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The aging bone marrow and its impact on immune responses in old age

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ABSTRACT

With aging the immune system undergoes significant age-related changes. These age-dependent changes are referred to as immunosenescence and are partially responsible for the poor immune response to infections and the low efficacy of vaccination in elderly persons. Immunosenescence is characterized by a decrease in innate and adaptive cell-mediated immune function in the peripheral blood and the bone marrow. The aging of bone marrow cells and in particular, of adaptive immune cells in the bone marrow has been addressed relatively rarely. It is therefore the goal of this review to summarize what is known about the effect of age on bone marrow immune cells and their precursors in mice and humans.

1. Immunosenescence: where do we stand?

The aged immune system undergoes significant age-related changes and numerous of its physiological functions decrease, leading to the increased incidence and severity of infections, poor responses to vaccination as well as an increased susceptibility to cancer [1–4]. These alterations of the immune system are being referred to as immunosenescence [5]. Immunosenescence affects many components of the innate and adaptive immune system.

The innate immune system represents the first line of defense against pathogens. Aging of the innate immune system is associated with a diminished function of epithelial barriers of the skin, lung or gastrointestinal tract, which enables pathogens to more reliably invade mucosal tissues, resulting in an increased challenge for the innate immune system in old age [6,7]. Beside phagocytic cells and NK cells, Interleukin-6 (IL-6), IL-1β and tumor-necrosis factor-alpha (TNF-α) have been postulated as predictive markers of functional disability, frailty and mortality in elderly people [8,9].

Whereas the innate immune system is less affected by aging, the adaptive immune system experiences significant alterations in lymphocyte population composition in the periphery and secondary lymphoid organs [10]. Within the adaptive immune system aging leads to substantial alterations of the B and the T cell compartment in humans and mice [9,11]. While age-dependent alterations of the B cell pool are less pronounced [12], changes of the T cell pool have been well studied and are one hallmark of immunosenescence. Naïve T cell counts are reduced in the periphery and lymphoid organs [13,14], whereas the numbers of memory and terminally differentiated effector cells increase with age. The initial trigger responsible for age-related changes of the T cell pool is the involution of the thymus, the T cell maturation organ. With aging the functional thymic mass decreases which results in a diminished output of naïve T cells. As a consequence, homeostatic forces have to assure cell survival and to maintain T cell numbers [11,15].

These alterations are more pronounced in $CD8^+$ than in $CD4^+$ T cells and can be accelerated by pathogens themselves, such as for instance the Cytomegalovirus (CMV) [16,17]. Although latent persistent CMV infection is systemically controlled by the immune system and only during times of reactivation viral particles are detectable, life-long exposure to CMV severely impairs the T cell system. Due to repeated reactivation of the virus followed by rounds of division of CMV-specific T cells, the number of highly differentiated $CD4^+$ and $CD8^+$ T cells increases [11,18,19].

Terminally differentiated effector T cells lack the costimulatory molecule CD28, a member of the tumor necrosis family that interacts with CD80 and/or CD86 expressed on activated antigen-presenting cells. Along with an appropriate TCR/MHC interaction, CD28 signaling provides the stimulus to achieve full T cell activation [20]. The loss of CD28 signaling has also been associated with decreased telomerase activity [21], which further contributes to the exhaustion of $CD28^-$ T cells. The loss of the co-stimulatory molecule CD28 is associated with a change of cellular function in T cells including decreased activation and proliferation as well as impaired ability to secrete IL-2, but high levels of cytotoxic mediators (granzymes and perforine) as well as proinflammatory

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cytokines that enable these cells to exhibit effector functions [11,22]. Due to their pro-inflammatory properties, terminally differentiated CD28$^-$ T cells are believed to contribute to a low-grade inflammatory background commonly observed in old persons, which has been referred to as "inflamm-aging" [23].

So far, most studies on the aging of the immune system have been performed on spleen and lymph node cells in mice and on peripheral blood (PB) in humans. The aging of bone marrow (BM) cells, and in particular, of adaptive immune cells in the BM has been addressed relatively rarely. In this review we will therefore specifically focus on the BM and its role for the maintenance of immunological memory in old age.

2. The bone marrow: the hematopoietic organ and age-related changes

The BM is the primary organ of hematopoiesis and is responsible for the generation of precursors to innate and adaptive immune cells. It is well understood that the amount of hematopoietic tissue decreases in the BM with age and is gradually replaced by fat tissue [24]. Hematopoietic stem cells (HSC) reside in the BM within a specialized microenvironment, the HSC niche. Human and animal studies have demonstrated that HSCs, which have a high potential for self-renewal and differentiation, are affected by age. Aged HSCs have an impaired ability to proliferate and have shortened telomeres, which may affect their proliferative and developmental capacity [25]. Furthermore, with age, the hematopoietic microenvironment changes and processes such as hematopoiesis become quiescent, while the deposition of adipose tissue increases. As a result of these changes B and T lymphopoiesis is decreased [10]. In contrast, the output of myeloid cells is maintained or even increases with age [10,25–27].

