) leads to the assembly of an information packet (antigen, costimulation, and cytokines) that is decoded by T cells.

70), as well as epigenetic changes in cytokine genes that increase their accessibility (*71*–*74*). This process is relatively inefficient, because stable T_H1 and T_H2 phenotypes are acquired after repeated stimulation in a progressive and stochastic manner.

During T cell differentiation, effector function and migratory capacity are coordinately regulated (*75*–*77*). Whereas naïve T cells traffic constitutively through secondary lymphoid organs, effector and memory T cells must migrate to peripheral tissues to perform their function (*78*, *79*). Naïve T cells express the chemokine receptor CCR7, which is required to enter lymph nodes through high endothelial venules and to localize to the T cell areas, where the cognate ligands SLC and ELC are present (*80*, *81*). In contrast, effector T_H1 and T_H2 cells lack CCR7 and express partially divergent sets of receptors specific for inflammatory chemokines that are required for migration to sites of delayed-type hypersensitivity or allergic inflammation (*82*–*84*).

The capacity to survive in the absence of antigen represents an essential part of the T cell differentiation program. Whereas survival of naïve T cells requires continuous low-affinity interactions with self-MHC molecules (*85*–*87*), antigen-primed T cells that survive after the primary immune response as memory cells are promoted to an MHC-independent life-style and slowly cycle in response to cytokines (*88*–*90*). For example, memory $CD8^+$ T cells respond to IL-15, which is essential for their maintenance, but they are inhibited by IL-2 (*91*, *92*). The cytokines responsible for the survival of memory $CD4^+$ T cells have not yet been identified. Thus, the acquisition of cytokine receptors by differentiating $CD4^+$ and $CD8^+$ T cells represents a critical factor in determining their life expectancy.

In summary, the duration of TCR stimulation (i.e., the duration of contact with APC) represents a major factor in T cell fate determination, because it drives cell proliferation, controls various differentiation programs (together with cytokines), and ultimately leads to activation-induced cell death.

Linear T Cell Differentiation: End Products and Intermediates

T_H1 or T_H2 polarization is not an inevitable consequence of T cell activation. Even under the strongest polarizing conditions, only a fraction of responding T cells acquires effector function and tissue homing capacity, while the rest remain nonpolarized, retaining lymph node homing capacity. Furthermore, naïve T cells can be activated and expanded in a nonpolarized state by supplementing cultures with transforming growth factor–β (TGF-β) (*82*, *93*) or by offering a short round of TCR stimulation (*67*). Nonpolarized T cells can be expanded with IL-2 and even cloned, and retain the capacity to differentiate into either T_H1 or T_H2 when restimulated under polarizing conditions (*93*). Nonpolarized cells generated in vitro in the presence of TGF-β or by short TCR stimulation maintain CCR7 expression and migrate to T cell areas of secondary lymphoid organs (*82*, *94*).

The inefficiency of T cell differentiation is dependent primarily on two factors: the probabilistic nature of T cell–DC interaction and the slowly progressive and stochastic nature of the T cell differentiation process. Consequently, a stimulated T cell clone can be viewed as a response unit comprising cells that achieve different levels of stimulation, thereby reaching different thresholds of differentiation.

For each of the numerous clones that are activated in a primary response, the fate can be described in terms of a linear differentiation model (Fig. 2). Depending on the duration of TCR stimulation and cytokine signaling, responding T cells are progressively pushed through hierarchical thresholds of differentiation (*57*, *67*, *95*). The capacity of each cell to achieve stimulation is determined by the TCR affinity for antigen and by the capacity to compete with other cells, of the same or of other clones, for limiting resources (DCs, antigen, and cytokines). Thus, cells that express a low-affinity TCR will achieve a lower level of stimulation than cells that express a high-affinity TCR. One mechanism to enhance the capacity of T cells to achieve stimulation is the up-regulation of receptors for chemokines produced by maturing DCs (*96*, *97*).

Although attention has been largely focused on the terminally differentiated T_H1 and T_H2 cells, it is indisputable that nonpolarized T cells are also generated in the course of the immune response. In trying to envisage a role for these cells, we suggest that these intermediates generated in a primary response survive in a partially differentiated state as memory cells and complete the differentiation process only upon a secondary antigenic stimulation. We also hypothesize that some intermediates may carry out specialized regulatory functions such as B cell help and T cell help or suppression. Finally, we consider the possibility that subthreshold stimulation may induce the cells to reach a stage where expression of chemokine and/or cytokine receptors may be insufficient to ensure access to survival signals. The differentiation through this stage of "non-fitness" may offer a window of opportunity for the induction of T cell tolerance (Fig. 2). Below, we consider the linear differentiation model in the context of the dynamic interactions that take place in the primary immune response.

