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Impact of proliferative stress on both adaptive and innate immune response

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Summary

Human ageing is by far one of the most complex biological phenomena which affects all cells and tissues, leading to gradual loss of function, decrement in proliferative activity, and impaired cellular response. One of the key mechanisms of cellular ageing is proliferative stress which results in telomeric attrition, DNA damage, and deposition of senescence-associated proteins. Allogeneic hematopoietic cells transplantation (allo-HCT) serves as a good model for cellular ageing. Here we review the ageing of the immune system and the impact of proliferative stress on both innate and adaptive immune response, reflected by immunosenescence and inflammageing phenomena, in the context of iatrogenic proliferative stress induced by allo-HCT.

Key words: immunosenescence, inflammageing, allo-HCT, proliferative stress

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Introduction

Ageing is a universal biological phenomenon that affects almost all cells in most living organisms. However, no universal definition of ageing exists due to its complexity. It can be described as a highly heterogeneous process that affects all tissues and systems, leading to a gradual loss of function. In the context of cellular ageing, it is characterized by dysregulation of the mitochondria, following increased reactive oxygen species (ROS) production, DNA damage, and telomeric shortening. Nowadays, there is a growing tendency to perceive ageing not only as a detrimental process but also as a constant adaptation to changing internal environment of the organism ("adaptage theory") [1]. The notion of "adaptage theory" was developed by prof. Tamas Fulop and encompasses all age-associated changes of the immune system which serves as an adaptation to changing internal conditions of the organism in contrast to traditional conception of those changes, perceived as mainly detrimental [1, 2].

To better understand that concept we need to go back to the first studies that originated the field of ageing on a molecular level. Since the 1960's we know that cells divide until they reach so-called Hayflick limit, which is a certain, finite number of cellular divisions, before entering senescence. It is due to telomeric shortening occurring with each cellular division [3, 4]. When telomeres shorten to a certain length, measured in base pairs (bp), further divisions are impossible without damaging the cell's coding DNA. Reaching the Hayflick limit is therefore considered parallel with entering cellular senescence or apoptosis [5]. One of the

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well-established explanations of this phenomenon may be impaired repair of telomeric DNA, due to high demand on the repair machinery, caused by damage to DNA by ROS, according to Olovnikov [6] who proposed the "theory of marginotomy" which postulates shortening of the replica in comparison to the DNA template. It has directly led to the discovery of telomeres. Those two studies gave a molecular basis for the discovery of the cellular senescence phenomenon.

In this review, we would like to focus on the ageing of one of the crucial regulatory systems, namely the immune system. A thorough understanding of the ageing of the immune system is crucial to adjust the treatment for aged individuals in the future and further development of personalized treatment that takes into consideration not only genomics but also the immune profile. However, the main purpose of our review is not to find the potential therapeutic molecular targets but to better understand how proliferative stress, which is the common denominator of many stressors, influences the immune system, leading to ageing and age-related changes.

The ageing of the immune system consists of two phenomena, mutually connected, namely immunosenescence and inflammageing. The immunosenescence is a plain decline in many immune parameters predominantly concerning the adaptive immunity, among others, the number of TCD4$^+$, expression of CD28, and naïve TCD4$^+$ cells, whereas inflammageing is a chronic, sterile, non-infectious, low-grade inflammation found in the elderly [7]. It is caused by the accumulation of proinflammatory factors and the change of the cell's (T-cells included) phenotype to proinflammatory one, which occurs with ageing [8]. Both inflammageing and immunosenescence play major role in the development of age-related diseases [9], however, recent findings suggest that they may also serve as an adaptation process in the course of life of an individual. Moreover, it remains unclear whether quantitative and qualitative changes in the immune cells are the result of the ageing process or an adaptation to life-long exposure to pathogens [10]. Until recently, it was assumed that ageing leads to age-related diseases (ARD's), such as cardiovascular and neurodegenerative diseases. Their occurrence was correlated with age-related changes in the immune system (immunosenescence).

Vaccine response in the elderly remains adequate when compared with young subjects [11] as well as response for immune checkpoint inhibitors even in old age [12]. Therefore, age-related changes in the immune system reflect rather its adaptation [7] to the pressure of environmental factors.

Almost all aforementioned changes in the immune parameters seem to have one common denominator, which is the proliferative stress. It can be simply described as the increased demand for cellular replication due to the need to fight pathogens, autoimmune processes, wound healing, growth, replacement of senescent cells and regeneration of hematopoiesis in case of allogeneic hematopoietic cell transplantation (allo-HCT).

The allo-HCT creates an immense demand for cellular replication since a very small population of hematopoietic progenitors must reconstitute functional hematopoiesis in the transplant recipient. It implicates immense proliferative stress to hematopoietic cells in general and specifically to lymphocytes. Therefore, in theory, it must lead to telomeric shortening and should increase senescence.

