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The effect of aging on cognate function and development of immune memory

Laura Haynes

Trudeau Institute, 154 Algonquin Avenue, Saranac Lake, New York 12983, USA

Abstract

Immunological memory is one of the central features of the immune system and can be described as the ability of the immune system to respond more efficiently to a second encounter with the same pathogen. The immune system is dramatically affected by age-related changes and it is becoming apparent that immune memory exhibits significant defects as a result of aging. Although immune memory generated during youth functions well into old age, that generated later in life functions poorly. Importantly, age-related defects in the cognate helper function of CD4⁺ T cells can potentially influence the development of both humoral and cell-mediated immune memory. These defects ultimately result in aged individuals who exhibit reduced responses to both infections and vaccinations.

Introduction

The concept of immunological memory is defined as the ability of the immune system to respond with greater efficacy to a second encounter with a specific pathogen, and is the basis for protection following vaccination [1]. As individuals age, the peripheral immune system becomes dominated by memory lymphocytes [2], but it has been unclear if these cells are functional and able to confer significant protection from infection. Recent studies suggest that immunological memory generated during youth functions well into old age, whereas that generated later in life does not function well at all [3,4]. This point is important, as the elderly are increasingly targeted for vaccinations for infectious diseases, such as influenza and pneumococcal pneumonia, even though these vaccines have significantly decreased efficacy in older individuals [5,6]. In fact, a recent study has shown that influenza vaccinations do not prevent mortality in the elderly and suggests that it might be better policy to vaccinate younger populations who are responsible for the spread of the virus, rather than the elderly [7].

New technologies that enable the visualization of small populations of antigen-specific memory cells have prompted novel studies examining the age-related changes in memory T cell populations. In this review, I summarize recent studies focused on how immune memory generation and function are influenced by aging.

Effect of age on CD4⁺ T-cell- and humoral-mediated memory

In general, immune-mediated protection from infection is attributable to circulating antibodies and CD8⁺ T cells, which are both generated as a result of previous infection or vaccination. Antibody production can be extremely long-lived and is thought to be a major mechanism of long-term protection from pathogens [8,9]. As individuals age their ability to

generate high-affinity antibodies that can protect from infection wanes. Older individuals not only produce lower titers of antibodies, they also produce antibodies that exhibit reduced functions (e.g. neutralizing and opsonizing activities) in comparison to younger individuals [10,11]. The initial generation of highly functional antibodies requires the cognate interaction of antibody-producing B cells and CD4⁺ T helper cells [12]. CD4⁺ T cells are also required for the generation of memory B cell populations. CD4⁺ T cells are important not only important for the development of humoral responses, but also for the development of functional CD8⁺ memory T cell populations [13,14]. CD8⁺ T cell memory is important for immunity against intracellular pathogens, such as viruses, leading to the rapid generation of highly functional effectors that can kill infected cells upon a second encounter with the specific pathogen [15]. Thus, age-related defects in CD4⁺ T cell function can potentially impact both humoral and cell mediated memory immune responses.

In most cases, the production of a protective antibody response and the generation of memory B cells require the formation of germinal centers (GCs), which in turn is dependent upon the correct function of CD4⁺ T cells [16]. Cognate help from CD4⁺ T cells drives the formation of GCs, thus enabling isotype switching and affinity maturation of antibodies to occur. Recently, our laboratory used an adoptive transfer model to examine the effects of age on helper function in both primary and memory responses to a haptenated protein [3,17*]. In this model, young or aged donor CD4⁺ T cells from T cell receptor transgenic (TCR Tg) mice were transferred into young or aged hosts lacking CD4⁺ T cells. We have shown that the naïve CD4⁺ T cells from aged TCR Tg mice exhibit significant defects in response to antigen both *in vitro* and *in vivo* in comparison to young T cells [18,19]. In a primary response, age-related defects in naïve CD4⁺ T cell helper activity were shown to lead to reduced GC formation, reduced antigen-specific B cell expansion and differentiation, and reduced IgG production. Interestingly, there was minimal impact of age on host components (B cells, antigen presenting cells) in this model.

