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The nonspecific face of adaptive immunity

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Memory T cells generated by infection or immunization persist in the organism and mediate specific protection upon rechallenge with microbial pathogens expressing the same molecular structures. However, multiple lines of evidence indicate that previously encountered or persisting pathogens influence the immune response to unrelated pathogens. We describe the acquisition of non-antigen specific memory features by both innate and adaptive immune cells explaining these phenomena. We also focus on the different mechanisms (homeostatic or inflammatory cytokine-driven) that lead to acquisition of memory phenotype and functions by antigen-inexperienced T lymphocytes. We discuss the implications of these new concepts for host defense, auto-immunity and vaccination strategies.

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Introduction

Immunologists have historically divided the immune system into innate and adaptive branches. Innate immune cells express germline encoded receptors that bind molecular patterns shared within a variety of microorganisms (termed pathogen associated molecular patterns, PAMPs), whereas adaptive immune cells express receptors produced by somatic recombination that can potentially interact with all pathogen-associated molecular structures (termed antigens). A critical component of the adaptive immune system is its capacity to remember prior encounters with the same antigen, a property referred to as immunological specific memory, which forms the basis for the efficacy of vaccines. However, some phenomena cannot be explained by this paradigm. Clinical evidence strongly suggests that certain live vaccines, in particular Bacillus Calmette-Guérin (BCG) and Measles vaccines, can reduce all-cause mortality, most probably through protection against non-targeted pathogens in addition to the targeted pathogen. In experimental animal models, it is well established that immune memory responses to previously encountered pathogens can sometimes alter the immune response to and the course of infection of an unrelated pathogen by a process known as heterologous immunity (reviewed in [1–3]). The latter is relatively common within closely related species of pathogenic agents but can also be seen with unrelated agents. In this review, we discuss recent advances allowing a better understanding of these phenomena.

The components and properties of immune memory

Trained immunity

Until less than a decade ago, there was a general assumption that the B and T lymphocytes of the adaptive immune system were the only components able to generate memory cells, and mount recall memory responses. Several recent studies have challenged this dogma (reviewed in [4]) suggesting that the innate immune system also displays adaptive properties. Natural killer (NK) cells can autonomously retain a memory of past antigen encounters and mediate more robust secondary responses [5]. Monocytes exposed *in vivo* to pathogens can also mount protective recall responses to re-infection [6], suggesting that even cells derived from the myeloid lineage in mammals may possess features of adaptive immunity. This phenomenon involves metabolic reprogramming, leading to epigenetic rewiring [7,8]. The term '*trained immunity*' has been proposed for the persistent enhanced state of the innate immune response following exposure to certain infectious agents, which may result in increased resistance to related or unrelated pathogens. As expected, a part of the cross-protection induced by vaccines seems to be dependent on trained immunity (reviewed in [9]). Other signals may increase regulatory/suppressor properties of innate immune cells in a prolonged fashion. For example, in the course of *Toxoplasma gondii* infection, local production of IFN-γ by bone marrow resident NK cells induces regulatory functions in monocyte precursors that persist after resolution of the infection [10].

Development of antigen-inexperienced memory T cells under homeostatic conditions

T cell populations are tremendously diverse in terms of phenotype, function, developmental plasticity, distribution, longevity, and protective capacity. The conventional

