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Aging, B Lymphopoiesis, and Patterns of Leukemogenesis

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Abstract

The production of B lymphocytes begins to decline steadily early in adult life and is severely compromised in the elderly. This occurrence has been attributed to intrinsic defects in early hematopoietic progenitors and B cell precursors as well as to microenvironmental changes in aged bone marrow. The aim of this review is to present an overview of B lymphocyte senescence and its underlying causes, and to discuss its impact on immune function and leukemogenesis in aged individuals.

1. Introduction

The current model of hematopoietic development proposes that all mature blood cells are derived from the hierarchical differentiation of hematopoietic stem cells (HSC) (Shizuru et al., 2005; Spangrude et al., 1988). An equilibrium between self-renewal and differentiation of HSC into common myeloid (CMP) (Akashi et al., 2000) and immature lymphoid specified progenitors (Igarashi et al., 2002) has been proposed to ensure the balanced production of myeloid and lymphoid lineage cells throughout life. However, recent studies have demonstrated that this balance becomes severely perturbed during aging. In particular, the production of B lymphocytes is markedly diminished in the aged (Allman and Miller, 2005; Min et al., 2005).

This review will discuss the age-related reduction in B lymphopoiesis and examine both the cell intrinsic and extrinsic factors that contribute to this phenomenon. In addition, the implications of diminished lymphopoiesis for both the immune response and the development of hematological disease in the elderly will be presented.

2. B Lymphopoiesis

B lymphocyte development occurs in the bone marrow in defined stages characterized by the status of immunoglobulin gene rearrangement in populations of cells that express specific combinations of cell surface antigens (Hardy and Hayakawa, 2001; Igarashi et al., 2002). There is as of yet no agreement on a terminology to delineate the most immature lymphoid specified progenitors that are directly derived from HSC. However, one candidate for such a progenitor, referred to as the early lymphocyte progenitor (ELP) (Hirose et al., 2002), was shown to differentiate into T cells in the thymus (Allman et al., 2003) and common lymphoid progenitors

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(CLP) (Kondo et al., 1997), which are now considered to be early B lineage specified progenitors, in the bone marrow (Bhandoola et al., 2003; Montecino-Rodriguez and Dorshkind, 2003). CLP sequentially differentiate into pre-pro-B and pro-B cells. During this differentiation process, these cells undergo immunoglobulin (Ig) heavy chain gene rearrangements. Successful rearrangement results in cytoplasmic μ expression, and transition to the pre-B cell stage. Pre-B cells initiate Ig light chain gene rearrangement and eventually mature into surface IgM⁺ (sIgM) B cells. The newly produced sIgM⁺ B cells undergo further maturation in the periphery where they ultimately encounter antigen. B lymphocytes derived from the bone marrow in this fashion are referred to as B-2 B cells (Figure 1).

3. The production of B lineage cells declines with age

The reduced production of B lineage cells in the aged was first noted as a decrease in the frequency and number of pre-B cells present in the bone marrow of old mice (Kirman et al., 1998; Kline et al., 1999; Stephan et al., 1996; Van der Put et al., 2004). However, more recent studies have shown that, in fact, the frequency and numbers of all B cell progenitors, including ELP, CLP, pre-pro-B and pro-B cells, are reduced in old bone marrow (Allman and Miller, 2005; Labrie et al., 2004; Miller and Allman, 2003; Min et al., 2006; Van der Put et al., 2004). It is becoming increasingly evident that diminished B lymphopoiesis is not an event that occurs abruptly at old age. Rather, studies of mice ranging from 2 to 24 months of age indicate that the decline in B cell production begins relatively early in adult life and progresses gradually thereafter (Miller and Allman, 2003). This observation suggests that declines in B cell production may be the result of a senescence mechanism that is preprogrammed in hematopoietic progenitors (Montecino-Rodriguez and Dorshkind, 2006).

4. Declines in B lymphopoiesis can occur during embryogenesis

The process of B lymphocyte development initiates during embryogenesis. The emergence of B-2 B cell progenitors described in the previous section occurs initially in the fetal liver around day 13 to 14 of gestation, and in the fetal bone marrow around day 16 to 17. However, it has recently been shown by our laboratory that prior to the onset of conventional B-2 B cell development, there is an earlier wave of B lymphopoiesis in the embryo beginning with the emergence of Lin⁻ CD45R^{-/lo} CD19⁺ cells at day 11 of gestation in the fetal liver and day 15 in the fetal bone marrow. This latter population has recently been shown to include progenitors for a second type of B lymphocyte referred to as a B-1 B cell (Montecino-Rodriguez et al., 2006). B-1 B cells play an important role in innate immunity and, at least in the pleural and peritoneal cavities, can be distinguished from B-2 B cells by their distinctive sIgM^{hi} sIgD^{lo} CD11b⁺ CD5^{+/-} phenotype (Baumgarth et al., 2005).

Interestingly, the number of these B-1 B cell progenitors in the mouse peaks at midgestation, and begins to decline during the final stages of embryogenesis. Consequently these Lin⁻ CD45R^{-/lo} CD19⁺ progenitors are present only at very low frequencies in post natal bone marrow (Montecino-Rodriguez et al., 2006). This finding suggests that the age-related decline in B lymphocyte progenitor production can in some cases begin during fetal life.

