The Role of the Bone Marrow for Adaptive Immunity in Old Age

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Abstract

Most studies on age-related changes of the human adaptive immune system have so far been performed using peripheral blood which contains less than 2% of the total body lymphocyte pool. Only few studies have addressed this issue in lymphatic organs. The human BM represents an organ which has only recently been recognized as an important site for the regulation and maintenance of immunological memory. Intrinsic changes in adaptive immune cells as well as changes in BM niches may be of relevance for changes in the immunological memory in old age. It is the goal of this review to summarize what is known about the effect of age on BM immune cells and their niches in mice and humans.

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Introduction

Antigen-specific memory cells generated during immune responses need to be maintained for a long time in an antigen-independent manner. Survival of memory T cells and long-lived plasma cells can be supported by cytokine/chemokine-producing cells located in the bone marrow (BM). Understanding how survival factors can maintain memory cells even for decades may be of interest to counteract the impairments in the adaptive immunity described in old age.

The Bone Marrow (BM) and Immunological Memory: Physiology

The BM Regulates the Survival of Memory T Cells and Plasma Cells (PCs)

After antigens (Ags) have been cleared from the body, some of the newly generated adaptive cells are maintained for long periods of time in the BM. In case of infections with the same Ags, these memory cells provide rapid protection. Maintenance of memory lymphocytes has been shown to depend on cytokines, molecules fundamental for the survival of immunological memory, since the blockade or removal of certain cytokines leads to the elimination of established memory cells (Schluns and Lefrancois 2003). The production of these molecules is particularly high in tissues which offer a proper environment for the long-term maintenance of adaptive immune cells. Recently, a key role in memory T cell homing and survival has been attributed to the BM, which has been shown to produce high amounts of T cell and plasma cell survival factors (Tokoyoda et al. 2010). It has been reported that this organ is important for the maintenance of immunological memory mediated by cytokine/chemokine-producing cells. Specific areas rich in these molecules known as niches are believed to support the homeostatic proliferation of memory cells, maintaining their pool for a long time after the clearance of the Ags.

$CD4^+$ Memory T Cell Niches in the BM

The BM is well understood to play a key role in $CD4^+$ memory (helper) T cell homing and survival in mice. A major proportion of Ag-specific memory $CD4^+$ T cells relocates to the BM within 3–8 weeks after their generation and is maintained there for a long time in distinct survival niches (Tokoyoda et al. 2009). Interleukin (IL)-7 has been described to promote the transition from short-lived to long-lived $CD4^+$ T cells

and has been indicated as survival factor for long-lived $CD4^+$ memory T cells (Li et al. 2003). In the BM, memory $CD4^+$ T cells are maintained in niches organized by $IL\text{-}7^+$ stromal cells which are characterized by the expression of vascular cell adhesion molecule 1 (VCAM-1) and collagen XI (Hanazawa et al. 2013; Tokoyoda et al. 2009). CD69 expressed on $CD4^+$ memory T cell precursors is necessary for the rolling of these cells on BM sinusoids. After this first step of weak adhesion, the transmigration of effector cells into the BM through the sinusoidal endothelia is possible thanks to CD49b (integrin α2), a collagen receptor subunit which guides the cell migration in the direction of the niches with the binding to collagen II and finally to collagen XI, expressed by $IL\text{-}7^+$ stromal cells. $CD4^+$ memory T cells can therefore find an environment rich in their most important survival factors where they can be maintained for long periods of time. In addition to IL-7, IL-15 may also play a role for $CD4^+$ memory T cells in the human BM, since interactions between $CD4^+$ T cells and $IL\text{-}15^+$ cells have been documented (Herndler-Brandstetter et al. 2011).

