Immunity and age: living in the past?

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Increasing age is associated with a decreasing ability to mediate effective immune responses to newly encountered antigens. It is generally believed that this reflects the age-associated decline in the number, repertoire and function of available naive T cells. Here, we propose that naive T cells become increasingly irrelevant to the immune system, and that responses to newly encountered antigens are progressively dominated by cross-reactive memory T cells as the individual ages. In addition, we propose that the majority, if not all, of the response to newly encountered antigens in the elderly is mediated by cross-reactive memory T cells. This predicts highly stochastic responses to new infections that should vary between individuals, and has important implications for vaccination strategies in the elderly.

Age-associated changes in the immune system

It has been well documented that increasing age is associated with a decline in humoral and cell-mediated immunity to newly encountered pathogens or vaccines [1–14]. This decline in immune responsiveness is a significant clinical problem because the elderly become highly susceptible to infection and, simultaneously, tend to be less responsive to vaccines. For example, the elderly are particularly susceptible to the secondary effects of influenza infection, and influenza vaccines are documented to be comparatively ineffective in the elderly [8,10,15,16]. Clearly, a thorough understanding of the factors that affect immune responsiveness in the elderly is important for developing vaccines that target this population.

The generation of a vigorous immune response to newly encountered pathogens depends on both the function and repertoire diversity of naive T cells. T cells must be able to proliferate in response to antigen, acquire appropriate effector responses (such as the production of cytokines and the delivery of T-cell help) and be able to migrate to the appropriate effector site. In addition, at the population level, naive T cells need to express a diverse array of T-cell receptors to ensure the recognition of appropriate antigenic determinants in the pathogen. Whereas the pool of naive T cells in young individuals generally fulfills these criteria, there is accumulating evidence that naive CD4^{+} and CD8^{+} T cells in aged individuals become increasingly compromised in their effector function and repertoire diversity. First, naive T cells in aged individuals exhibit significantly impaired proliferative responses and capacity to mediate pathogen clearance, graft rejection,

delayed hypersensitivity and tumor rejection [5,17,18]. In addition, studies of the humoral response in experimental animals and humans have shown that aged individuals have a significantly reduced ability to initiate an effective antibody response following infection or vaccination, presumably a consequence of dysfunctional aged CD4^{+} T-cell 'help' [19,20]. Second, the numbers of naive T cells are profoundly reduced during aging, resulting in limitations in the breadth of the naive T-cell repertoire. This is believed to be a consequence of thymic involution, which results in the decreasing production of new naive T cells [21]. Importantly, the decline in naive T-cell numbers could result in a weaker and more-stochastic response, because the numbers of naive T cells capable of responding to a particular antigen could drop below a necessary threshold. Thus, it is apparent that the aging individual not only has fewer naive T cells but that these cells are less functional and show reduced diversity, in terms of antigen-specificity, than the equivalent cells in young individuals.

Recognition of new antigens in the aged – a hypothesis

A question raised by the age-related physiological changes in naive T-cell numbers and function is to what extent they alter the T-cell response to newly encountered antigens. One possible factor that is not generally considered when addressing this question is the impact of memory T cells. A major characteristic of the aging immune system is that the ratio of naive to memory T cells becomes dramatically skewed in favor of memory cells [21–23]. This is partly caused by the increasing antigen experience of the individual and the associated decline in numbers of naive T cells. We speculate that the increasing dominance of the memory T-cell pool forces competition between naive T cells and fortuitously cross-reactive memory T cells in mediating responses to newly encountered antigens. Whereas this competition strongly favors naive T cells in young mice, which have a limited memory T-cell pool and a robust naive T-cell pool, we propose that this competition progressively favors memory T cells during aging. In addition, we propose that memory T cells comprise the majority, if not all, of the primary T-cell response to newly encountered antigens in aged individuals. Several lines of evidence support this basic idea.

(i) The T-cell immune systems of the elderly are comprised predominantly of memory cells. There are three major factors that contribute to the gradual skewing of the repertoire from largely naive in neonates to mainly antigen-experienced and memory in the elderly. First, a hallmark of the aging immune system is the progressive involution of the thymus and the corresponding decline in

