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Immune memory and aging: An infinite or finite resource?

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Summary of recent advances

Recent developments in the field of immune memory research and the accumulating literature on age-related alterations in homeostasis, primary and memory T-cell responses make it pertinent to address whether and how memory responses are affected by aging with regard to their generation, maintenance and protective function. New knowledge of T-cell repertoire maintenance over long periods of time, particularly when confronted with persistent pathogen challenge, is now enriched further by studies on whether recent immunological memory can “overflow” and/or constrict prior memory responses. Along with studies on potentiation of memory responses by dietary/metabolic interventions and the recent advances on regulation of primary responses with aging, these findings provide a platform for new approaches to vaccination of older adults.

Introduction

Adaptive immune responses in the course of a lifespan undergo numerous changes and the last third of lifespan is characterized by well-documented alterations in lymphocyte subset composition, homeostasis and responsiveness. One of the most important characteristics of adaptive immunity, the ability to generate long-lasting, protective immunological memory, is key to the success of long-lived vertebrates in defending against previously encountered infections. Surprisingly, our knowledge of the generation and maintenance of immunological memory in old age is rather incomplete and is generally characterized by the belief that immunological memory functions remain intact with advancing age. While this may be the case when one examines systemic responses of peripheral blood lymphocytes (PBL) with regard to gross parameters of immune responsiveness (e.g. cytokine secretion), more refined and recent studies have indicated that several aspects of these responses could be compromised with aging in mice and humans [1–3]. In this review, we summarize these advances and outline the outstanding questions in the field.

A simplistic summary of our current understanding of aging of the innate and adaptive immune responses is that defects in innate immunity are more variable or less pronounced and still insufficiently understood, whereas defects in adaptive immunity are unambiguous and reproducibly observed in almost any group of mammals in the last third of lifespan. Primary adaptive immune responses, generated by stimulation of naïve T and B cells by new microbial challenge, are the most drastically affected. On the other hand, memory responses to recall challenge appear to suffer less with aging. We will critically examine the latter

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claim, including intrinsic (cell-autonomous) and extrinsic (environmental) age-related influences that could potentially impact immune memory (Table 1).

Intrinsic age-related changes in formation and function of immune memory

Typically, the term “intrinsic/cell-autonomous” age-related defect is used to denote shortcomings observed when a given cell type is isolated *ex vivo* and shown to underperform its adult counterpart in the absence of other cellular partners needed to generate the response. Such defects were described in primary responses of naïve lymphocytes, including the classical discoveries of poor T-cell proliferation and IL-2 production [4–6] made over 30 years ago and thus will not be discussed further. We recently extended these observations using relevant human pathogens (the West Nile virus, WNV and *Listeria monocytogenes*, LM), showing that primary T-cells *in vivo* exhibit incomplete effector pathway differentiation, which is likely to be largely cell-autonomous [7,8]. The development of anti-LM resting memory CD8 T cell populations in adult and old C57BL/6 mice (B6) mice were comparable (relative and absolute numbers of antigen-specific CD8+ T cells), regardless of differences in the magnitude of the primary effector CD8 response. Yet upon rechallenge with live *Listeria*, old LM-memory cells were still inferior in their ability to expand and achieve full effector differentiation [3]. This is reminiscent with the conclusions reached in some, but not all studies using TCR transgenic mice [9,10].

With regard to the maintenance of memory responses generated in youth, Hammerlund et al. demonstrated long-lived memory over many decades (both for T- and B-cells) was achieved in humans naturally infected or vaccinated against smallpox [11]. The functional capabilities of these memory responses were demonstrated in individuals infected with monkeypox, where previously exposed and/or vaccinated individuals experienced only mild or no disease symptoms, including individuals vaccinated 13–43 years before MPXV exposure [11]. Thus, memory responses generated in youth not only persist, but can remain strongly protective in older adults. Importantly, it is possible that a different scenario exists in memory/effector cells specific for latent persistent viruses over the entire lifespan, where cells are receiving periodic restimulation. However, we discovered that long-term memory or effector memory responses against HSV-1 in mice [12] or CMV in monkeys [13] are not affected by aging, either in their functional or proliferative capabilities.