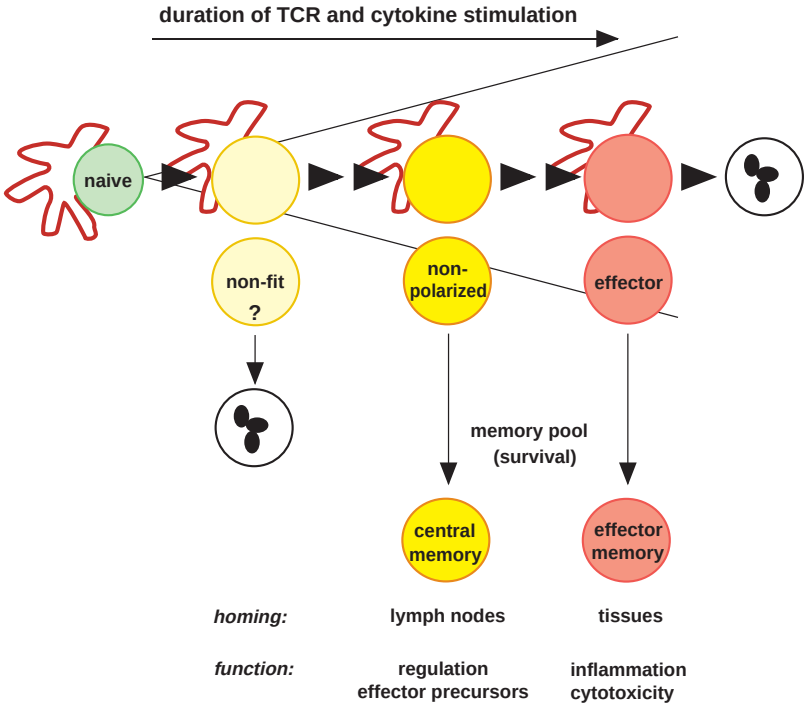

Fig. 2. Linear T cell differentiation driven by the duration of TCR stimulation. In the primary immune response activated T cells proliferate and, depending on the duration of stimulation by DCs and cytokines, reach hierarchical levels of differentiation characterized by distinct effector function, homing, and survival capacity. Proliferating T cells may be eliminated at two levels. Cells receiving excessive stimulation die by activation-induced cell death, whereas cells receiving insufficient stimulation may remain non-fit and die by neglect. The fittest cells survive and enter the memory pool as central and effector memory T cells. This model applies to both $CD4^+$ and $CD8^+$ T cells.

Dynamics of Primary Responses

At a time when reductionism represents a standard and successful approach to understanding biological systems, the complexity of the interaction between DCs and T cells in a primary immune response offers an important challenge to immunologists. There are several aspects that add to this complexity: (i) the number of DCs and the packets of information carried by each cell (antigen, costimulatory molecules, and cytokines); (ii) the number of responding T cells and their affinity and kinetics of recruitment; and (iii) the positive or negative feedback that T cells can exert on DCs (Fig. 3).

In the absence of pathogens, the few DCs that migrate to the lymph nodes carry either no or low levels of tissue antigens and are poorly stimulatory. Antigens that are transported may be released and re-presented by the more abundant lymph node–resident tolerogenic DCs (*19*, *98*, *99*). In contrast, in the presence of pathogens (or adjuvants) many DC precursors are continuously recruited into inflamed tissues and from there continuously migrate to the draining lymph nodes where they arrive endowed with T cell–stimulatory and –polarizing capacity (*100*–*102*). Indeed, although a single DC may drive a naïve T cell through the first division, it is unlikely that it would be sufficient to sustain the stimulation of a rapidly proliferating T cell clone for a period of several days. Consequently, a sustained T cell stimulation is critically dependent on a continuous supply of antigen-carrying DCs.

Pathogens (and adjuvants) differ significantly in their capacity to prime DCs for IL-12 production. Those that induce IL-12 production will directly prime T_H1 responses. However, because IL-12 is produced only transiently after DC maturation, its availability in the lymph nodes will depend on a continuous migration of recently stimulated ("active") DCs. As soon as the influx of active DCs ceases, those present in the lymph node will exhaust their capacity to make IL-12, and conditions for priming of T_H2 responses will develop (Fig. 3). Thus, even for pathogens that strongly induce IL-12, this mechanism allows the immune system to balance a T_H1 response with a subsequent T_H2 response.