The Role of the BM for $CD8^+$ T Cell Survival

Maintenance of effector/memory $CD8^+$ (cytotoxic) T cells requires both IL-7 and IL-15 (Mcleod et al. 2012). IL-7 produced by BM stromal cells binds to the IL-7Rα expressed on $CD8^+$ memory T cells. In addition, myeloid and stromal cells produce and transpresent IL-15 to the IL-15Rα on $CD8^+$ effector/memory T cells, which also highly express the common IL-2/IL-15Rβ and γ chains (Di Rosa 2009). IL-7 and IL-15 may synergize, giving rise to a survival and/or proliferation signal which is effective only when both cytokines are produced. While IL-15 is mainly considered a T cell proliferation factor, generation and maintenance of memory T cells depend on IL7Rα signaling (Osborne et al. 2007). After the effector phase of an immune response, most $CD8^+$ effector cells die and only few memory $CD8^+$ T cells survive, being available in case of reinfections. During this phase, two subsets of effector $CD8^+$ T cells can be identified: Memory precursor effector cells (MPECs), committed to the differentiation into long-lived memory $CD8^+$ T cells, and short-lived effector cells (SLECs) which die shortly after antigenic clearance (Joshi et al. 2007). While MPECs express high levels of IL-7Rα after acute infection, SLECs downregulate the receptor and overexpress the senescence markers killer cell lectin-like receptor subfamily G member 1 (KLRG-1) and CD57 (Kaech et al. 2003; Schluns et al. 2000). IL-15 can rescue $IL\text{-}7R\alpha^{lo}$ $KLRG\text{-}1^+$ SLECs for a short time, but does not guarantee their long-term survival, which would require IL-7R signaling (Joshi et al. 2007).

IL-15 is produced at high concentrations in the BM (Herndler-Brandstetter et al. 2011; Herndler-Brandstetter et al. 2012). IL-15-expressing cells can be found throughout the entire organ, particularly around small blood vessels (Cui et al. 2014). The highest IL-15 expression was found in $VCAM\text{-}1^+$ reticular stromal cells. Interestingly, many of these $IL\text{-}15^+$ $VCAM\text{-}1^+$ cells also express IL-7. IL-15 is additionally known to be produced by various myeloid cell types, such as dendritic

cells, monocytes, and macrophages (Mortier et al. 2009; Musso et al. 1999; Stonier et al. 2008). Furthermore, the bioavailability of IL-15 is higher in the BM compared to other lymphatic organs such as the spleen or lymph nodes (Snell et al. 2012). This suggests that MPECs may be recruited to the BM, where they bind to IL-7 produced by stromal cells and differentiate into long-lived memory $CD8^+$ T cells. Memory cell proliferative renewal may also require IL-15, although a recent report indicates that this cytokine is mostly needed for the preservation of short-lived cytotoxic $CD8^+$ T cells and not for the long-term memory maintenance (Li et al. 2015). SLECs also enter the BM, where they may survive for a short time in close proximity to IL-15-producing cells.

In accordance with high IL-15 production, the IL-15-inducible molecules B cell lymphoma-extra large (Bcl-x(L)), macrophage inflammatory protein (MIP)-1α, MIP-1β, and C-C chemokine receptor type 5 (CCR5) are upregulated in the human BM (Herndler-Brandstetter et al. 2011).

The impact of IL-15 and IL-6 on the activation, proliferation, and differentiation of human $CD8^+$ T cells from peripheral blood (PB) in vitro has also been studied (Herndler-Brandstetter et al. 2012). In combination with IL-15, IL-6 significantly increased the percentage of $CD69^+CD8^+$ T cells. This increase of $CD8^+$ T cell activation was accompanied by an increased number of proliferating $CD8^+$ T cells by IL-15 and IL-6 compared with IL-15 alone. In contrast, only few $CD4^+$ T cells were activated and proliferated following stimulation with IL-15 and IL-6 or IL-15 alone. The stimulation with IL-15, and IL-15 in combination with IL-6, also led to a significant downregulation of CD28 on proliferating $CD8^+$ T cells.

Plasma Cell (PC) Niche in the BM

Multiple cell types have been described to contribute to the organization of the PC niche in the mouse BM. Long-lived PCs are attracted to, and retained in a niche defined by the C-X-C motif chemokine 12 (CXCL12; SDF-1), expressed mainly by CXCL12-abundant reticular (CAR) stromal cells, a cell population also positive for the marker VCAM-1. The majority of PCs were found in close and stable contact with reticular stromal cells and were sessile in their position (Fooksman et al. 2010). CXCL-12 binds to its receptor CXCR4 expressed by PCs and by many other cell types. Binding of CXCL-12 to its receptor triggers the recruitment of cells producing PC survival factors (Chu and Berek 2013). The survival of PCs in the BM is stimulated by a proliferation-inducing ligand (APRIL) and IL-6. Both factors are mainly produced by cells of hematopoietic origin like granulocytes, in particular eosinophils, megakaryocytes, and monocytes (Belnoue et al. 2012; Huard et al. 2008; Winter et al. 2010). Neutralization of both survival cytokines in vivo depletes Ag-specific PCs in the BM, whereas the presence of one of them is sufficient to sustain the PC population in the murine system (Huard et al. 2008). In humans, neutrophils are believed to be important for the production of APRIL in the BM (Benson et al. 2008). Interestingly, it has recently been suggested that long-lived human PCs do not necessarily express the classical B cell marker CD19 (Halliley et al. 2015).

