Chapter 2
Age-Related Changes in Primary and Secondary Lymphoid Organs

Valquiria Bueno

Abstract Bone marrow is a primary lymphoid organ which gives rise to leukocytes and provides maturation of B cells whereas thymus is also a primary lymphoid organ and promotes T cells maturation. Spleen and lymph nodes are secondary lymphoid organs with a favorable microenvironment for immune cells response to pathogenic materials present in blood/lymph and development of long-term adaptive immunity. Therefore, changes in the architecture of primary and secondary lymphoid organs during the ageing process can contribute for the impaired immune response to infections, vaccines, and tumors observed in old individuals. The literature is scarce in aged human lymphoid organs and most of the data are from post mortem or individuals submitted to some type of clinical procedure. Thus, data about lymphoid organs are mostly results of rodent investigation. Conflicting results in architecture and physiology between rodents and human can explain the differences in cells proportions and functions reported in literature. Nevertheless, even considering the limitation of data disposable, in this chapter, the focus will be human lymphoid changes during the ageing process. Considering the importance of lymphoid organs in infections, this chapter also reports data obtained in recent literature about COVID-19 and lymphoid organs.

Keywords Lymphoid organs · Bone marrow · Thymus · Lymph nodes · Spleen

Abbreviations

AID	Activation-induced deaminase
Bcl6	B-cell lymphoma 6 protein
BM	Bone marrow
CT	Computed tomography
HEV	High endothelial vessels

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HPSC Hematopoietic progenitor stem cells
HSC Hematopoietic stem cells
MDSC Myeloid-derived suppressor cells
NKT Natural killer T cells
PD-1 Program cell death protein 1
TCR T-cell receptor
TEC Thymic epithelial cells
Tim-3 T cell immunoglobulin and mucin domain-containing protein 3
TREC T cell receptor excised circles

2.1 Bone Marrow and Hematopoiesis

Hematopoietic stem cells (HSC) give rise to leukocytes including myeloid and lymphoid subtypes that are responsible for innate and adaptive immunity. HSC develop at bone marrow (BM) niche, and it has been reported decreased numbers, increased numbers, or no changed numbers of HSC during the ageing process (Povsic et al. 2010; Kuranda et al. 2011; Ogawa et al. 2000). Povsic et al. (2010) observed opposite trends according to the tissue investigated, with an age-related decline in circulating hematopoietic progenitor stem cells (HPSC, $CD133^{+}CD34^{+}$) and no relationship between BM-resident progenitors and age.

Signals from BM niche components contribute for the complex process that regulates HSC production. Therefore, variations observed in BM architecture due to age and morbidities can contribute for the heterogeneity of HSC numbers in the aged population. Tuljapurkar et al. (2011) observed an age-related increase of fat content in the femoral BM in man which was associated with decrease in HSC. Aguilar-Navarro et al. (2020) observed a significant decrease in hematopoietic area and an increase in adipocyte content in older adult BM (65–92 years). In agreement, Justesen et al. (2001) found decrease in the hematopoietic tissue and increase in the adipocyte tissue, both age-related. Moreover, patients with osteoporosis (52–92 years) displayed an increase in the adipocyte tissue compared to healthy normal individuals (30–100 years). Another characteristic observed in aged individuals is the bias in leukocyte generation leading to increase of myeloid progenitor cells and decrease of lymphoid progenitor cells. Aguilar-Navarro et al. (2020) found that older adults (65–92 years) presented a higher percentage of maturing myeloid cells in the hematopoietic area of BM which correlated with a peripheral increase in total myeloid cells and decrease in lymphoid cells in these individuals. In agreement Pang et al. (2011) observed in old individuals (65–85 years) that human HSC exhibit myeloid-biased differentiation potential compared with young HSC.

Considering these findings, it has been suggested that aged individuals present a decrease in the number of leukocytes in circulating blood and an increase in the myeloid-derived suppressor cells (MDSC) in comparison with the young population. In addition, morbidities can act as enhancers of these alterations in blood components.

