

Age-related changes in lymphocyte development and function

Phyllis Jean Linton & Kenneth Dorshkind

The effects of aging on the immune system are widespread and extend from hematopoietic stem cells and lymphoid progenitors in the bone marrow and thymus to mature lymphocytes in secondary lymphoid organs. These changes combine to result in a diminution of immune responsiveness in the elderly. This review aims to provide an overview of age-related changes in lymphocyte development and function and discusses current controversies in the field of aging research.

Involution of the thymus and diminished output of T lymphocytes are arguably the most recognized changes in the immune system with age. However, it is increasingly evident that the effects of aging on the immune system are widespread, extending from hematopoietic stem cells and lymphoid progenitors to mature lymphocytes in secondary lymphoid organs. Together, the changes in these populations combine to cause a substantial diminution in immune responsiveness in the elderly.

Many of the age-related phenomena that affect the immune system have been recognized for some time. However, studies of how aging affects them are moving beyond description and are now focused on identifying the mechanisms responsible for changes in lymphocyte development and function during senescence. The ability to do so is directly related to our increased understanding of the molecular and cellular controls of these processes. The information obtained should be of practical relevance to increasing the efficacy of vaccination in the elderly and in restoring immunity in immunocompromised individuals. The aim of this review is to provide an overview of the current issues and controversies in the field.

Aging and hematopoietic stem cells

Hematopoietic stem cells (HSCs) are defined by their ability to proliferate and generate new HSCs as well as more differentiated progeny from which myeloid and lymphoid cells develop¹. Because all lymphocytes are ultimately derived from HSCs, age-associated perturbations that affect lymphopoiesis could have a considerable effect on the immune system.

It is becoming increasingly apparent that the proliferative potential of HSCs and the size of the HSC compartment are under

genetic control², and genes that influence these properties have been mapped to several quantitative trait loci²⁻⁶. These genes could encode functions such as DNA repair or responsiveness to environmental signals², and age-related changes in expression or activity of their products could in turn affect the quality of HSCs. The results of competitive repopulation studies, in which young and old cells from the same strain are mixed and transplanted into the same recipient, are particularly illustrative of this point: HSCs from old mice show a decreased repopulating efficiency compared with their young counterparts⁷, and this effect must be intrinsic, as these cells were competing in an identical hematopoietic microenvironment.

One explanation for these results is that the ability of HSCs to replicate decreases with age². In addition, there is mounting evidence that aging may also affect HSC developmental potential. Blood cell production represents a balance between stem cell self-renewal and the production of daughter cells destined to generate myeloid or lymphoid progeny (Fig. 1). However, many studies have demonstrated that bone marrow or purified HSCs from old mice do not efficiently generate lymphoid progeny⁸⁻¹¹. These findings are consistent with recent evidence that the frequency and number of bone marrow common lymphocyte progenitors (CLPs) are considerably reduced by 7 months of age¹². Although the decrease in CLP number with age suggests that the diminished lymphopoietic potential of aged bone marrow is due to inefficient generation of normal numbers of lymphoid committed progeny, it is also possible that those lymphoid progenitors that are produced have defects in survival and/or proliferative potential. The degree to which decreases in lymphocyte production, compared with age-associated defects that accumulate in mature B and T cells (as described in subsequent sections here), contribute to decreased immunity with age remains to be determined.

Little is known regarding how age-related perturbations in the hematopoietic microenvironment might affect HSC self-renewal and lineage commitment^{13,14}. However, many studies have indicated that extramedullary changes with age, and those in the endocrine system in particular, may affect hematopoiesis.