5. Multiple factors direct the age-related decline in B lymphopoiesis

Cellular senescence is a normal consequence of aging that is associated with an impaired ability to respond to stressors, and changes in the expression of various genes, including those involved in DNA repair, have been documented. Interestingly, gene profiling of young and old HSC indicate that the latter do not exhibit changes typically associated with aging in non-blood cells (Rossi et al., 2005). Instead, age-related defects in the hematopoietic system appear to preferentially affect lymphoid development and leave myelopoiesis relatively unaffected. For example, the expression of lymphoid specific gene sets are significantly reduced in HSC

isolated from the bone marrow of old mice, while genes directing myeloid development are upregulated (Rossi et al., 2005). There may be multiple consequences of these alterations on lymphopoiesis. First, the balance of HSC differentiation may become skewed with age, resulting in the decreased production of early lymphoid progenitors. This event, in turn, would have a cascade effect on the production of all downstream lymphoid progeny. Second, defects in the lymphopoietic potential of HSC may diminish the quality of lymphoid progenitors that are subsequently produced.

In regard to this latter point, changes in HSC may underlie the defects that accumulate in B cell progenitors. For example, it has been demonstrated that aged B cell progenitors have defects that compromise their ability to differentiate efficiently (Johnson et al., 2002a). In particular, the CLP to pre-pro-B (Min et al., 2006) and pro-B to pre-B cell (Labrie et al., 2004; Riley et al., 2005; Stephan et al., 1996) transitions seem particularly compromised in old mice. In addition, the proliferative potential of CLP, pre-pro-B, and pro-B cells isolated from the bone marrow of old mice is markedly reduced (Min et al., 2006), and pro-B cells isolated from old mice do not efficiently respond to the lymphopoietic cytokine interleukin-7 (IL-7) (Miller and Allman, 2003; Stephan et al., 1997). Similarly, adult bone marrow derived B-1 B cell progenitors are significantly less responsive to thymic stromal lymphopoietin (TSLP), another stromal derived cytokine to which B lineage cells respond, compared to their fetal counterparts (Montecino-Rodriguez et al., 2006). Thus, the proliferative and differentiative defects in hematopoietic progenitors that accrue with age are seemingly responsible for the reduced number of B cell progenitors present in the bone marrow of older mice.

In addition to intrinsic hematopoietic defects, alterations in the bone marrow microenvironment may also hinder the efficient production of B lineage cells. For example bone marrow stromal cells isolated from old mice inefficiently secrete IL-7 (Heng et al., 2005; Stephan et al., 1998). A recent study reported that the production of B cells was rescued following transplantation of aged B lineage progenitors into a young but not an old environment (Labrie et al., 2004). The implication of this study is that the age-related decline in B lymphopoiesis is entirely the product of extrinsic environmental changes. The fact that environmental alterations contribute to the age-related decline in lymphopoiesis is not in contention, but the assertion that they are exclusively responsible for said decline is difficult to reconcile with the abundance of lymphoid progenitor intrinsic defects discussed previously.

6. The age-related decline in B lymphopoiesis results in a reduced immune response in the elderly

Both the reduced production and the diminished quality of aged B lineage cells have a significant impact on immunity in old mice (Linton and Dorshkind, 2004). The number of naïve B cells that migrate from the bone marrow to the spleen is reduced in aged mice, and in turn is thought to contribute to the diminished production of follicular B cells (Johnson et al., 2002b). In addition, the function of peripheral B cells may also be compromised by aging, and this in turn contributes to a diminished immune response (Solana et al., 2006; Weng, 2006). The latter diminution of function may be secondary to age related defects in T cells. However, given the intrinsic changes in B lymphoid progenitors described above, it would not be surprising if cell autonomous changes in B cells from old mice underlie, at least in part, decreased isotype switching (Nicoletti and Cerny, 1991), reduced expression of costimulatory molecules (Zheng et al., 1997), and defects in B cell receptor signaling (Whisler and Grants, 1993).

7. The age related decline in B lymphopoiesis may alter patterns of leukemia development

In addition to changes in immune responsiveness, the changing patterns of lymphopoiesis may alter the development of hematological disease in the elderly. For instance, while the majority of pediatric leukemias are of lymphoid origin, leukemias that present in adults more frequently involve myeloid lineage cells. One such example is chronic myeloid leukemia (CML), which primarily develops in adults following a chromosomal translocation t(9q34;22q11) (Rowley, 1973) that occurs in HSC (Fialkow et al., 1967; Fialkow et al., 1977; Takahashi et al., 1998) and results in the formation of the BCR-ABL fusion oncogene (Ben-Neriah et al., 1986). Despite originating in HSC (Kabarowski and Witte, 2000), CML presents as a myeloid hyperplasia with infrequent lymphoid involvement (Wong and Witte, 2004). CML presents almost exclusively in adults, particularly in the elderly (CDC, 2005), when lymphopoid cell production is most severely compromised. Thus, the lower than expected lymphoid involvement in CML may be a consequence of the reduced production of lymphocytes in the elderly.

8. Perspective

As discussed above, the patterns of B lymphocyte development follow a distinctive pattern with age. Populations of B lineage progenitors peak early in life, in some cases during fetal development, and decline steadily thereafter (Figure 1). It will be of interest to determine if the early decline in lymphocyte production, which does not correlate with chronological age, is related to the unique necessity of lymphoid progenitors to repair double stranded DNA breaks during antigen receptor gene rearrangement. Defects in this gene rearrangement machinery may in turn increase the risk of chromosomal translocations, DNA mutations, and subsequent malignant transformation. Consequently, the relatively high rate of acute lymphocytic leukemia observed in children is not necessarily surprising given that lymphocyte production is at its peak at this stage of life.

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Fig 1.

Effect of aging on B-2 B cell production. The current model of B lymphocyte development from hematopoietic stem cells in the bone marrow. B-2 B cell production begins during embryogenesis, and increases through early postnatal life. After reaching its peak, B-2 B cell production begins to steadily decline early in adult life, and is severely diminished in old age. HSC, hematopoietic stem cells; MPP, multipotential progenitors; ELP, early lymphocyte progenitors; CLP, common lymphoid progenitors; B-2, B-2 B cells.