$CD19^-$ $CD38^{hi}$ $CD138^+$ cells were the only population of cells secreting Abs specific for measles and mumps virus more than 40 years after infection.

The BM and Immunological Memory in Old Age

Although solid data on age-related changes of BM memory cells has recently emerged for the human system, relatively little is still known on murine memory cells in the BM in old age. This review will therefore focus on human data and refer to murine results as far as is available.

The Impact of Aging on BM T Cells

The number of helper (CD4) and cytotoxic (CD8) T cells in the BM is not altered between young and elderly persons. However, although the overall numbers of $CD4^+$ and $CD8^+$ T cells in the BM do not change with age, it has been demonstrated in the PB that aging alters the composition of the $CD4^+$ and $CD8^+$ T cell repertoire (Effros et al. 2003; Hong et al. 2004; Kovaiou and Grubeck-Loebenstein 2006). Similar to the situation in the periphery, $CD4^+$ naïve T cells decline while effector memory T (T_{EM}) cells increase in the BM (Herndler-Brandstetter et al. 2012). $CD4^+CD45RA^+$ effector memory T (T_{EMRA}) cells are not increased in the BM. $CD8^+$ naïve T cells also decline, but $CD8^+$ T_{EMRA} cells increase with age. The BM contains fewer naïve T cells and more T_{EM} cells than the PB (Herndler-Brandstetter et al. 2011; Palendira et al. 2008).

As the loss of CD28 and the acquisition of CD57 have been associated with $CD8^+$ T cell aging in the PB (Brenchley et al. 2003; Effros et al. 2005; Focosi et al. 2010), the percentages of $CD8^+CD28^-$ and $CD8^+CD57^+$ T cells have also been analyzed in the BM of young and elderly persons (Herndler-Brandstetter et al. 2012). As in the PB, $CD8^+CD28^-$ T cells were increased during aging in the BM. $CD8^+CD57^+$ T cells which characteristically also lack CD28 can increase in the PB in old age to almost 50% of $CD8^+$ T cells, while in the BM only 14% of $CD8^+$ T cells were $CD57^+$ in elderly persons. The high percentage of $CD8^+CD28^-$ T cells may be due to the fact that the BM has been shown to be a preferred site of IL-15-driven activation and proliferation of memory $CD8^+$ T cells in human and mice (Becker et al. 2005; Herndler-Brandstetter et al. 2011).

The analysis of $CD4^+$ and $CD8^+$ T cells regarding their production of interferon (IFN)-γ, tumor necrosis factor (TNF), and IL-2 following stimulation with phorbol myristate acetate (PMA) revealed that a higher number of polyfunctional $CD4^+$ and $CD8^+$ T cells resided in the BM compared with the PB (Herndler-Brandstetter et al. 2011). Interestingly, the high percentage of polyfunctional memory $CD4^+$ and $CD8^+$ T cells in the human BM was maintained during aging (Herndler-Brandstetter et al. 2012). BM-resident $CD8^+$ T cells also express CD107a, indicating intact cytotoxicity. These data suggest that age-dependent changes of the BM microenvironment do not impair the life-long maintenance of polyfunctional memory T cells and Ag-mediated T cell cytotoxicity in the BM.

The Impact of Aging on BM PCs

Pritz et al. recently demonstrated that the proportions of PCs and memory B cells were significantly lower in both the bone marrow mononuclear cells (BMMCs) and peripheral blood mononuclear cells (PBMCs) from elderly persons compared to young persons, whereas no significant difference could be seen with age for the immature or naïve B cells (Pritz et al. 2015). This may be due to defects in the Th system and weaker germinal center responses, as suggested by studies in old mice (Han et al. 2003; Zhang et al. 2014).