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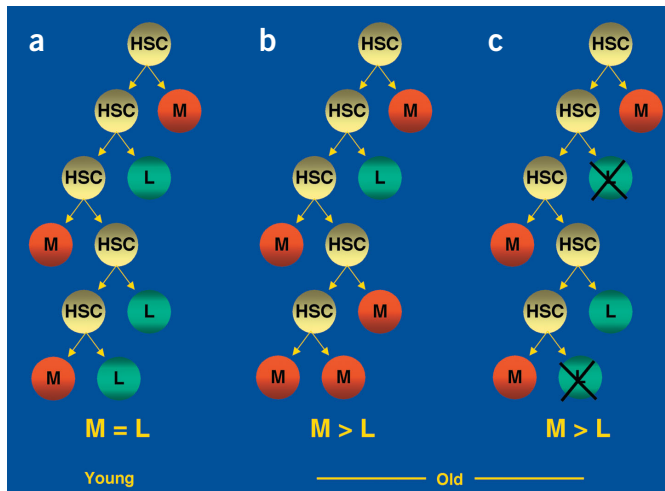


Figure 1 Bone marrow from old mice does not efficiently generate lymphoid progeny. (a) Bone marrow HSCs from young mice can self-renew and generate precursors from which myeloid and lymphoid cells are generated. In young individuals, there is a balance between these events. (b,c) It is not known why bone marrow cells from old donors are less efficient at generating lymphoid progeny. One possibility (b) is that old HSCs may produce fewer lymphoid progenitors. Another (c) is that they are produced in normal numbers but show decreased proliferation and/or survival with age. M, myeloid progenitors; L, lymphoid progenitors.

Decreases in the production of anterior pituitary-derived growth hormone occur with age¹⁵ and have been linked to the well-recognized phenomenon that within much of the skeletons of elderly individuals, hematopoiesis becomes quiescent with age and deposition of adipose tissue increases. Administration of growth hormone to old rats reverses this trend by replacing adipose tissue with active marrow and increasing hematopoiesis¹⁶. One explanation for this finding is that HSCs or their progeny are responsive to growth hormone, or growth hormone-induced mediators such as insulin-like growth factor I (IGF-I), and with age the combined effects of diminished hormone concentration and intrinsic HSC changes reduce the number of precursors capable of sustaining hematopoiesis in all bones. Consequently, adipose cells increase by default to fill the available space. Additionally, the function and/or maintenance of bone marrow stromal cells may be dependent on the growth hormone-IGF-I axis, and as concentrations decrease, stromal cells convert to adipocytes incapable of supporting hematopoiesis (Fig. 2). As will be emphasized throughout this review, these possibilities indicate that age-related changes in multiple systems may combine to affect the development and function of hematopoietic cells.

Aging and primary B lymphocyte development

The bone marrow is the site of antigen-independent, primary B lymphocyte development. The most immature B lineage-committed cells are referred to as pro-B cells. If immunoglobulin heavy chain gene rearrangements are productive at this stage, pre-B cells develop in which immunoglobulin heavy chain protein of the μ class is expressed in the cytoplasm and at the surface in association with the surrogate light chains V-pre-B and $\lambda 5$. Subsequently, immunoglobulin light chain genes rearrange and the surrogate light chains are replaced by κ or λ light chain protein. Cells at these stages of development can be identified based on expression of various cell surface determinants¹⁷ (Fig. 2).

Consistent with the approximately 90% reduction in CLP numbers in 20-month-old mice, the frequency and number of pro-B cells is also reduced substantially with age¹². For example, the frequency of CD45R⁺CD43⁺CD19⁺AA4⁺ pro-B cells in 20-month-old male and 18-month-old female mice is reduced by 87% and 75%, respectively. This observation is not in accord with earlier studies indicating modest or no significant decreases in the pro-B cell compartment in old mice^{18,19}. The reason for this discrepancy may be the strategies used to identify and count pro-B cells. Pro-B cells in the bone marrow are CD43⁺B220^{lo}, and cells with this phenotype also include non-B lineage cells. The report concluding that there is a diminution in pro-B cell numbers with age excluded the latter cells from analysis¹², whereas the other two reports analyzed the total CD43⁺B220⁺ population^{18,19}.