or true memory cells are induced via TCR stimulation by foreign antigen, in the context of productive costimulatory and cytokine cues. Several distinct populations of unconventional or innate memory T cells develop in the thymus and phenotypically resemble conventional memory T cells but do not require antigen experience to obtain this status. Some of them display a highly restricted (oligoclonal) TCR repertoire and have limited tissue distribution. Invariant NKT (iNKT) cells are the prototype of cells belonging to this family. Others include CD8αα intraepithelial lymphocytes and mucosal-associated invariant T cells. In addition, CD8SP thymocytes may also acquire memory-like phenotype during their differentiation under the influence of IL-4, produced locally by NKT cells. Acquisition of memory traits by antigen-inexperienced CD8 T cells also occurs in the periphery under normal or lymphodepletion conditions. Under normal laboratory conditions, the pool of these 'virtual memory' (VM) cells represents 10–25% of unprimed CD8 T cells in C57BL/6 mice and this proportion greatly increases upon ageing [11]. Development of VM cells requires high expression of T-box transcription factor Eomesodermin (Eomes) that controls CD122 expression, the transducing IL-15 receptor beta chain [12]. Type I IFNs, produced under homeostatic conditions or during infections, drives Eomes expression by CD8 T cells and IL-15 *trans* presentation by myeloid cells, thereby promoting the development and expansion of memory-like $CD8^+$ T cells [13•,14•]. Recently, $Eomes^{hi}$ $CD45RA^+KIR^+NKG2A^+$ 'innate/memory-like' $CD8^+$ T cells were also identified in human adult and cord blood samples [15,16]. As for their mouse counterpart, these cells were shown to traffic to the liver and to accumulate with age [14•]. $CD4^+$ T cell repertoire analysis of highly purified T cell populations from naive animals revealed that the Ag-specific clones displayed effector and central 'memory' cell surface phenotypes even prior to having encountered their cognate antigen [17•]. However, for $CD4^+$ T cells, the underlying mechanisms of virtual memory formation are still unclear. Taken together, these data indicate that T cells expressing differentiated memory phenotype can be 'naïve' with respect to their history of antigen recognition.

TCR cross-reactivity and bystander activation

Polyspecificity of TCR

The 'polyspecificity' (also termed polyreactivity, plasticity or degeneracy) of T cell receptor (TCR) (functionally the ability of a single receptor to specifically recognize many different antigens) is now well documented (reviewed in [18,19]). Thus, TCR cross-reactivity to environmental antigens may lead to expansion of memory T cells potentially able to recognize pathogens that have never been encountered. Indeed, healthy adults display abundant memory $CD4^+$ T cells specific for viral antigens to which they have never been exposed [20]. Theoretical arguments suggest that TCRs probably recognize, on average, at least 1 million individual peptides [21] and experiments have shown that peptides do not necessarily need to show high sequence homology to cross-react with the same T cell [22]. A theoretical study suggests that although cross-reactivity is a rare event for immunologically naive individuals, the probability of finding cross-reactive memory T cells becomes very high following successive infections [23].

Bystander (cytokine-driven) activation

T lymphocytes express pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), that are able to interact with PAMPs or stress-induced molecules and induce or modulate their activation [24]. In addition, several cytokines, including IL-15, IL-18, IL-12 and type I IFNs, can activate memory $CD8^+$ T cells in a bystander manner in the absence cognate antigen [25]. Nevertheless, IL-12 and other proinflammatory cytokines were shown to transduce signals through the TCR signalosome in a manner that requires Fyn activity and self-peptide–MHC interactions [26]. Recent evidence suggests that innate-like/VM CD8 T cells may represent an important early line of defense against chronic viral infections [27] and that these cells provide a robust, non-cognate-antigen bystander protection against bacterial challenge [14•]. However, bystander activation may also have deleterious consequences for the host. For example, exposure to prolonged bystander inflammation was shown to impair the effector to memory transition upon infectious challenge [28]. In the context of active chronic HCV infection, Alanio *et al.* recently showed that antigen-specific inexperienced cells differentiate into memory cells resulting in a highly reactive $CD8^+$ T cell compartment [29]. Along this line, increased IL-15 levels in HIV-infected patients were shown to drive bystander activation of CD8 T cells, that is linked to increased morbidity and mortality [30•].

Tissue education by infection

Infection can also durably remodel the architecture of mucosal tissues (reviewed in [31,32]). This phenomenon could favor or impair immune responses against unrelated pathogens. For example, in the lung, successive infections modify epithelium adherence and change the lymphatic network and the frequency of inducible bronchus-associated lymphoid tissue (iBALT) [33,34]. In addition, particular memory T cells persisting at the site of infection have been described. These cells, termed resident memory T cells, do not circulate between secondary lymphoid organs and non-lymphoid tissues such as effector memory T cells (reviewed in [35]) and can also be induced via bystander activation [36]. Resident memory T cells can promote early activation of innate immune mechanisms in response to infection [37]. In humans, when stimulated with IL-15, skin resident $CD49a^+$ memory T cells express effector molecules, such as perforin and granzyme B [38]. Taken globally,

remodeling of mucosal tissues and local persistence of memory T cells constitute a form of 'tissue memory' partially independent of antigen specificity.