Defects in B cell generation have been described, as age has an impact on B cell development [12]. In mice, it has been shown that fewer pro-B cells are generated and their transition to pre-B cells is decreased due to impaired V-D-J heavy chain gene recombination [28]. This results, at least partly, from changes in the expression and activity of the E2A encoded transcription factors E12 and E47. E12 and E47 are key regulators of B cell function. They promote early pre-B cell survival, initiate Ig rearrangement and are involved in class switching of mature B cells in the periphery. It has been shown that aged BM pro-B/pre-B cell precursors exhibit a reduced expression of E2A proteins and have a reduced ability to bind DNA [29]. Another explanation for a decreased overall transit from pro- to pre-B cells with age could be due to a suboptimal expression of Interleukin-7 (IL-7) in old age. IL-7 is expressed by stromal cells and induces proliferation and transition induction of pre-B cell differentiation [10,30,31].

3. The bone marrow: a secondary lymphoid organ and age-related changes

Over the last decades it has become clear that the BM also plays an important role as a secondary lymphoid organ [32]. While its capacity to house long-lived plasma cells [33,34] and its role in supporting memory T cell survival [35–38] have been studied in mice and humans, less is known about changes during aging [39].

Upon stimulation of the immune system with a T cell-dependent antigen, high affinity memory B cells and plasma cells are generated in the germinal centers (GC) of secondary lymphoid organs. Within the GC, the variable region gene segments of the antibody genes undergo hypermutation and cells with high affinity receptors are selected to differentiate into memory B cells and plasma cells. While memory B cells mainly relocate and remain in the spleen, plasmablasts leave the GC, enter the blood stream and home to the BM guided by a chemotactic response. CXCR4 is a chemokine receptor for stromal cell-derived factor 1 (SDF-1) and thereby regulates B lymphopoiesis [40]. However, interaction of CXCR4 with its ligand CXCL12 allows plasmablasts to lodge in the BM and differentiate into plasma cells [41]. Studies in chimeric mice demonstrate that, in mice which were reconstituted with CXCR4-deficient fetal liver cells, plasma cells fail to accumulate in the BM [42].

BM eosinophils are also an important factor for the proper development of plasmablasts to plasma cells [41,43]. It has been shown in GATA 1-depleted mice, which lack eosinophils, that the maturation of plasmablasts into plasma cells is impaired [43]. Plasma cells can survive in distinct BM survival niches for a long period of time, probably years, without DNA synthesis, or cell division, but highly activated in terms of protein synthesis as they constitutively produce antibodies [44]. A study by Manz et al. demonstrated that 60% of OVA-specific plasma cells survive up to 120 days in the murine BM [45].

It has been demonstrated in mice that plasma cells of both low and high affinity are diminished in the BM of aged mice compared to young animals. These results suggest that two mechanisms contribute to an impaired humoral immune response in old age: (1) Due to the diminished germinal center activity, lower numbers of high affinity antibody-secreting cells are generated, (2) The long-term survival of antibody-secreting cells in the BM is impaired due to alterations of the BM environment [46]. Ueda et al. also demonstrated that TNF-α mediated inflammation suppresses CXCL12 expression and, as a consequence the homing of plasmablasts to the BM [47]. Therefore, a low-grade inflammatory background induced by pro-inflammatory cytokines ("inflamm-aging") [23] could be associated with a decrease of CXCL12 expression as well as plasma cell numbers in the aged BM. Still, little is known about age-related changes of plasma cells in the human BM. Recent data from our group suggest that the percentage of BM plasma cells decreases with age in humans. We also observed that CXCL12 mRNA expression declines in human BM in an age-dependent manner (Pritz et al., manuscript submitted).

It has been postulated that the BM also plays a major role in the long-term survival of memory T cells. First studies demonstrated that murine primed CD4$^+$ T cells migrate to the BM and contribute to the development of memory antibody responses [48]. A study in mice demonstrated that animals which were tracked with LCMV-specific CD4$^+$CD44^{hi} T cells were mainly present in spleen and lymph nodes but not in BM after 4 days. The number of CD4$^+$CD44^{hi} T cells decreased in the spleen and lymph nodes from day 28 onwards, whereas in the BM their number increased. More than 80% of total CD4$^+$ T cells resided in the BM from day 60 onwards. They persisted in the BM at constant numbers for more than 134 days which was the period of observation. In another experiment, which was performed to analyze the immune response to ovalbumin as well as KLH and complete Freund's adjuvant, antigen-specific memory CD4$^+$ T cells migrated to the BM with similar kinetics and remained there constant for more than 90 days [35].

Further studies showed that memory CD8$^+$ T cells relocated to the BM and survived there [32,49]. It was shown that the BM contained one of the largest pool of antigen-specific CD8$^+$ T cells. In one of these studies memory responses using P14 transgenic T cells, which are specific for the DbGP33-41 LCMV epitope, were analyzed. Transgenic T cells were transferred into B6 mice 1 day before LCMV infection and memory CD8$^+$ T cells were analyzed at ~60 days post infection. P14 memory CD8$^+$ T cells were still detectable in the BM at this time point [49].

Additionally it has been demonstrated that murine memory CD4$^+$ T cells migrating to the BM utilize CD49b and CD69 and survive in the BM as resting but highly reactive cells [35]. CD49b (alpha 2 integrin) forms the adhesion molecule very late activation antigen-2 (VLA-2), which serves as a collagen receptor (collagens I,