The transition of pro-B cells into pre-B cells also decreases with age¹⁸⁻²⁰ because of impaired V-DJ heavy chain gene recombination²¹. This decrease is not because of decreased amounts of recombination activation gene products, but could instead be related to changes in the expression and activity of the E2A-encoded E12 and E47 transcription factors²². E12 and E47 are basic helix-loop-helix proteins that bind to the immunoglobulin heavy chain enhancer, and their expression is required for immunoglobulin heavy chain expression. E2A family members also regulate the expression of surrogate light chains, which would explain the observation that pre-B cells from old mice show diminished expression of V-pre-B and $\lambda 5$ (ref. 23). Whether downregulation of E2A expression is the event that triggers the decrease in B lymphopoiesis or is an epiphenomenon is unclear. Expression of immunoglobulin transgenes, which would bypass the above defects, does not compensate for poor B cell development²⁴. Thus, mechanisms other than decreased E2A expression must be involved when decreases in primary B lymphopoiesis are found.

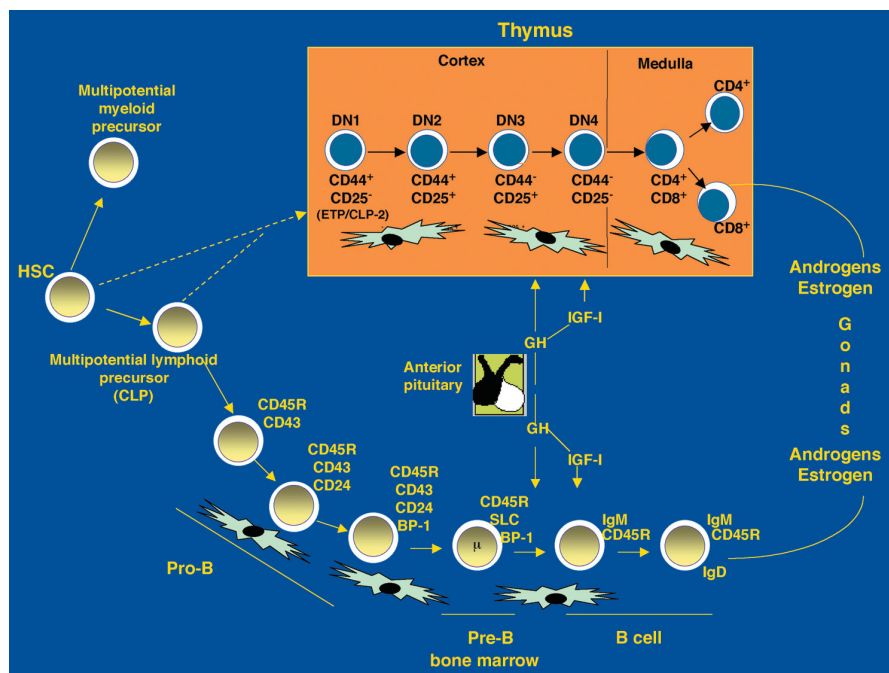
There is disagreement in the literature regarding the effects of aging on the number of surface immunoglobulin-positive cells in the bone marrow. One study made the unexpected observation that their number was relatively normal¹⁹, whereas another report indicated the immunoglobulin-positive B cell numbers were reduced¹⁸. Despite these differences, the consistent finding in both reports is that numbers of B cells were higher than would have been predicted, given the decreases in the pre-B cell compartment. Hypotheses to explain this finding include relaxation of the mechanisms that normally regulate the pre-B-to-B cell transition with age, increased lifespan of immature B cells and reduced migration of B cells from the bone marrow¹⁹.