In contrast, when DCs are primed by stimuli that do not elicit or inhibit IL-12 production, e.g., inflammatory cytokines, cholera toxin, and PGE2 (*103*, *104*), T_H2 responses may be generated. In this case, the responding T cells produce some IL-4 that drives their own T_H2 polarization (*105*, *106*). Furthermore, stimuli provided by secreted nematode products or fungal hyphae are able to directly set DCs in a T_H2-stimulatory mode by inducing IL-4 production (*39*, *107*). However, in all cases it is possible that activated, memory T cells, by recognizing antigen on DCs, may trigger IL-12 production through CD40L (*37*, *108*), thereby shifting the response toward T_H1. The first scenario may apply to situations of chronic, low-level stimulation by environmental allergens, whereas the second may be the basis of a successful desensitization therapy.

Because of the stochastic nature of the T cell stimulation and differentiation processes, it is inevitable that under all conditions considered so far some activated cells will receive less stimulation and will remain in a nonpolarized intermediate state. However, we envisage that at late stages of the primary response, when antigen-carrying DCs become limiting, the conditions will favor the generation of such nonpolarized T cells. In addition, one should consider that antigen-specific naïve T cells are rare and enter the lymph node asynchronously. Therefore, T cells that enter early will receive a longer and qualitatively different stimulation than those that enter late in the response.

A further level of complexity is related to the ability of T cells to stimulate or inhibit DCs and in this way facilitate or suppress the response of other T cells that recognize antigen on the same DCs. Activated helper T cells expressing CD40L not only boost IL-12 production (*37*, *109*), but can also "license" DCs to prime $CD8^+$ T cells (*110*–*112*). This mechanism is dispensable for CTL responses to viruses that can directly license DCs, but is required to induce CTL responses to minor histocompatibility antigens or tumor antigens that are not associated with a danger signal. Some regulatory T cells are capable of inhibiting DC function by secreting TGF-β and IL-10 or by direct contact (*113*–*116*). These cells are present in healthy mice and can be induced by oral immunization or by antigenic stimulation in the presence of nondepleting antibodies to CD4 or to CD8 molecules (*6*, *117*, *118*). In spite of convincing evidence for their existence and for their role in mediating tolerance in a variety of experimental systems, it has proved difficult to isolate and maintain these cells in tissue culture.