Regarding to mature leukocytes presence in BM due to migration from peripheral blood, it was observed by Herndler-Brandstetter et al. (2012) that the number of $CD4^+$ and $CD8^+$ T cells is maintained in BM of ageing individuals (66 ± 3.1 years) with a decline of naïve and increase in effector memory T cells. Ogawa et al. (2000) performed immunohistology in biopsies of BM (newborn—100 years) and observed that older individuals (80–100 years) presented low cellularity, decreased proliferative activity and increased apoptosis. T cells, B cells and macrophages were also diminished in BM of older individuals. In addition, committed $CD34^+CD19^+$ B-lymphoid progenitors were also found in reduced percentage in BM with age (>70 years) (Kuranda et al. 2011).

Pritz et al. (2015) found in BM biopsies mainly plasma B cells whereas a higher percentage of memory B cells was preferentially observed in peripheral blood. Frequencies of plasma and memory B cells either in bone marrow and blood decreased with age, while no effect was observed in immature and naïve B cells. BM plasma B cells specific for tetanus and diphtheria declined, whereas influenza A- and cytomegalovirus-specific BM plasma cells were not affected.

Naismith et al. (2019) found in BM an increase of total T cells and also of highly differentiated $CD8^+$ T cells with age (39–87 years old). Conversely, natural killer T cells (NKT), monocytes, B ($CD19^+$) cells and naïve $CD8^+$ T cells presented age-related decrease. Concentrations of diphtheria-specific antibodies in blood correlated negatively with highly differentiated $CD8^+$ T cells and $CD8^+$ and $CD4^+$ exhausted central memory in BM.

Changes observed in the studied cells should be considered as they probably impact the efficacy of immunity after vaccination in older individuals.

2.1.1 Thymus and Thymopoiesis

The migration of stem cells from BM to thymus (thymocytes) and subsequent steps lead to T cell development. This complex process denominated thymopoiesis comprises: (1) rearrangement of T-cell receptor (TCR) genes with unique specificities, (2) positive and negative selection that will lead to immunocompetent T cells capable to develop immune responses against non-self-antigens and absence of autoreactivity, (3) acquisition of maturation markers by T cells, and (4) migration of naïve T cells to peripheral blood.

Thymus is composed by cortex and medulla, with a network of epithelial and stromal cells. The perivascular space is outside of this network and contains thymus vessels. Thymus epithelium (thymic epithelial cells – TEC) decreases during the ageing process whereas thymic perivascular space becomes more prominent and presents infiltrates of peripheral lymphocytes and adipose tissue (reviewed in Hale 2004). Main causes of thymic involution during the ageing process include reduction in numbers and intrinsic defects in HSC, loss of thymic epithelial cells (TEC) and alterations in thymus stroma; effects of extrinsic factors such as hormones, growth factors, cytokines (reviewed in Dixit 2010). The evaluation of the perivascular space

has shown T cells expressing memory markers and B cells with somatic mutations in immunoglobulin genes suggesting that these cells have migrated from periphery to thymus (Flores et al. 1999, 2001).

Despite the prevailing findings of thymic involution and changes in the thymus architecture and composition, some authors have reported activity in thymic tissue in aged individuals (Flores et al. 1999; Jamieson et al. 1999; von Gaudecker 1978; Bertho et al. 1997). However, the total T cell pool in periphery seems to be maintained by homeostatic expansion of preexisting T cells instead of exporting cells from thymus (Goronzy and Weyand 2005; Yager et al. 2008).

To identify cells exported from thymus, an assay measures T cell receptor excised circles or TRECs that are episomes retained after DNA excised from the chromosome due to TCR rearrangement and has been validated as surrogate marker for thymopoiesis in aging individuals (Flores et al. 1999). TRECs cannot replicate and are lost when T cells expand after encountering an antigen in periphery, thus naïve T cells are measured in periphery as $CD3^{+}CD45RA^{+}TREC^{+}$. TCR diversity is another assay for the evaluation of thymic function can also be evaluated by the TCR diversity. During the ageing process it has been reported a decrease in the naïve T cells in periphery and a decline in TCR diversity (Kimmig et al. 2002; Kohler et al. 2005) that are possible causes for the progressive deficiency in response to vaccine and infection. T cell phenotype ($CD4^{+}$ and $CD8^{+}$) has been based on surface markers such as $CD45RA^{+}$ and $CD27^{+}$ present in naïve cells, in addition to $CCR7^{+}$, $CD31^{+}$, and TREC. After activation via antigens/mitogens, T cells acquire distinct phenotypes, based on CD45RA and CD27, as it follows (Alves et al. 2018):

$CD45RA^{neg}CD27^{+}$ Central Memory, $CD45RA^{neg}CD27^{neg}$ Effector Memory, $CD45RA^{+}CD27^{neg}$ Effector Memory RA.