The impaired generation of B cells in old mice reconstituted with young donor bone marrow cells and the inefficient secretion of interleukin 7 (IL-7) by stromal cells from old mice indicate that the B lymphopoietic support potential of the hematopoietic microenvironment decreases with age^{25,26}. However, extrinsic effects alone cannot explain decreases in the number of B lineage cells with age, because pro-B cells exposed *in vitro* to nonlimiting amounts of IL-7 proliferate less than their young counterparts^{12,27}. Pro-B cells from old mice express the IL-7 receptor α and common γ chains in normal amounts²⁶, so age-related defects in IL-7 responsiveness might instead be due to aberrations in IL-7 signaling pathways. If this were the case, it could help to explain defects in V-DJ joining in pro-B cells, which is an IL-7-dependent event²⁸. A similar interplay between microenvironmental and intrinsic changes in B cell progenitors could also affect human B lymphopoiesis. However, IL-7 does not have the same obligate function in humans that it has in mice²⁹.

Despite the changes noted above, not all old mice show a severe decrease in B lymphopoiesis. This unexpected finding was demonstrated in a study of 50 old mice that demonstrated that half had pre-B



Figure 2 Primary lymphocyte development in the bone marrow and thymus. The cellular stages of mouse B cell development in the bone marrow and T cell development in the thymus. Cells at distinct stages of development in each organ can be identified based on their expression of various cell surface determinants. Aging may result in the accumulation of developmental defects within lymphoid precursors and within supporting stromal cells that form the bone marrow and thymus microenvironments. Extramedullary and extrathymic changes that occur with age, and those in the endocrine system in particular may exacerbate decreases in lymphoid production. In particular, there is decreased production of growth hormone (GH) and IGF-I and an increase in the production of sex steroids with age. The growth hormone-IGF-I axis is thought to enhance lymphopoiesis, whereas sex steroids produced in the gonads have negative effects on B and T cell production. SLC, surrogate light chain.



cell numbers similar to those in young mice¹⁹. Because young and old mice from the same strain were analyzed, genetic effects alone cannot provide an explanation for this finding. Instead, these data make it necessary to consider that environmental factors are involved when decreases in B cell production are found in old mice. Mice within a colony are known to adopt a dominant or submissive posture, and assumption of either role may be stressful³⁰. This in turn could stimulate an increase in production of steroid hormones in particular old mice. Because post-pubertal animals already have increased amounts of sex steroids¹⁵, which are known to suppress B lymphopoiesis³¹, the additive effects of these hormonal changes could exacerbate intrinsic changes that occur in B cell precursors and lead to more pronounced decreases in B cell production in selected subpopulations of animals. The effect of environmental factors may be of relevance when reconciling disparate data from different laboratories.

Aging and secondary B cell development

After their emigration from the bone marrow, newly produced B cells enter the spleen and progress through various transitional stages before maturing into follicular or marginal zone B cells. The continual entry of immature B cells into the spleen and selection into the follicular and marginal zone pools ensures a constant turnover of splenic B cells and maintenance of the B cell repertoire³² (Fig. 3).

There is agreement that aging results in perturbations of peripheral B cells in two important ways. The number of newly made B cells that migrate to the spleen from the bone marrow is reduced. This reduction could be due to the inability of bone marrow B cells to respond to cues that stimulate their exit from the marrow and/or to the diminished production of those stimuli, and the resultant buildup of B cells in the marrow could explain why numbers are relatively normal in old mice^{18,19}. In addition, there is an accumulation of B lineage cells in the splenic transitional and mature compartments that do not label with 5-bromodeoxyuridine, even after extended administration times^{18,19}. Many of these latter cells are antigen-experienced memory B cells that have filled peripheral niches because of diminished production of follicular B cells²⁴.

These changes in the composition of the peripheral B cell pool in turn have consequences for humoral immunity. For example, the duration of the humoral response in aged individuals is relatively shorter than it is in the young, and the immunoglobulins produced are less protective because of their low titer and affinity^{33–36}. Furthermore, even though they are capable of isotype switching, the proportion of immunoglobulin M antibodies secreted by aged B cells is increased, and the V region genes used are distinct from those used by young adults^{37,38} (Fig. 3). Many of these effects may be a consequence of functional defects intrinsic to the B cells, including reduced expression of costimulatory molecules such as B7 (CD86)³⁹ and defects in signaling through the B cell receptor⁴⁰, but others may be secondary to age-related changes in CD4 T cells and the aged microenvironment. CD4 T cells are required for germinal center formation⁴¹ and the activation of somatic mutation genes⁴², so defects in T helper function with age may contribute to the diminished ability of aged individuals to produce a vigorous, high-affinity antibody response in the germinal center reaction³⁹. Indeed, aged CD4 T cells are less efficient at inducing germinal center formation and promoting somatic hypermutation^{39,43}.