The above studies strongly suggest that T-cell memory, when generated in old animals for the first time, is defective, whereas memory responses established in youth may be much more resilient and better maintained. It remains to be established whether this is strictly due to intrinsic defects or whether extrinsic influences (e.g. those from antigen presenting cells, cytokines or other microenvironmental sources) also affect memory formation, maintenance and function.

Lastly, it is important to consider that memory responses may be differentially impacted by aging depending on the anatomical site that is examined. This was elegantly shown by a recent study assessing recall responses to skin antigens [1]. Many old individuals were nonresponsive to T-cell skin tests such as PPD/tuberculin and candida, despite the fact that blood T-cells in these individuals responded strongly to such antigens. The problem was that T-cell localization to the site of cutaneous challenge was impaired. T-cells expressed all the proper migration-related receptors, but cutaneous capillaries were devoid of proper ligands to attract them. This was due to defective TNF α production by cutaneous macrophages. In turn, these macrophages could produce the cytokine if directly stimulated with LPS. That left the primary defect unresolved, and authors speculated that TLR signaling, Treg activity or initial T-cell: monocyte communication could be responsible. These results show that

functional systemic memory is not always a reliable indicator of robust tissue-specific responses.

Extrinsic age-related alterations to T-cell homeostasis and repertoire maintenance relevant to immunological memory

The ability to generate protective immunity against a wide array of pathogens depends on the diversity of T cells. T cell repertoire diversity remains remarkably constant throughout adulthood when new naïve T cells can be produced either from lymphocyte precursors in the thymus or by autoprolieration of existing naïve cells stimulated by IL-7 and other homeostatic cytokines in the periphery. However, with age, the thymus involutes, drastically reducing the generation of new T cells, while the naïve T cell pool continually converts to memory T cells by lifelong homeostatic proliferation and exposure to antigens [14–17]. The diversity of the T cell pool is further compromised by the development of age-associated CD8⁺ T cell clonal expansions which in mice can comprise >80% of the entire CD8⁺ T cell compartment [15,17–19]. Altogether, these changes have the potential to precipitate a massive loss of naïve T cells and an overrepresentation of memory T cells that significantly restricts T cell repertoire diversity in old individuals.

Making matters worse, life-long infections with persistent pathogens (e.g. HSV, CMV) result in bouts of viral reactivation, which repeatedly stimulate memory T cells specific for these pathogens and further contribute to the imbalance between naïve and memory T cells [20]. Given that T cell stimulation is intermittent (only during reactivations), these T cells do not exhibit the cardinal signs of exhaustion seen in chronic infections (HCV, HIV), and are usually very efficient in providing immune control. However, over time the pool of memory T cells dedicated to controlling persistent pathogens may continue to expand [21] and can comprise up to 50% of the human memory pool [22]. Recently, it has been estimated that every individual is infected with ~8–12 lifelong viral infections [23], suggesting these types of responses may be normal components of the aging process and should be considered in models of human immune aging.

Several studies have investigated to what extent the naïve T cell compartment is depleted in old age. Naylor et. al demonstrated that in humans CD4 T cell diversity is maintained up to 60 years of age, but is then followed by a dramatic 100 fold decline in diversity after the age of 70[24]. These authors observed a compensatory two fold increase in homeostatic T cell proliferation as thymic output decreased, and the phenotypic distinctions between naïve and memory T cell populations became blurred when this threshold age was reached. Similarly, Ahmed et. al demonstrated a decrease in naïve T cell diversity in old mice (as shown by skewed spectratyping analysis) with evidence of clonal expansions [25]. As these studies were performed in specific pathogen free mice, it would also be informative to repeat these studies in mice harboring persistent viral infections. Altogether, these reports indicate that the age-related decrease in T cell diversity is due to both reduced thymic output and exaggerated activity of homeostatic mechanisms invoked to correct this naïve T-cell lymphopenia. Further support for that scenario was obtained in monkeys for CD8⁺ T-cells [26]. In this study, naïve cells declined with aging, and surprisingly their turnover was increased in old animals, with a clear threshold effect - only when naïve CD8 T-cell pool in blood decreased below 5% of the total, was there pronounced naïve T-cell turnover. While these pioneering studies provide a broad perspective on how aging shapes our T cell compartments, deep sequencing analysis may be required to resolve precisely how the clonotypic structure of the T cell responses is altered within and among older individuals.