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the production of new thymic emigrants [3,24]. By a certain age, thymic output can cease completely, although there could be other sites of naive T-cell development [25–28]. Studies in humans have shown that the age-associated decline in the number and repertoire diversity of naive T cells is non-linear. Despite the steady decline in thymic output, diversity seems to be well-maintained until 65 years of age, suggesting that peripheral T-cell numbers are maintained by cell division. The dramatic decline in naive T-cell numbers after 65 years of age is probably owing to further age-associated changes in the homeo-static proliferation of naive T cells and increased spontaneous T-cell activation [21,29,30]. Consequently, the naive T-cell pool represents an increasingly smaller proportion of the total number of available T cells with aging. Indeed, in people older than 100 years of age, naive $CD8^+$ T cells are essentially absent [31]. Second, there is an increasing representation of T cells with a memory phenotype, driven largely by the accumulated experience of the individual with pathogenic challenge and by the homeostatic proliferation of the memory T-cell pool [21]. For example, in the murine system, the ratio of memory to naive $CD8^+$ T cells already approaches 90% by 18 months, which is much lower than the upper age limit of laboratory mice (E. Yager, D. Woodland and M. Blackman, unpublished). The age-associated emergence of dominant clones, largely of $CD8^+$ T cells, could also have an important role in establishing the dominance of the memory T-cell pool [32–35]. These clonal expansions are common in healthy adults and are thought to be driven largely by chronic infections, particularly cytomegalovirus (CMV) [36].

(ii) T-cell responses are known to be highly cross-reactive. Antigen recognition by T cells is extremely degenerate [37,38]. Studies by Selin and co-workers have documented substantial degeneracy in the T-cell responses to viruses, resulting in a large amount of cross-reactivity with apparently unrelated antigens [39,40]. Indeed, cross-reactive memory T-cell responses seem to be the rule instead of the exception for some responses modeled in the mouse, and, in most cases, the cross-reactivity is unpredictable [41]. Evidence also exists for similar cross-reactive responses to human pathogens, for example, between influenza virus and hepatitis C virus, influenza virus and Epstein–Barr virus (EBV), human papilloma virus and coronavirus, and between different strains of dengue virus [42–45]. Importantly, these changes can have a profound impact on the characteristics of the response in terms of T-cell specificity and immunopathology, and might also affect the outcome of the response in terms of pathogen clearance [43,46–48]. For example, cross-reactive responses generally involve a restricted repertoire of T cells, are usually of low avidity (although in rare cases the avidity can actually be increased) and focus on only a few epitopes. They might direct the immune system to focus on subdominant epitopes or result in an excessively immunopathological response to a generally innocuous pathogen. We propose that, with the increasing age-associated constriction of the naive repertoire, the proportion of responses based on cross-reactive memory should increase, and eventually dominate the reactivity pattern of the individual.

(iii) Naive T cells but not memory T cells become functionally impaired with age. In addition to progressive changes in the relative numbers of naive and memory T cells, there are also changes in the functional attributes of naive cells [49,50]. It is well-established that naive $CD4^+$ T-cell function declines with age [5]. Studies by Haynes and colleagues using T-cell receptor transgenic mice indicate that this progressive loss of proliferative activity is caused by a defect in interleukin (IL)-2 production and that proliferative responses can be restored through the addition of exogenous IL-2 [51,52]. Importantly, this group recently showed that dysfunction in $CD4^+$ T cells from aged mice depended on the age of the $CD4^+$ T cell and not the age of the mouse, and that newly emerging $CD4^+$ T cells in aged mice, induced by CD4 depletion or the construction of bone marrow chimeras, were highly functional [53]. The impact of age on the function of naive $CD8^+$ T cells is less well characterized. Although some reports show an age-associated functional decline [54,55], others have found no evidence for dysfunction [56,57]. Also, it is unclear whether reported deficiencies result from reduced numbers of $CD8^+$ T cells recruited to the response or functional impairment on a per-cell basis. It is also unknown whether functional defects are inherent to $CD8^+$ T cells or are a consequence of functionally defective $CD4^+$ T cells. It is currently possible that the failure of the thymus to produce new naive T cells forces the existing pool to continually replicate by homeostatic mechanisms to maintain the naive pool. This could induce the observed impairment and also further limit the available T-cell repertoire. In contrast to naive T cells, memory T cells retain their capacity to mediate effector responses over the long-term, and, in the case of $CD8^+$ T cells, actually increase in efficacy over time on a per-cell basis [58,59]. Even though the absolute numbers of memory T cells for a given pathogen can decline over time, the constant exposure of the host to pathogens ensures a robust memory T-cell pool [60,61]. The exception to this rule is that some memory cells in aged individuals undergo dramatic clonal expansions, and some of these cells can exhibit impaired function [62]. In addition, CD28-null memory T cells tend to accumulate in the elderly, and these cells can generally suppress immune responses [63–66]. However, the majority of memory cells in the aged individual are highly functional. Thus, in the face of the declining function of naive T cells with age, these observations reinforce the hypothesis that memory T cells dominate the cellular immune responses to newly encountered antigens in aged individuals.