The bone marrow is the main source of antibody-forming cells (AFCs) in both man and mouse⁴⁴, and antigen-reactive B cells and AFCs in the bone marrow contain more somatic mutations and produce antibody with higher affinity than do their splenic counterparts⁴⁵. Given that the presence of long-lived AFCs in the bone marrow is dependent on their production in germinal centers⁴⁶, the finding of reduced numbers of high-affinity AFCs in the bone marrow of aged mice⁴⁷ is not unexpected. However, additional age-related changes in the bone marrow microenvironment may also affect the ability of AFCs to undergo somatic hypermutation, selection and/or survival⁴⁷.

Aging and primary T cell development

The thymus does not contain endogenous stem cells capable of unlimited self-renewal and must be 'seeded' periodically with bone marrow-derived precursors that could include HSCs and/or more

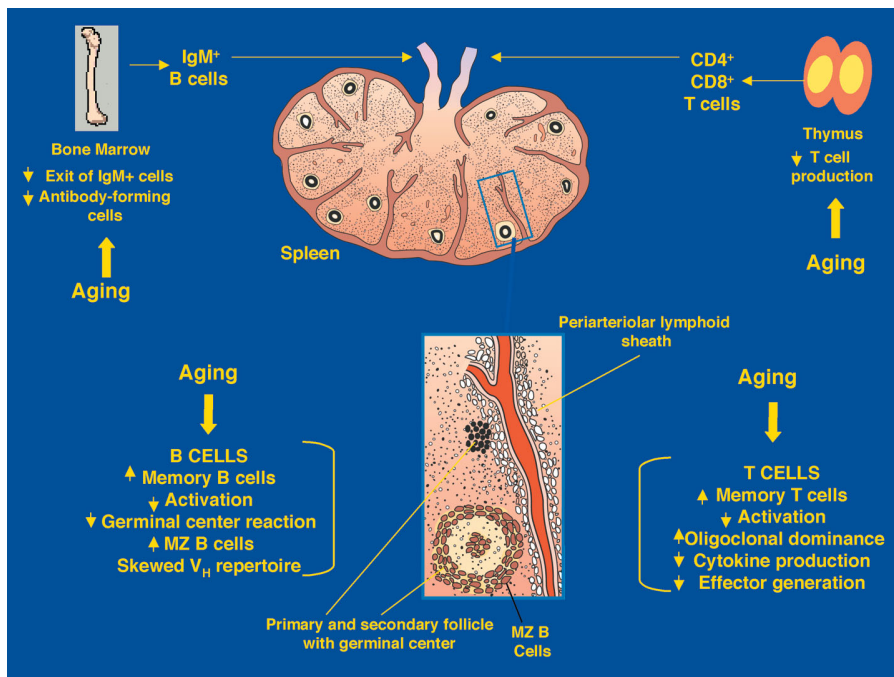


Figure 3 Age-related changes in B and T cells in secondary lymphoid organs. After their production in the bone marrow and thymus, lymphocytes home to particular sites within secondary lymphoid tissues such as the lymph nodes and spleen. With age, fewer mature B and T cells are produced and these may not emigrate efficiently from their tissue of origin. Additional age-related perturbations that occur in mature B and T cells in the periphery contribute to decreases in both humoral and cell-mediated immunity in the elderly. Yellow arrows: ↓, decrease; ↑, increase.