To examine the memory response in mice, *in vitro* generated effectors from young or aged TCR Tg donors were transferred into young hosts and allowed to return to a resting state. To ensure equivalent primary responses, *in vitro* effectors were generated in the presence of IL-2 and type 1 (e.g. IL-12) or type 2 (e.g. IL-4) polarizing cytokines, and these effectors exhibited no age-related differences in phenotype or cytokine production at the time of transfer [19]. Four weeks after transfer into hosts, the effectors had returned to a resting phenotype and there was no difference in the recovery of young and aged memory CD4⁺ T cell populations. Upon *ex vivo* re-stimulation with specific antigen, however, memory cells generated from aged donors exhibited significant defects in both proliferation and cytokine production compared to those from young donors. These aged effector-derived memory cells also exhibited dramatic *in vivo* defects in proliferation and cognate helper activity, leading to greatly reduced B cell expansion and antibody production. Importantly, memory cells generated from young donors did not exhibit any *ex vivo* defects in response to re-stimulation, even one year after initial generation.

Similar results have also been reported in a model of lymphocytic choriomeningitis virus (LCMV) infection [4]. CD4⁺ memory T cells generated in young and aged animals did not exhibit any significant differences in persistence over a 24 week period, but memory CD4⁺ T cells generated in the aged animals showed an almost 50% reduction in IFN- γ production in response to re-stimulation with viral antigens compared to memory cells generated in the young animals. These studies show that, even though CD4⁺ memory T cells generated in aged individuals can persist in the periphery, their ability to respond upon re-encounter with specific antigen is dramatically impaired.

Another recent study examined the generation of CD4⁺ memory T cells following influenza vaccination of young and aged adults [20]. This study found that the frequency of virus-specific CD4⁺ T cells from the peripheral blood that secreted IFN- γ or TNF- α upon *ex vivo* re-stimulation was significantly reduced in the elderly subjects three months post-immunization. Interestingly, it was also found that the aged individuals had an increased percentage of central memory CD4⁺ T cells (CCR7⁺CD45RA⁺), a decreased number of effector memory cells (CCR7⁻CD45RA⁺) and reduced levels of serum IL-7 when compared to young individuals. The authors propose that alterations in the CD4⁺ memory T cell subsets are a result of the reduced levels of IL-7 observed in the elderly, and that this results in a reduced ability to maintain an effective memory CD4⁺ T cell response.

Although the previous experiments examined memory cells generated in young in comparison to aged individuals, Homann *et al.* [21] examined virus-specific CD4⁺ memory T cells generated following LCMV infection in young animals over a period of three years. With time, memory CD4⁺ T cell numbers did wane slightly, but these memory cells maintained robust function. When re-stimulated *ex vivo* with viral proteins, memory CD4⁺ T cells at 45 and 206 days post-infection produced similar levels of IFN- γ and, at the single cell level, the older memory cells even produced more IFN- γ than the younger memory cells.

Thus, in both an adoptive transfer model and viral models, results show that memory CD4⁺ T cells generated in aged animals can persist but do not function well, whereas CD4⁺ memory T cells generated in young animals function well over a period of more than one year following initial priming.

Effect of age on CD8⁺ T-cell-mediated memory

Although CD4⁺ T cells are not required for the primary responses of CD8⁺ T cells, it is now apparent that the development of protective CD8⁺ memory T cells is dependent upon the proper cognate function of CD4⁺ T cells during priming. CD4⁺ T cells are thought to provide help for CD8⁺ T cells, especially in response to non-inflammatory antigens via the regulation of TNF-related apoptosis-inducing ligand (TRAIL) [22]. CD8⁺ memory T cells generated without appropriate CD4⁺ help are defective in their abilities to respond in a recall response and undergo activation-induced cell death upon re-stimulation [14,22,23]. As the B cell helper function of CD4⁺ T cells exhibits age-related defects, it is likely that this defect also has an influence on the generation of functional CD8 memory T cells.