2.1.2 Lymph Nodes

Human lymph nodes are composed by B cells follicles and T cells follicles in cortex, paracortex, and centrally the medulla region. T cells, B cells, dendritic cells, macrophages and stroma cells can be observed in all compartments of the lymph nodes (Willard-Mack 2006; Hoorweg and Cupedo 2008). In these secondary lymphoid organs, the lymphatic fluid encounter with macrophages and stromal cells that are initial responders (Junt et al. 2008). In addition, cell–cell interactions occur between components such as sinus macrophages and T lymphocytes, afferent veiled cells and T/B lymphocytes, and dendritic cells and afferent antigens. Therefore, lymph nodes present favorable microenvironment for immune cells rapid response to pathogens from blood and lymph and development of long-term adaptive immune responses. The number of lymph nodes, in addition to area and volume of cortex, paracortex and medulla have been reported to decrease during the ageing process (Luscieti et al. 1980; Ahmadi et al. 2013).

Hadamitzky et al. (2010), evaluated superficial inguinal lymph nodes from cadaveric donors and observed diffuse degeneration and a tendency to lymphocyte loss (T and B cells) in aged donors. Lymph nodes presented in majority of the individuals older than 46 years to death very few high endothelial vessels (HEV) suggesting a disconnection from the vascular system and decrease in the immune function. Fibrosis has highly prevalent in age groups 61–75 and 76 + years and lipomatosis was more prominent in donors older than 46 years to death. Taniguchi et al. (2004) found that donors from 72 to 95 years to death presented in lymph nodes very rare germinal centre and secondary follicles larger than the primary follicles or B lymphocyte clusters. Lazuardi et al. (2005) observed in old individuals (67–88 years) that lymph node architecture was maintained but the relative proportion germinal centre/mantle zone was negative correlated with age. Germinal centres were reduced whereas perifollicular B cells tended to be increased. Naïve T cells were diminished in lymph nodes which was probably thymus involution-related with a reduction in $CD8^+$ T cells and not altered numbers of $CD4^+$ T cells. In comparison with young donors, aged individuals presented lower numbers of IgM^+ cells and no difference in IgG^+ cells. Erofeeva et al. (2020) found in mesenteric lymph nodes from cadaveric donors' active fibrosis, lipomatosis, small lymphoid nodules (mainly without a germinal centre), and decrease in Ki-67^+ lymphocytes (proliferation) in both B- and T-dependent zones. Changes were more pronounced in senile age (88 ± 5 years) in comparison with old age (66 ± 3 years) cadaveric donors.

2.1.3 Spleen

Reconstructions of human spleens indicate that the marginal zone is highly-vascularized implying a role in the filtration of pathogens and antigens from the blood (Kusumi et al. 2015). In the red pulp, a large number of macrophages (phagocyte) remove mainly red blood cells, micro-organisms, and cellular debris. In the white pulp, B and T lymphocytes can be activated and proliferate.

Ageing-related changes in the microarchitecture of the human spleen have been described by Alex et al. (2015). They observed that thickness in splenic capsule was influenced by age, thickening post-adolescence and into middle age before thinning again in old age. Increased atrophy of splenic tissue was found in donors of advanced age (70 + years) and corroborated with the decrease in the number and size of B cell follicles with age. Cellularity and vascularity decreased in both red and white pulp and follicles were totally atrophied by the eighth decade. Conversely, Banerjee et al. (2000, 2002) showed that spleens either from post mortem or splenectomized donors (17–81 years) presented no age-related difference in B cells follicle content or in the size of individual follicles. In T cell zones but not in B cells follicles, $CD8^+$ proportion was significantly reduced in the older age group. Moreover, in B cell follicles there was a reduction in the proportion of $CD4^+$ T cells in the older group (Banerjee et al. 2000, 2002).

2.2 Lymphoid Organs and COVID-19

High affinity pathogen-specific antibodies and long-lasting memory B cells are essential against viral infections and after vaccination. The complex mechanisms evolved in this process are highly dependent on T and B cells (generation, maturity, and T-B cells interactions) and, consequently, lymphoid organs integrity is crucial for the adequate immune response. Thus, dysfunctional lymphoid organs may be a predisposing factor for severe COVID-19 disease. A brief report from data obtained in recent literature about COVID-19 and lymphoid organs is listed as it follows.