T lineage progenitor⁵⁷ and CLP-2 (ref. 58; **Fig. 2**). The precise developmental relationship between early T lineage progenitor and CLP-2 is unclear at this point, but a determination of how these two populations are affected by age may provide a more accurate picture of how aging affects the most immature intrathymic progenitors.

Even if such analyses show defects in the T cell progenitor pool, changes in the thymic microenvironment may nevertheless contribute to thymic involution⁵⁹. That this is the case is supported by studies demonstrating

differentiated HSC progeny. This process is highly regulated, and input of precursors into the thymus occurs only at distinct temporal ‘windows’⁴⁸. The most immature intrathymic, bone marrow–derived progenitors are included in the double-negative 1 (DN1) fraction, defined by its $CD3^-CD4^-CD8^-CD44^+CD25^-$ phenotype⁴⁹. These progenitors mature through various cellular stages before generating CD4 helper and CD8 cytotoxic T cells (**Fig. 2**).

Thymic involution has generally been considered to initiate at puberty, but atrophy of the epithelial space begins by 1 year of age in humans. By the time of middle age, most parenchymal tissue is replaced by fat, although functional thymic tissue remains in humans at least until the sixth decade of life^{50,51}. In both mouse and man, fewer T cells are produced and exported to secondary lymphoid organs as aging progresses. This in turn has consequences for the maintenance of the naive repertoire in the peripheral T cell pool, as discussed below. Because thymic involution progresses more rapidly in some strains of mice, genetic factors undoubtedly underlie that process⁵².

As noted before, bone marrow cells or purified HSCs from old mice do not efficiently generate T cells after transfer into young recipients^{8–11}, indicating that intrinsic defects that accumulate with age affect their developmental potential. However, current models of thymic involution propose that the frequency of DN1 thymocytes increases and their absolute number does not decrease with age. In addition, DN1 thymocytes from old mice are thought to have normal developmental potential, but their maturation is blocked because of defects in the thymic microenvironment^{53–56}. Proposing that intrathymic T cell progenitors are developmentally normal is puzzling, if T lymphopoietic defects exist in bone marrow precursors. Some studies that have reported increased numbers of T cell progenitors in the aging thymus have based this conclusion on analysis of DN1 cells defined by a $CD3^-CD4^-CD8^-CD44^+CD25^-$ phenotype. However, this fraction includes a high frequency of non-T lineage cells, with T cell progenitors constituting only a fraction of cells within it⁴⁹. Two studies have localized T cell progenitor activity within the DN1 fraction to two subpopulations of cells called early

that thymic involution is not reversed by administration of young bone marrow cells to old mice⁶⁰ and that decreases in the expression of various epithelial cell genes that include IL-7 (ref. 61), keratin-8 and Foxn1 (ref. 62) occur with age. The challenge in this area is to determine the degree to which age-related decreases in the thymic microenvironment affect thymopoiesis and whether changes that do occur result from loss of particular thymic stromal cell types and/or changes in their function.

Any model proposing changes in T cell progenitors or thymic stromal cells alone as the cause of thymic involution may be too simplistic, particularly given studies demonstrating that these two compartments are developmentally and functionally symbiotic^{63–66}. The thymic anlage is a third pharyngeal pouch derivative, and thymic epithelial cell precursors arise from its endoderm by thymocyte-independent mechanisms. However, maturation of these epithelial progenitors into cortical and medullary thymic stromal cells and the maintenance of these populations are T cell dependent⁶⁶, and mice with T cell developmental defects have poorly developed and organized thymic stromal cells^{63–66}. These findings indicate a working model in which age-related defects in both T cell progenitors and thymic stromal cells contribute to involution of the thymus. These changes could occur simultaneously in each compartment or one could precede the other. In either case, changes in one compartment with age could initiate a downward spiral of degenerative events that affect the other compartment. Even if thymic epithelial progenitor cells⁶⁷ were present in the postnatal thymus and attempted to replenish the thymic stromal cell pool, their numbers might eventually be depleted.