(iv) Memory T cells are more-readily activated than naive T cells. A fundamental characteristic of memory T cells is that their activation requirements are less stringent than those of naive T cells. This reduced requirement for co-stimulatory signals and accessory molecules enables memory T cells to respond to reduced antigen doses compared with naive cells [67–69]. Given the high level of cross-reactivity in the memory T-cell pool, these relaxed activation requirements would enable the triggering of relatively low-avidity cross-reactive memory T cells. We speculate that this provides an inherent bias

> **Box 1. Hypothesis: cross-reactive memory T cells dominate responses to newly encountered pathogens in aged individuals**
>
> • The T-cell recognition of antigen is degenerate and, therefore, highly cross-reactive. There is a high probability that memory cells will be able to recognize a newly encountered antigen.
> • The numbers and diversity of the naive T-cell pool decrease with age, resulting in the T-cell immune systems of the elderly consisting predominantly of memory cells. This increases the chance that the response to a new antigen will be mediated by fortuitously cross-reactive memory T cells.
> • Naive T cells, but not memory T cells, become functionally impaired with age. This further increases the chance that the response to a new antigen will be mediated by fortuitously cross-reactive memory T cells.
> • Memory T cells have lower activation and co-stimulatory requirements than naive T cells. Therefore, cross-reactive memory cells might compete effectively with aged naive T cells in the response to a newly encountered antigen.
> • Implications: *de novo* responses to new antigens will be mediated almost exclusively by cross-reactive memory T cells, leading to a highly stochastic response of reduced avidity, resulting in a compromised ability of the elderly to respond to new infections and vaccines.

towards the activation of cross-reactive memory cells from previous infections, particularly if the naive repertoire is compromised, as in aged animals.

Implications

Considered together, these observations (Box 1) suggest that, as the numbers and function of the naive T cells decline with age, there are increasing numbers of potent memory T cells with the potential to cross-react with new pathogens. Thus, with increasing age, the immune response to newly encountered antigens might progressively be mediated by pre-existing memory T cells. Although it has been previously suggested that cross-reactive memory cells can modulate immune responses, we now extend this idea to suggest that the majority, if not all, of the response to newly encountered antigens in the elderly is mediated by these cells. Furthermore, the complete dependence on memory T cells to generate new responses might be reached as early as the age of 65, when homeostatic regulation of the naive T-cell pool seems to break down [21,29,30].

The increasing dependence on cross-reactive memory cells in the aged would tend to result in weaker and delayed responses because T cells with lower avidity would tend to be drawn into the response [17]. In addition, the dependence on cross-reactive memory cells would predict highly stochastic T-cell responses to new pathogens in the elderly, reflecting their previous antigen experience. The stochastic nature of the response would be further influenced by the individually unique clonal expansions of memory T cells that emerge with increasing age. Depending on the nature of the prior antigenic experience, the impact of persistent infections (e.g. EBV and CMV) [36], the distinct clonal expansions and the stochastic residual naive repertoire, the peripheral T-cell repertoire of an aged individual will be highly unique and extremely restricted. Indeed, there is a strong likelihood of 'holes' in the repertoire that might preclude the ability to

generate a vigorous response to a new pathogen. In this regard, individual mice with large clonal expansions respond poorly to *de novo* herpes simplex virus-1 infection [62]. In addition, some individual aged H-2^b mice that show no evidence of clonal expansions have highly skewed responses to *de novo* influenza virus infection (E. Yager, D. Woodland and M. Blackman, unpublished), and there are cases of selective loss of reactivity to the normally immunodominant nucleoprotein epitope, which elicits a restricted T-cell response [70]. Together, these age-associated constraints in the T-cell repertoire caused by reductions in naive T-cell numbers and the increasing reliance on fortuitously cross-reactive responses have significant implications for vaccination of the aged population. For example, vaccination strategies for the elderly should consider previous pathogen exposure, and should, perhaps, focus on boosting pre-existing memory T-cell responses. The age-associated decline in naive T-cell availability also highlights the importance of therapeutic approaches to improve the survival and maintenance of naive T cells, in addition to efforts to increase thymic output in the elderly [71–73].

In conclusion, we hypothesize that the age-associated decline in the presence and function of naive T cells, and the resulting dominance of the repertoire by memory cells, restricts the *de novo* T-cell response to newly encountered pathogens to fortuitously cross-reactive memory cells, resulting in a severely compromised ability to respond to new infections and vaccines. Importantly, this hypothesis is directly testable in animal models, as are novel vaccination strategies for the elderly and therapeutic approaches for preserving the naive T-cell repertoire.

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