Practical implications and perspectives

The paradigm of the antigen specificity of immune memory has dominated the field of immunology for decades. Considering the non-specific side of adaptive memory could have several important theoretical and practical consequences.

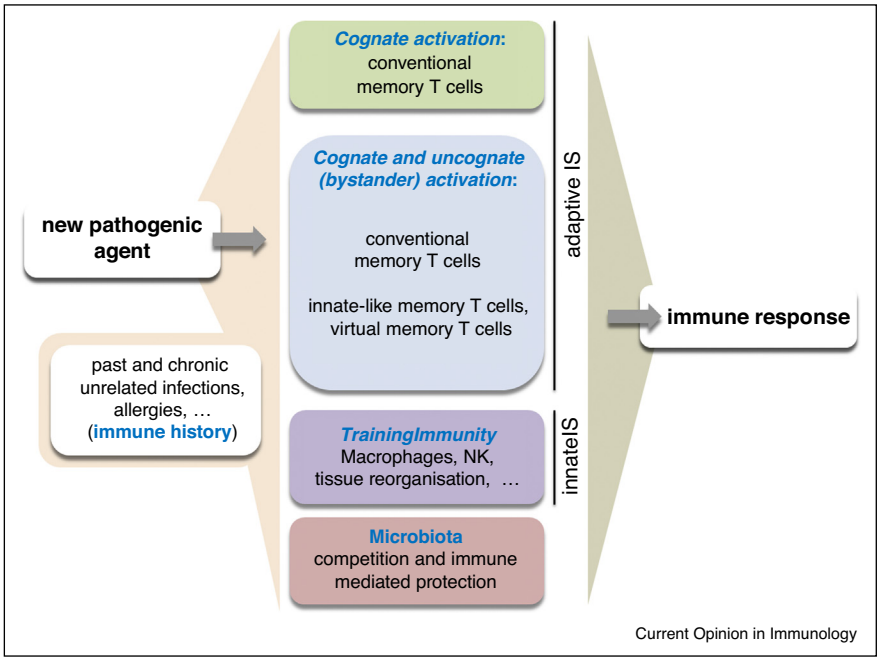
Immune memory viewed as scalable network

Recent studies support an ecological view of immune memory. The immune characteristics of 'clean' laboratory mice are very different from that of mice that have been naturally exposed to pathogenic microbes [39••]. Infection of mice with multiple common pathogens modified yellow fever vaccine-induced immune responses [40]. Simultaneous coinfection results in substantial variation in the specific CD8 T cell response to each pathogen leading to unpredictability in terms of protection [41]. Viewed as a whole, these data support the idea that a significant part of immunity to infectious diseases is not specific to the antigens expressed by pathogens and is dependent on the past and present interactions of the host immune system with its environment. It therefore suggests that memory T cells do not form fixed and isolated clusters of cells but rather an interactive and evolving nonlinear network. Antigenic challenge due to the microbiota, chronic infection and encounter of a new pathogenic agent can alter the reactivity of the immune network by modifying the frequency of T cells and their polarization (summarized in Figure 1). Trained immunity suggests that the innate immune system can also participate in this network, memorize past experiences and durably affect the polarization and reactivity of lymphocytes. From an evolutionary point of view, it would appear that the selection of an immune system displaying the potential to mediate cross-protective reactions is ineluctable to counter the selective pressure of rapidly adapting pathogens displaying complex escape immune mechanisms [42]. Antigenic variation is one of the most common escape strategies of pathogens. The possibility of non-antigen-specific activation of immune effectors can potentially offer partial protection against new antigenic variants of pathogens.