This interplay between developing thymocytes and thymic stromal cells may be sensitive to changes in the endocrine system described above and in **Figure 2**. Both developing thymocytes as well as thymic stromal cells express receptors for one or more hormones that include growth hormone, IGF-I and sex steroids^{68,69}. Growth hormone and IGF-I are generally considered to have antiapoptotic effects on thymocytes and to stimulate production of cytokines by thymic stromal cells. In contrast, increasing concentrations of steroids are thought to be toxic to developing thymocytes. Thus, changes in the relative concentrations

of these hormones at puberty could negatively affect thymocyte development and/or thymic stromal cell function and exacerbate thymic involution. This seems to apply particularly in males, given reports that androgens accelerate thymic involution⁷⁰ and orchietomy can reverse, at least in part, that process⁷¹. Ovariectomized mice also have increased thymus size, although not to the same degree as do castrated males, indicating that the effects of estrogens on thymopoiesis may not be as deleterious as those of androgens⁷¹.

Many rodent studies have demonstrated that administration of growth hormone or IGF-I to old mice can stimulate thymopoiesis^{68,72}, and these data have provided the rationale for clinical trials in which growth hormone administration increases thymus size in humans⁷³. However, growth hormone or IGF-I administration to old mice does not restore thymus cellularity to the numbers found in young animals⁶⁸, providing additional evidence that thymic involution is a multifactorial process. As with growth hormone, administration of IL-7 can also increase thymus cellularity in old mice^{59,74}, but cellularity is not restored to match the numbers found in the young, indicating that decreases in its production are yet another, but not the only, factor contributing to thymic atrophy. Because it seems to be a multifactorial event, rejuvenation of the involuted thymus to the levels found in young animals may be difficult. The critical issue is whether increased thymopoiesis that results from a single intervention, such as growth hormone or IL-7 treatment, is sufficient to mitigate changes in the peripheral T cell pool described below.

Aging and secondary T cell development

After their production in the thymus, newly produced T cells migrate into distinct sites within secondary lymphoid organs. Splenic T cells are found in the periarteriolar lymphoid sheath (Fig. 3). Total T cell numbers in these sites and the CD4/CD8 ratio are relatively unaffected by aging.

Despite the maintenance of normal T cell numbers with age, there is a considerable decrease in CD4- and CD8-mediated responses^{75,76}. For example, naive CD4 T cells in the aged secrete less IL-2, leading to decreased expression of CD25 (IL-2R α), and show reduced proliferation and incomplete differentiation to T helper type 1 or type 2 effector cells⁷⁷. In addition, CD4 memory T cells derived from aged naive precursors divide and produce cytokine poorly, whereas CD4 memory T cells derived from young mice function well into old age⁷⁸. In CD8 T cells, the kinetics and magnitude of the overall antiviral response is reduced, resulting in delayed viral clearance^{79,80}. This diminished cytolytic response seems to be due to a lower frequency of virus-specific CD8 cells, because on a per-cell basis CD8 activity remains unchanged⁷⁹. Despite the lower frequency of virus-specific CD8 cells at the peak of the primary response, the frequency of those memory cells that are generated is maintained over time and their population expands in response to secondary viral exposure⁸⁰. Because the magnitude of the initial response to immunization is the main determinant of the magnitude of subsequent responses⁸¹, these findings indicate that maintenance and restimulation of memory CD8 cells are normal in the aged.

One reason cell-mediated immunity decreases with age is the substantial reduction in the representation of naive T lymphocytes with a concomitant increase in memory T cells⁸². This shift in populations is thought to be the consequence of compensatory homeostatic proliferation in response to the reduced numbers of naive cells generated by the thymus as well as to the influence of cumulative exposure to foreign pathogens and environmental antigens. The effect of a reduction in naive T cells in the peripheral pool is the contraction of the T cell repertoire, which leads to an increased incidence of poor responsiveness to new antigens.