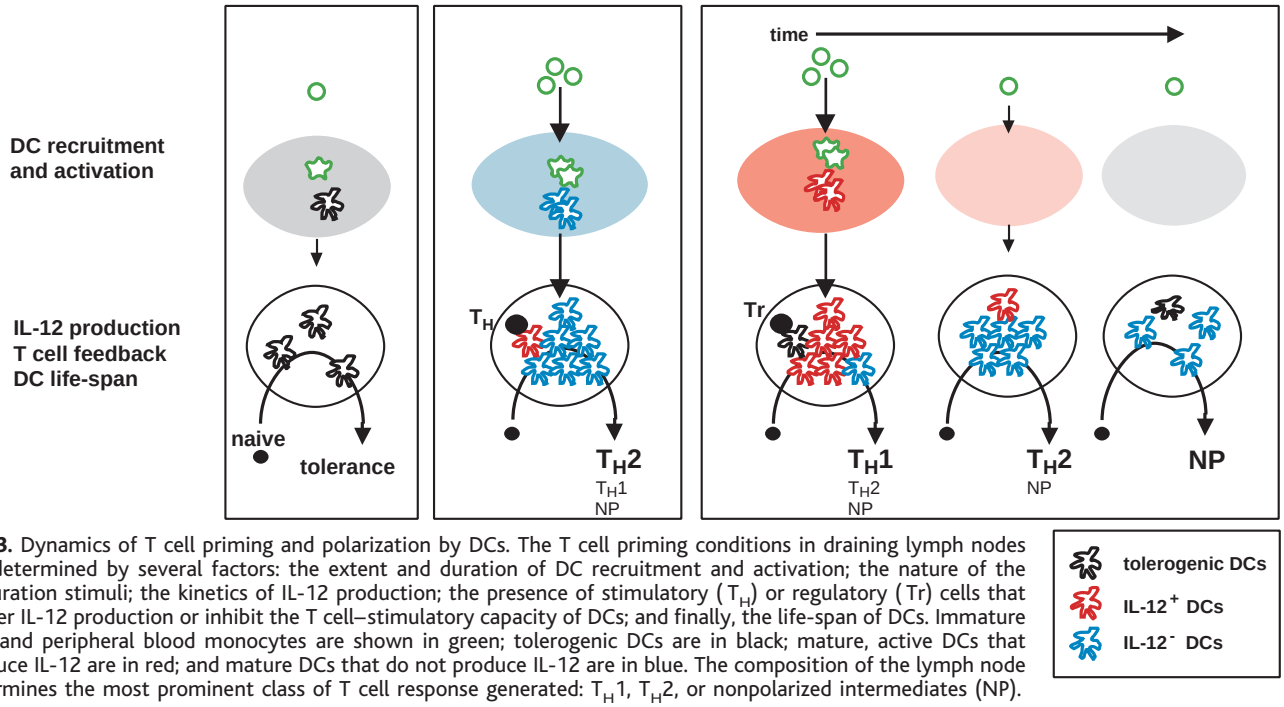

Fig. 3. Dynamics of T cell priming and polarization by DCs. The T cell priming conditions in draining lymph nodes are determined by several factors: the extent and duration of DC recruitment and activation; the nature of the maturation stimuli; the kinetics of IL-12 production; the presence of stimulatory (T_H) or regulatory (Tr) cells that trigger IL-12 production or inhibit the T cell–stimulatory capacity of DCs; and finally, the life-span of DCs. Immature DCs and peripheral blood monocytes are shown in green; tolerogenic DCs are in black; mature, active DCs that produce IL-12 are in red; and mature DCs that do not produce IL-12 are in blue. The composition of the lymph node determines the most prominent class of T cell response generated: T_H1, T_H2, or nonpolarized intermediates (NP).

In summary, the population of antigen-carrying DCs present in the lymph node is highly dynamic, and its density, composition, and function change as a consequence of DC recruitment into tissues, activation by pathogens, and positive as well as negative feedback signals delivered by T cells.

A Role for T Cell Intermediates in Immunological Memory and Immune Regulation

T cells specific for recall antigens with nonpolarized and polarized phenotype can be detected several years after priming and represent two distinct subsets of memory T cells (*108*). "Effector memory" T cells represent terminally differentiated cells that produce IFN-γ and IL-4 or contain prestored perforin. These cells lack lymph node homing receptors but express receptors to enter into inflamed tissues; therefore, their function is to provide immediate protection to contain pathogens in peripheral tissues. In contrast, "central memory" T cells represent intermediates that produce essentially IL-2 (and some IL-10) and express the lymph node homing receptors CCR7 and CD62L. These cells are much more responsive to TCR stimulation than are naïve T cells and can potently stimulate DCs to produce IL-12. Furthermore, central memory T cells can undergo terminal differentiation upon restimulation with antigen.

The presence of these two subsets of memory T cells is consistent with the generation of nonpolarized as well as terminally differentiated T cells during the primary response followed by their rescue during the establishment of memory (*119–124*). It is not clear what the basis is for the selective survival of memory cells. It may involve both the induction of antiapoptotic molecules by costimulation, as well as the induction of high levels of cytokine and chemokine receptors.

In any case, the differential expression of homing receptor implies that central memory and effector memory T cells occupy different niches and therefore may access different types of survival signals. It is interesting to consider the possibility that cytokines and self-MHC molecules may drive antigen-independent slow proliferation and differentiation of central memory T cells. This homeostatic T cell differentiation may occur in vivo during chronic infections characterized by T lymphocyte depletion such as acquired immunodeficiency syndrome.

Besides being a source of effector cells in secondary responses, central memory T cells may be endowed with important regulatory functions. For example, they can stimulate antigen-carrying DCs, thereby behaving as helpers for T_H1 and cytotoxic responses (*108*). Alternatively, they may migrate to the B cell areas to help B cells. Furthermore, it is possible that at least some of the regulatory T cells that suppress DC activation belong to the central memory subset. Indeed, IL-10–producing cells are present within central memory T cells (*125*). The failure to culture in vitro regulatory T cells may simply reflect the fact that, being intermediates, these cells differentiate and lose their property after restimulation.

Flexibility and Robustness of the Immune Response

The capacity of DCs to classify pathogens accounts for the remarkable flexibility of the immune response in terms of class regulation. DCs convey to secondary lymphoid organs packets of information assembled in peripheral tissues. This information is decoded by T cells in terms of differential fates.