Similar findings in elderly persons have been reported by some groups (Breitbart et al. 2002; Chong et al. 2005; Frasca et al. 2008; Shi et al. 2005), while others have shown the opposite (Colonna-Romano et al. 2003; Veneri et al. 2009). This discrepancy may be explained by variations in age groups or cohort sizes or by the use of different analysis techniques. In contrast, most studies in mice agree that a decrease of newly generated B cells is accompanied by an increase of antigen-experienced cells in old age [reviewed in (Kogut et al. 2012; Miller and Cancro 2007)]. In both species, our knowledge on the specificity of BM PCs is still poor, not to mention potential age-related changes. In humans, the frequency of tetanus- and diphtheria-specific PCs in the BM was seen to decrease with age, whereas no age-related changes were seen for influenza A- or cytomegalovirus (CMV)-specific BM PCs (Pritz et al. 2015). BM PCs can generate persistent high affinity Abs and are therefore very important in providing long-lasting immune protection, specifically in old age (Hofer et al. 2006). In the cases of tetanus-, diphtheria-, and influenza A-specific PCs, a positive correlation could be seen between BM PCs and peripheral Ag-specific IgG Abs of the same specificity. However, no correlations were seen for CMV-specific PCs/Abs. This indicates that immune responses to CMV reactivation and the production of Abs are predominantly maintained by other lymphoid organs.

As no correlation with age was seen for influenza- and CMV-specific BM PCs, it can be assumed that certain Ag-specific PCs are unaffected by age, and that recruitment of PCs in the elderly is still possible. However, little is known about the functional properties of these later generated PCs, and how they would compare with PCs generated in early childhood such as during measles or mumps infection, which can induce a life-long immunity (Amanna et al. 2007). Reduced Ab avidity in old age has been discussed (De Bruijn et al. 1999; Kolibab et al. 2005), but seems unlikely in view of numerous reports on unimpaired Ab functionality in old age (Sasaki et al. 2011; Stiasny et al. 2012).

The Impact of Aging on BM Niches for Adaptive Immune Cells

A crucial question for the aging of immunological memory is whether intrinsic age-related changes of immune cells, of their niches, or both, are the main culprits. Therefore, age-related changes of BM niches for adaptive immune cells in human

tissues were recently analyzed (Pangrazzi et al. 2017). For this purpose, the expression of effector/memory cell survival factors in BMMCs from 65 donors of different age was studied at the mRNA level, and it was demonstrated that IL-15 and IL-6 mRNA increase with age, while the expression of IL-7 and APRIL decreases. No age-related changes were observed for the chemokine CXCL-12, with great deviations at all ages. Flow cytometry experiments confirmed the results described for mRNA at the protein level. These results indicate that the expression of molecules important for the long-term maintenance of effector/memory T cells and long-lived PCs in the BM changes during aging. It was of interest that pro-inflammatory molecules accumulated in the BM in old age inducing a basal level of inflammation in accordance with the concept of "inflamm-aging" (Franceschi et al. 2000). Thus, in addition to IL-15 and IL-6, the mRNA expression of IFN-γ and TNF was increased in BMMCs in old age. Aging per se as well as pro-inflammatory molecules have been shown to influence reactive oxygen species (ROS) levels, contributing to oxidative stress (Chougnet et al. 2015; Mittal et al. 2014). In accordance with these observations, high ROS levels were found in the BM of old persons, which may contribute to further IL-15 production.

Accumulation of $CD8^+CD28^-$ T Cells in the BM in Old Age

A recent study indicates that regulatory T cells (Tregs) for which the BM is a reservoir (Zou et al. 2004) control $CD8^+$ T cell quiescence, memory function, and longevity during antigenic clearance, through the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)-CD28-B7 axis (Kalia et al. 2015). In particular, Tregs may be important for the suppression of $CD8^+$ T cell effector programs, promoting the persistence of $CD127^{hi}$ KLRG-1^{lo} MPECs and the generation of long-lasting memory cells by inhibiting the terminal differentiation into $CD127^{lo}$ KLRG-1^{hi} SLECs. In this process, the expression of the costimulatory molecule CD28 on $CD8^+$ T cells is required.