One important question is whether age-related changes impact the composition of the naïve T cell compartment in a stochastic manner, or whether there are preferential and predictable

biases. For example, it is still not known whether CD8⁺ T cell epitopes have different lifespans or susceptibilities to aging. A recent study addressed this important question by examining the influence of aging on co-dominant influenza epitopes derived from the viral nucleoprotein (NP366-374) and acid polymerase (PA224-233) proteins [2]. TCR sequencing established that the NP366-specific repertoire was dominated by a few public clonotypes shared among individuals; while the PA224-specific repertoire was much more diverse and individualized [27–31]. Yet the PA224-specific repertoire consisted of ~10 times more naïve precursors [2]. However, the key finding was that old mice (>18 months) preferentially lost the less abundant and more restricted NP366-specific clonotypes. This could indicate that with advancing age, we first shed epitope-specific CD8⁺ T cells with a low naïve precursor frequency, so that in old age we are only left with the pools of epitope-specific CD8⁺ T cells that were initially most diverse and abundant.

Recently, a tetramer-enrichment approach has been used to quantify and isolate endogenous antigen-specific T cells from naïve mice [32]. Using this technique, the sizes of epitope specific CD8⁺ and CD4⁺ T cell precursor pools were estimated at 80–1200 and 20–200 cells per mouse, respectively [32,33]. Interestingly, Kedl and Jameson examined the phenotype of naïve precursors in young adult mice and found that up to >30% of these naïve precursors already shows signs of extensive homeostatic proliferation and can masquerade as memory T cells [34]. These studies suggest that a significant proportion of our memory compartment, at least in mice, may be derived from homeostatic proliferation rather than exposure to foreign antigens. Moreover, the precursors exhibiting prior signs of homeostatic proliferation were also found to be the more responsive upon stimulation with peptide. It will be important to reexamine the phenotype and functionality of these precursors pools as they become increasingly reliant on homeostatic mechanisms with advancing age. It is possible that epitopes undergoing the fastest rates of homeostatic proliferation may have divided many times and will be those that first become senescent in old age. Therefore, correlating precursor frequency, T cell diversity, rates of homeostatic proliferation, and immune functionality for various epitopes in old individuals should provide us with better guidelines in choosing the most robust targets for vaccination in the elderly.

Influences of timing and age on memory T cell responses

The age-related decline in number, diversity and functionality of naïve T cells also presents significant challenges in developing efficacious vaccines for the elderly. Vaccination provides the most successful means for the prevention of infectious disease, but vaccine efficacy plummets in individuals over the age of 65. Finding the correct balance between safety and immunogenicity for vaccine candidates applicable to the elderly becomes substantially more difficult. The more immunogenic live attenuated vaccines (e.g. FluMist, yellow fever vaccine) were associated with increased incidence of complications in the elderly, and are not recommended for use in individuals over 50[35]. Meanwhile, dead or highly attenuated vaccines, like the annual influenza subunit vaccine, show only modest efficacy (~17–53%) in the elderly [36]. These impaired responses against vaccines stem from basic defects that preclude generation of robust primary and likely memory responses against new antigens. Consequently, vaccines tailored for the elderly may require new adjuvants, different routes, doses and regimens of vaccination to generate responses that are comparable to those observed in younger adults.