The function of CD8⁺ memory T cells in young and aged animals was examined using the same LCMV model discussed above [21]. A more vigorous primary CD8⁺ response was seen in young animals following infection, but five months post-infection there was no significant difference in the number of memory CD8⁺ T cells found in the periphery of the young and aged animals. Importantly, however, upon re-stimulation with viral proteins, the secondary response of the CD8⁺ memory T cells generated in the aged animals was reduced in comparison to young animals. These results indicate little or no age-related defects in the generation and maintenance of memory CD8⁺ T cells but significant defects in their function in recall responses. By contrast, when young animals were infected with LCMV, the resulting CD8⁺ memory T cells remained stable and highly functional in response to viral proteins over a period of >1 year.

Defective memory CD8⁺ T cell function in aged individuals has also been shown in other models. Anti-viral responses of young and aged adults following immunization were examined in an influenza model [24]. In this study, virus peptide-specific CD8⁺ T cells were identified by MHC class I tetramer staining of peripheral blood lymphocytes. It was found that there was no difference in the frequency of viral peptide-specific memory CD8⁺ T cells

in the periphery up to six months post-immunization. Upon *ex vivo* re-stimulation, however, virus-specific CD8⁺ memory cells from the aged individuals proliferated less and produced reduced levels of IFN- γ compared to those from young individuals.

A study using a murine tumor model also demonstrated that young mice implanted with a tumor could develop protective CD8⁺ T cell immunity to rechallenge with that tumor, although aged mice could not develop a similar protective response [25^{*}]. When additional co-stimulation, such as anti-OX40 antibody, was provided at the time of initial priming, the aged mice could develop protective immunity and they exhibited enhanced tumor-specific CD8⁺ T cell expansion and cytotoxic T lymphocyte (CTL) activity compared to the untreated aged controls. Interestingly, the authors propose that this effect may be due to the co-stimulation-enhanced function of the CD4⁺ helper T cells in the aged animals, but this remains to be determined.

These studies illustrate that, in both viral and tumor models, similar to memory CD4⁺ T cells, memory CD8⁺ T cells generated in aged individuals show decreased recall responses, even though the maintenance of the memory populations is not different in the young and aged groups. Additionally, CD8⁺ memory T cells generated in young individuals can persist and function well in recall responses for a prolonged period of time.

Conclusions

One of the main characteristics of the immune system is that immunological memory confers enhanced protection upon a secondary encounter with a specific pathogen. The studies highlighted in this review demonstrate that the generation of functional memory T cells in aged animals and humans exhibits significant defects and that memory generated in young individuals remains highly functional for an extended period of time following initial priming (see Figure 1). Remarkably, very similar results were observed for both CD4⁺ and CD8⁺ memory T cell populations. Age-related defects in the cognate helper activity of memory CD4⁺ T cells results in reduced humoral responses and is possibly responsible for the reduced CD8⁺ memory T cell function found in these studies. Ongoing studies are currently examining the specific age-related defects in the cognate function of CD4⁺ T cells and how this influences both humoral and cell-mediated responses.

It is also important to note that, in older animals that were primed during youth, antigen-specific CD4⁺ and CD8⁺ memory T cells respond well, whereas the naïve T cells in these aged animals have significant defects in primary responses [3,4]. These observations suggest that age-related defects that negatively influence the primary response of naïve T cells do not have the same detrimental effects on memory cells. Furthermore, they also indicate that, whatever mechanisms mediate the aging defect, they have distinct effects on T cells at different stages of differentiation (i.e. naïve versus memory). These findings are quite important and begin to provide an understanding of why the efficacy of new vaccinations are significantly reduced in elderly populations.

Future studies are needed to examine why the generation of functional memory cells declines with aging. In addition, it will also be important to determine how this defect can be overcome to increase the efficacy of vaccines in the elderly.

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- of special interest
- of outstanding interest

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Figure 1.

The progression of an immune response following immunization. During the immune response to a primary immunization, effector populations are generated from naïve T and B cells. This response is robust if the naïve cells are young, but is greatly reduced if the naïve cells are aged. Correspondingly, memory cells generated from young naïve cells respond well upon rechallenge, whereas those generated from aged naïve cells respond poorly. This figure is based upon [3,17*].