Bone marrow: post mortem studies conducted in COVID-19 by Falasca et al. (2020) showed that BM presented the hematopoietic tissue replaced by yellow adipocyte-riche marrow either in patients with (27–92 years) or without comorbidities (35–65 years), whereas Ihlow et al. (2021) observed mild fibrosis of BM medullar area (62–79 years). In patients with no comorbidity it was found megakaryocytes hyperplasia (Falasca et al. 2020). Another study, found immaturity of myelopoiesis, severe loss of $CD20^+$ B cells and normal $CD3^+$ T cells (Bao et al. 2020).

Thymus: computed tomography (CT) showed a significant correlation between increased thymus fat tissue and presence of lung involvement in COVID-19 patients (Çakmak et al. 2021). Cuvalier et al. (2021) found that 66% of patients ($n = 50$; 63.2 $\pm$ 16.5 years) with COVID-19 presented enlargement of the thymus which was associated with more extensive lung injury on CT scans but a lower mortality rate. Patients had a higher concentration of IL-7 in circulation and increased production on new lymphocytes (based on TREC levels). Authors suggested that increased thymus mass in COVID patients was a beneficial adaptation to virus-induced lymphopenia. Moreover, thymosin alpha 1 (Tα1), produced by thymic epithelial cells, was administered to patients (21–92 years) with severe COVID-19 and thymic output was measured in periphery by TREC expression and markers of cell exhaustion (PD-1 and Tim-3). The treatment reduced mortality, increased T-cell counts including older patients and in patients with chronic diseases. Cell exhaustion markers decreased in $CD8^+$ T cells and increased thymus output based on levels of TREC (Liu et al. 2020).

Lymph nodes: Kaneko et al. (2020) found in thoracic lymph nodes of severe ill patients that succumbed either before 8 days of admission (66.2 $\pm$ 11.2 years) or succumbed later (63.9 $\pm$ 9.3 years) lack of germinal centre and decrease of B and T cells. The same was reported in 11 patients (66 to 91 years) by Lax et al. (2020). Conversely, Elsoukkary et al. (2021) observed in 32 cases (30–100 years) lymph node architecture preservation, sinus dilatation and congestion. In perihilar and paratracheal lymph nodes, Menter et al. (2020) also found congestion and sinus dilation in lymph nodes in addition to increased number of reactive plasmablasts ($n = 21$; 53–96 years).

Spleen: it was observed atrophy of white pulp (Buja et al. 2020) and lymphocyte depletion (Lax et al. 2020). In agreement, Kaneko et al. (2020) found in severe ill patients, paucity of white pulp, B and T cell reduction. Germinal centre presented B cells with reduction in $Bcl6^+$ and preservation of AID^+ (activation-induced deaminase). Falasca et al. (2020) observed in autopsy of 22 patients (35–65 years) with

COVID-19, reduced volume and size in addition to congested red pulp and lymphoid hypoplasia. Ihlow et al. (2021) found in post mortem samples from patients with COVID-19 (62–79 years), spleen with atrophy of peri-arteriolar white pulp, loss of $CD20^+$ B cells and regular distribution of peri-arteriolar $CD3^+$ T cells. In patients COVID-19 with severe disease (41–79 years) there was more spleen shrinkage than mild patients (16–71 years) (Bao et al. 2020).

2.3 Conclusions

- there are age-related structural changes in primary lymphoid organs that have been associated with reduced cell numbers leaving BM and myeloid-biased generation.
- in periphery cell numbers are maintained by proliferative homeostasis.
- changes in thymus lead to a decreased percentage of naïve lymphocytes and reduced TCR repertoire.
- age-related changes in secondary lymphoid organs lead to impairment in the immunity against infections and/or after vaccination.
- in COVID-19, a higher percentage of aged patients presented more vigorous infection and exacerbation of inflammatory responses.
- structural changes were observed in primary and secondary lymphoid organs of patients with COVID-19.
- it is not possible to differentiate changes caused by age and those associated to COVID-19.
- the further knowledge about changes in lymphoid organs due age and infections could be used to improve the development of vaccines and other therapies.

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Compliance with Ethical Standards

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