Singularization and unpredictability of the immune response, two beneficial consequences of non-specific immune memory

Systems level analysis has revealed a major impact of non-heritable environmental factors on human immunological parameters [43••]. Convergence in immune status occurs during cohabitation, suggesting that multiple factors including chronic viral infections and microbiota composition shape the immune system [44••]. The latter can affect the responsiveness of the innate immune system [45], induce a cross-reacting immune repertoire able to

Figure 1



Polyspecificity of TCR and bystander activation allow memory T cells to form an interactive and evolving nonlinear network. Consequently, immune response against a new pathogenic agent could be influenced by past and chronic unrelated infections, but also allergies and auto-immune diseases (together forming the immune history of the host), and by the composition of the microbiota.

recognize pathogens (reviewed in [46]) and impact the composition of peripheral memory T cells [47]. This probably results from inflammatory signals and cross-reactivity between the antigens recognized by memory T cells and antigens derived from the members of the microbiota. This singularization of the immune system implies that invasion and immune escape mechanisms developed by pathogens will not be successful in all cases, as the specific targets and organization of the immune response are somewhat unpredictable. In an heterogeneous population where each individuals display particular immune response to infection, the probability that a pathogen is able to infect all individuals is reduced as compared to an homogeneous population (discussed in [48]).

Revisiting the theory of immune tolerance

Classical self-tolerance theories propose that self-specific lymphocytes are eliminated during thymic development and that the decision of the immune system to tolerate or reject is based on the detection of a 'simple' qualitative signal such as a microbial signature (stranger/pattern recognition theory [49]), damage signatures (danger theory [50]), or an abrupt discontinuity of the antigen signal (discontinuity theory [51]). The link between chronic infection and autoimmunity is well-established [52,53] and until now, it has been mainly explained by antigen mimicry and the presentation of self-antigen in association with PAMPs. However, it is likely that both polyspecificity of the TCR and bystander activation of T cells are also frequently involved. For example, Pane *et al.* [54] showed that rotavirus induces bystander activation of autoreactive T cells from NOD mice by triggering TLR7 signaling and IFN-α production in plasmacytoid dendritic cells. However, autoimmunity is fortunately not a systematic consequence of chronic infection. But if T cells can be activated independently of their antigenic specificity, how is tolerance maintained? We have previously proposed [3] that immune tolerance could be the result of an elaborate computation by the immune network based on a very large set of parameters including microbial and damage signatures, but also a great number of other contextual parameters such as the location and duration of antigenic signals, the individual immune history and the general state of the host organism (bow tie hypothesis). In other terms, the immune network could acts as a 'cognition system', like the central nervous system, and be capable of information processing, learning, memorization and adaptation. From this perspective, tolerance results from the interpretation of multiple signals in a general context. Of course, this does not mean that all signals have the same value. The immune system can focus on some signals, such as PAMPs or DAMPs, but the decision process remains dependent on the general context and requires information processing. This suggests that a better understanding of tolerance can only come from an holistic approach to processing information networks within the immune system and the identification of the genetic and environmental factors influencing this process.

Rethinking vaccination strategies

Several live vaccines display important non antigen-specific protective effects dependent on the innate or adaptive immune system [55–57]. This suggest that live vaccines could have important beneficial effects on populations even if their respective target diseases have been eliminated. Consequently, it may be important to quantify the nonspecific beneficial effects associated with each live vaccine before restricting their use or replacing them by subunit vaccines. This is particularly the case for vaccines that can be administered early in life such as oral polio vaccine or measles vaccine as they may lower general mortality and morbidity in low-income setting. In addition, in the context of vaccination campaigns, it might be important to avoid uniformization of the immune responses. As individual diversity constitutes a fundamental protection against epidemics, it could be of interest to administer distinct vaccines targeting the same pathogen within a given population.

Conclusions

From an historical perspective, representation of the immune system as a complex network of interacting components is not new. The 'idiotypic network theory', proposed by Niels K. Jerne in 1974 [58], was based on the postulate that specific lymphocyte receptors recognize high-affinity binding sites on antigens but also on antigen receptor expressed by other lymphocytes, leading to the formation of a network of interacting immune cells. This theory that included only the adaptive components of the immune system, already predicted that homeostatic interactions inside this network could shape lymphocyte repertoire but also control immune responses against pathogens and the self. The new advances presented here underlie the importance of the interactions between innate and adaptive immune components and the microbiota, leading us to predict the emergence of a 2.0 version of immune network theory. This unified and dynamic view of the immune system will undoubtedly explain better many natural phenomena but will be harder to analyze experimentally. One can hope that new systems-based and computational approaches will allow to address this challenge.

Conflict of interest statement

Nothing declared.

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