In simple biochemical networks some fundamental properties are selected to be robust, i.e., to be insensitive to the precise value of the parameters (*126*). This may also occur for the complex cellular networks, which control the immune response. One property that the immune system selects to be robust is the capacity to respond under extremely different conditions of antigen concentration, giving a variety of functional outputs while avoiding exhaustion. The dynamics of DC activation and T cell–DC interaction and the linear differentiation model account for the generation of both effector cells and intermediates. The latter play a role in immunological memory and may be responsible for regulatory functions such as help, suppression, and tolerance. A better understanding of the properties of these cells will contribute to our capacity to manipulate the immune response.

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127. We thank J. Howard, M. Colonna, and A. Gett for critical reading and comments. Supported by the Helmut Horten Foundation (A.L.).

VIEWPOINT

The Ins and Outs of Body Surface Immunology

Adrian Hayday[1]* and Joanne L. Viney[2]

Rather than being confined to the secondary lymphoid tissue of the spleen and lymph nodes, large numbers of lymphocytes are intrinsically associated with the epithelial surfaces of the body. The best studied is gut-associated lymphoid tissue, but distinct epithelium-associated lymphoid tissue also exists in the reproductive tract, the lung, and the skin. The multiple cell types and functions composing these lymphoid tissues are increasingly seen as the key to how antigens delivered to body surfaces can elicit either immunogenic or tolerogenic responses. In some instances, these responses occur purely within the local body surface tissue, yet in other cases both local and systemic responses are elicited.

The immune system at body surfaces has become a contemporary paradigm for understanding systemic immune function, because local and systemic immune responses are probably connected via an "informational relay" (Fig. 1). The relay starts locally, where body surface antigen-presenting cells, such as dendritic cells (DCs), can be provoked to take up, process, and present antigens locally, or to differentiate and migrate to draining lymph nodes to present antigen to systemic T cells (*1*). The same relay system is also likely to be operational for systemic B cells, which can be also activated by DCs bearing intact antigen from elsewhere (*2*). Migration of the systemically activated cells back to infected body surface areas is facilitated by changes in the expression of homing molecules and chemokine receptors, and the informational relay is completed. Understanding this relay paradigm is critical for aiding the development of vaccines against pathogens [such as mycobacteria, human immunodeficiency virus (HIV), and influenza] that enter hosts across epithelial layers, and for targeting the pernicious cancers that also strike epithelia. But attempts to transform the body's surfaces into crucibles of immunoresponsiveness must respect the immunological tolerance that the host displays toward myriad innocuous agents (such as commensal bacteria, food antigens, pollen, or fertilized embryos) that reside at or engage our epithelia (Fig. 1). Indeed, systemic tolerance to body surface antigens can be so durable that antigen delivery via oral or nasal routes has been actively pursued as a way to reduce pathologic autoimmunity (*3*). To understand the variable outcomes of antigen exposure at body surfaces, the relay paradigm must be built upon by considering the protective and regulatory functions that are constitutively resident at body surfaces.

[1]Peter Gorer Department of Immunobiology, Guy's King's St Thomas' Medical School, University of London, Guy's Hospital, London, SE1 9RT, UK. [2]Department of Immunobiology, Immunex Corporation, Seattle, WA 98101, USA.

*To whom correspondence should be addressed. E-mail: adrian.hayday@kcl.ac.uk

Purely Local Responses

Body surfaces inherently limit infection. Absorptive mucosal epithelia are covered in a thick electrostatically charged glycocalyx, but essential absorptive functions preclude epithelial layers from being impervious. Additional protection is provided by various means. Paneth cells, for example, are provoked by bacterial products to secrete lysozyme, type II phospholipase A2, and α-defensins, which combine within minutes to insulate their neighboring epithelial cell progenitors from infection (*4*). Such rapid-acting innate responses seem particularly appropriate at body surfaces, where epithelial cells survive for only a few days. Nonetheless, local protection is also provided by cells of the adaptive immune system, notably B cells that produce secretory immunoglobulin A (sIgA) (*5*, *6*). The effectiveness of mucosal IgA (and IgM) is not limited to pathogen neutralization in the gut lumen but is extended by its capacity to bind endocytosed pathogens during transcytosis across epithelial cells (*7*). This encounter occurs at the apical recycling endosome, where low pH may release pathogens from lipid carriers and expose novel pathogen-associated epitopes, beyond those displayed ex-

Dynamics of T Lymphocyte Responses: Intermediates, Effectors, and Memory Cells

Antonio Lanzavecchia and Federica Sallusto

Science **290**, 92 (2000);
DOI: 10.1126/science.290.5489.92