A number of recent studies have also shed light on factors that are involved in increasing the proportion of effector T cells that develop into memory T cells. Two landmark studies have shown that metabolic pathways are critical in the decision process to become long-lived memory T cells and that a switch from anabolic to catabolic metabolism is necessary for memory differentiation [37,38]. While Arkai et. al. inhibited components of the mTOR

pathway, and Pearce et. al. blocked fatty acid metabolism, higher numbers of memory CD8+ T cells were observed in both cases. A better mechanistic understanding of these decision processes may allow us to generate more memory T cells from fewer naïve T cells, and thereby develop new vaccination strategies for the elderly.

Given that diversity is still maintained throughout much of adult life, one possible strategy may be to vaccinate individuals well before the catastrophic crash in T cell diversity is reached. Promise for this approach comes from human studies demonstrating remarkably long-lived persistence of memory B cells (>50 years) and CD8+ T cells (>10 years) following anti-viral vaccination [39–43]. However, the key question is to what extent immunological memory is preserved with subsequent exposure to acute and persistent pathogens. Some of the initial studies argued that there is an upper limit to the memory T cell pool, and that pre-existing memory T cells must be depleted in order to make room for newly formed memory T cells [44]. These conclusions were based on results that showed a significant loss of pre-existing memory T cells, which correlated with the number of subsequent heterologous viral infections. Importantly, these data suggest that administering vaccines too early in life may consequently subject memory T cells to a higher level of attrition.

This paradigm was re-addressed by Vezys et. al., who observed an increase in the total number of CD8+ T cells following heterologous prime-boost immunizations with only modest erosion in numbers of pre-existing memory T cells [45]. The authors concluded that the memory CD8+ T cell compartment is not fixed in size but can accommodate substantial increases in effector memory T cells in the spleen, blood, bone marrow and liver. In similar experiments, Huster et. al confirmed many of these findings, but showed that the protective capacity of pre-existing *Listeria*-specific effector memory T cells becomes impaired following infection with modified vaccinia virus Ankara [46]. One major difference in infections that ablate pre-existing memory versus those that do not, may relate to the amount of interferon that is produced. Previous studies suggest that interferons (both type I and type II), produced early in infections, results in high levels of memory T cell apoptosis and/or attrition [47–51]. Therefore, it is possible that reduction in numbers and functionality is only observed following infections that produce substantial levels of interferons. Given that persistent infections also result in intermittent production of interferons and generate massive numbers of memory T cells, it will be important to formally determine the long-term impact of these infections on pre-existing memory T cells. Together, these studies underline the need to better understand how an individual's 'pathogen resume' may influence their ability to generate both new and recall T cell responses.

Conclusions and Outlook

In summary, the most recent advances are showing that memory responses in aging individuals need to be carefully dissected to understand potential vulnerabilities. Long-lived memory responses established in youth tend to survive and function well, albeit tissue-specific coordination of such responses could be compromised. Memory responses generated in the old age are blunted and methods to improve them are necessary. In that regard, fatty acid and rapamycin treatments have been successful in adults and should be examined in elderly. The maintenance of memory T-cell repertoire remains a critical topic.

Overall, we are conceptually moving from the era of empirical vaccination of the elderly and into the vaccination strategies based upon molecular, mechanistic findings that define defects in immunity with the old age. This should start with screening to evaluate availability of naïve and memory cells. Memory formation should be stimulated in vaccine formulations in youth and also in those older adults with sufficient naïve T-cell reserve,

whereas immune rejuvenation is likely to be necessary if the naïve reserve drops below critical levels. Definition of intervention thresholds in humans will be key to effective treatments.

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Table 1

Age-related differences in T cell responses

Intrinsic differences	Extrinsic differences
Impaired TCR signal transduction	Decline in thymic output
Defects in cytokine production (IL-2 most prominent)	Reduced TCR diversity
Impaired proliferation/differentiation	Increase in proportion of memory T cells
Reduced immune synapse formation	Dampened innate immune responses?
Altered reception of innate immune signals?	

Highlighted areas are strongly supported by current evidence. Not highlighted are defects and changes that could play a role but are not unequivocally established. Questionmarks denote areas where more research is needed to establish whether the indicated phenomenon occurs reproducibly with aging.