A second key change is that the activation potential of the memory T cells that accumulate is altered^{83,84}, leading to hyporesponsivity⁸². These changes have been particularly well documented in CD4 T cells, for which studies of both humans and mice have documented changes in tyrosine- and serine/threonine-specific kinase activity, decreased ζ chain phosphorylation, decreased Raf-1/MEK/ERK kinase activation, decreased CD28-mediated JNK kinase activation, translocation of the transcription factor NFATc to the nucleus and decreased calcium flux after T cell receptor engagement or mitogen stimulation^{82,83,85}. These signaling defects are not due to changes in the concentration of the T cell receptor-CD3 complex⁸⁵. Instead, confocal microscopy has shown age-related alterations in the formation of the immunological synapse between CD4 T cells and antigen-presenting cells⁸⁶. Specifically, there is a decrease in the proportion of aged T cells that successfully recruit a set of signal-transducing molecules such as PKC- θ , Vav and LAT to the supramolecular complex at the synapse.

Finally, there is an increased, oligoclonal expansion of nontransformed T cell populations. Although clonal expansions of CD4 T cells can occur, CD8 T cell expansion is most prominent^{87,88}. In most mice and in almost all humans over the age of 40, expanded clones of CD8 cells exist that are large enough to distort the $\alpha\beta$ T cell repertoire⁸⁹. In humans, these expanded cell populations seem to be resistant to apoptosis, lack expression of the CD28 costimulatory molecule and have shortened telomeres⁹⁰. Although the etiology of clonally expanded populations is not thoroughly understood, evidence is accumulating that repeated viral infections drive the CD8 repertoire toward oligoclonality through either antigen-specific mechanisms or bystander proliferation in response to type 1 interferon^{91,92}. Clearly, many of these effects are the result of intrinsic changes in T cells with age. A major challenge is to determine the degree to which the senescent environment contributes to decreases in cell-mediated immunity in the elderly.

Aging and the innate immune system

Studies of age-related effects on innate immunity are not as advanced as those of the adaptive immune system. In humoral immunity, an increase in marginal zone and B-1 B cell numbers with age has been reported²⁰. B-1 B cells are thought to be a source of autoantibodies, and their increased number with age could explain the increased frequency of self-reactive immunoglobulins in the elderly²⁴.

There is also evidence that monocytes and macrophages from aged mice show a reduced functional potential. Both splenic and activated peritoneal macrophages from aged mice express much lower amounts of Toll-like receptors and alterations in the secretion of various chemokines and cytokines that include IL-6 and tumor necrosis factor^{93,94}. In addition, monocytes and macrophages from old mice have been shown to inhibit T cell proliferative responses⁹⁵. Very little is known about dendritic cell changes with age, although their number in the epidermis decreases with age^{96,97}.

Similarly, additional studies of natural killer (NK) cells are needed. There are indications that the number of NK cells increases with age, but on a per-cell basis their cytotoxic activity is diminished. The later decrease may be because of age-related changes in the protein kinase C-dependent pathway⁹⁸. Aging mice also accumulate an NK-like CD8⁺ population of cells that are not present in young animals⁹⁸.

Conclusions

As discussed above, a wide range of age-related changes in immune system development and function have been identified. However, a mechanistic understanding of these changes is still far from complete,

and further analyses, particularly at the intracellular level, are needed. Some areas, such as the identification of epigenetic changes that might affect the aging immune system, are still in their infancy⁹⁹.

A more complete understanding of the aging immune system has practical applicability. Although many of the changes that occur are subtle and may not be of much consequence to an individual in normal, steady-state conditions, they may become very relevant in conditions of stress. For example, even though HSC function decreases with age, such changes may not be noticeable until an individual is subjected to several rounds of chemotherapy that require HSC replication. Similarly, decreases in mature lymphocyte function may only be demonstrable in situations such as severe infection or vaccination¹⁰⁰. As the size of the aging population increases, these issues will undoubtedly become more prominent.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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