High numbers of $CD8^+CD28^-$ T cells are a hallmark of aging and can be detrimental, since their accumulation has been linked to impaired responsiveness to vaccination, high inflammation levels, and increased risk of mortality (Effros et al. 1994; Fagnoni et al. 1996; Posnett et al. 1994). $CD8^+CD28^-$ T cells are also pro-inflammatory, as they produce large amounts of type 1 cytokines (Almanzar et al. 2005; Saurwein-Teissl et al. 2002; Zanni et al. 2003). Interestingly, it has been described that apoptosis of $CD8^+CD28^-$ T cells could be successfully prevented by IL-15, suggesting that this cytokine may play a role in the survival and the age-related accumulation of $CD8^+CD28^-$ T cells in humans (Brunner et al. 2012). Given that IL-15 is produced at high concentrations in the BM (Herndler-Brandstetter et al. 2012; Pangrazzi et al. 2017), the aged BM may offer the right environment to promote the maintenance of Ag-experienced $CD8^+$ T cells and, particularly, of potentially harmful exhausted T cells.

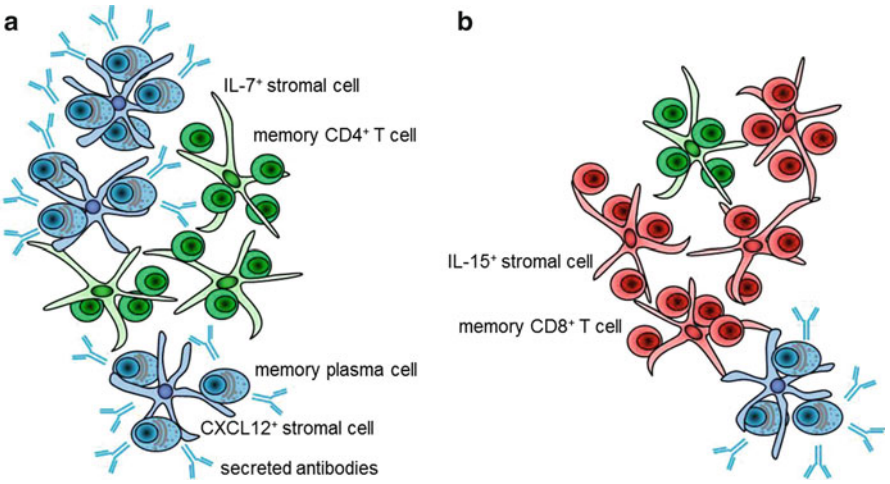

Fig. 1 Schematic illustration of BM niches. (**a**) Distinct niches within the murine BM hosting different types of Ag-experienced immune cells have been suggested. Long-lived PCs are in close contact to $CXCL12^{+}IL\text{-}7^{-}VCAM\text{-}1^{+}$ stromal cells, whereas $CXCL12^{-}IL\text{-}7^{+}VCAM\text{-}1^{+}$ cells support the survival of memory $CD4^{+}$ T cells (Tokoyoda et al. 2010). (**b**) A modification of this concept was proposed, namely that an IL-15-producing BM niche housing memory $CD8^{+}$ T cells exists and that an age-related increase in size of the IL-15 niche as well as the number of $CD8^{+}$ T cells result in displacement and/or functional impairment of the other niches

Competition for Immunological Space in the Aged BM: A Hypothesis

Elderly people have a lower cellularity and therefore there is less BM available for supporting adaptive immune cells. For this reason, immunological space required for the maintenance of memory T cells and PCs in the BM may be restricted, particularly in old age. As it is now clear that the expression of pro-inflammatory molecules like IL-6, IL-15, TNF, and IFNγ increases in the human BM in old age, it can be hypothesized that the aged BM niche environment may directly support the accumulation of highly differentiated $CD8^{+}CD28^{-}$ T cells. They may occupy space normally needed for other cells such as memory $CD4^{+}$ T cells and PCs (Fig. 1). As stromal cells also produce less IL-7 in old age, the maintenance of $IL7R\alpha^{+}$ memory T cells can be affected, leading to impaired B cell responses, low PC counts, and decreased Ab production after infection and/or vaccination.

Conclusions and Future Directions

In conclusion, the BM should be considered as an important organ for the maintenance of immunological memory in old age. Changes in BM niches combined with intrinsic changes of immune cells may be of relevance for future studies.

Cross-References

- ▶ Age, T Cell Homeostasis, and T Cell Diversity in Humans
- ▶ Cytokine Expression and Production Changes in Very Old Age
- ▶ Diversity of $CD28^{null}$ T Cells in the Elderly: A Glimpse in a Biological Adaptation of Aging
- ▶ Inflammaging
- ▶ Older Human B Cells and Antibodies

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