Innate immune response and inflammageing

Inflammageing is considered to be the physiological response to antigenic stress over the lifespan of an individual and might be considered beneficial as long as it remains balanced by anti-inflammatory mechanisms (such as lipoxin A4, prostanoids, adenosine, nitric oxide and annexin) as shown in some recent studies [13, 14]. Low-grade proinflammatory state is not only commonly found in centenarians but also correlates strongly with longevity as shown by Arrai et al. [15], Witkowski et al. [16] and Fulop et al. [17]. It is suggested that it is epigenetically regulated [18]. The consequence of chronic low-grade inflammation is a decrease in the function of the innate immune system called immune paralysis [19], which leads to increased protection against self-inflicted damage (e.g. autoimmune diseases) at the expense of decreased protection against PAMPs (pathogen-associated molecular patterns) and DAMPs (danger-associated molecular patterns).

With ageing the need for more economical energy expenditure increases, which is reflected by changes in the innate immune system, which gradually becomes more important than senescing adaptive immunity. In aged individuals, this can be reflected by the phenotype shift from macrophages M1 (proinflammatory) to M2, which promotes angiogenesis and cancer growth [20]. A gradual decrement in antigen presenting cells (APC's) in aged individuals is observed, which in addition are

characterized by impaired antigen presentation and TCD4$^+$ activation [21]. There is evidence that those innate immunity cells, even in the quiescent state, are able to produce proinflammatory cytokines, which would contribute to increased inflammageing, portraying the mutual interplay between innate and adaptive immune systems. Moreover, it would indirectly account for significant basal activation of APC's in older individuals [22]. There is also some data on the impact of the innate response on adaptive immune response with ageing which could be well exemplified by the down-regulation of CD28 expression in CD4$^+$T cells, which results in decreased clonal expansion of those cells [23].

Therefore, inflammageing may be interpreted not only as increased concentrations of proinflammatory cytokines (Il-1, Il-4, Il-6, TNF-α, Il-17F and others) but as a complex interplay between proinflammatory and anti-inflammatory proteins and qualitative and quantitative changes in innate immune cells phenotype.

Adaptive immune system and immunosenescence

Immunosenescence is a decline in many immune parameters of aged individuals when compared to young healthy subjects. It is considered detrimental due to the accumulation of proinflammatory factors as well as the development of inflammageing [2]. However, from the evolutionary perspective, those changes can be considered adaptive (among others, increment in central memory and effector memory T-cells counts and increased percentage of T cytotoxic cells). The most important changes in adaptive immunity occurring with ageing are decrement in the proportion of naïve TCD8$^+$ and TCD4$^+$ due to thymic involution, loss of CD28 antigen, and an increase of the number of T central memory (Tcm) and T effector memory (Tem) expressing either CD8 or CD4 antigens [24, 25]. Especially terminally differentiated effector memory (TEMRA) CD8$^+$ T cells increase in number and percentage. That shift is commonly explained as a result of chronic antigenic stimulation throughout the lifespan of an individual, with the pivotal role of CMV infection [26]. Inverted CD4$^+$/CD8$^+$ ratio is also a common finding in the elderly [27, 28].

Ageing of the immune system is associated with gradual involution of the thymus [29, 30]. Thymic involution is an evolutionary adaptation since its high metabolic activity is energy-consuming. However, it leads to a decrease in the production of naïve T cells [31] and, therefore, a decrease in TCR repertoire. Although, decrease in TCR repertoire is also affected by clonal selection of the T-cells. Recent findings, however, are contradictory [32]. It has been postulated that aged organism is well adapted to fight mainly known pathogens which it had encountered over the years, whereas the demand for new pathogens recognition is scarce. Furthermore, an increased percentage of Tcm and Tem cells serve the purpose of ameliorating antipathogenic response [33].

As mentioned above, with ageing, the percentage of TCD8$^+$ cells increases (though their count decreases). Those cells play a pivotal role in direct response against pathogens by elimination of virally-infected and cancer cells in the elderly. Surprisingly, recent data suggest that the increment of naïve TCD8$^+$ percentage is not associated with prolonged lifespan [34].

Another factor that influences the immunophenotype of aged individuals is cytomegalovirus (CMV) infection. CMV is not only detrimental, as it was thought to be the main cause of age-related immune changes, but according to novel studies, it may be the main stimulatory factor that sustains immune response for e.g. vaccination [35]. However, it has been proven that CMV infection does not influence the longevity of the aged individuals [36].

With ageing considerable change in the secretory phenotype of the T-cells occurs. It is characterized by the secretion of pro-inflammatory molecules, which stimulates inflammageing [37]. Senescent T-cell presenting with the above mentioned SASP (senescence-associated secretory phenotype) [38] could also be detrimental due to their decreased ability to proliferate as well as impaired response to antigen stimulation [39]. TCD8$^+$ CMV-specific memory cells, which were previously considered to be inactive, have the SASP and contribute to the development of inflammageing [40] which underlines beforementioned parallel of immunosenescence and inflammageing.

Hematopoietic stem-cell transplantation as a model for studying senescence of the immune system

Chronic stress (like serial bone marrow transplantations (BMT's)) may lead to the decline of function of hematopoietic stem cells (HSC's) and lead to their exhaustion in humans [41]. In the murine model, the usage of chemotherapy like 5-fluorouracil (5-FU) promotes quiescent HSC's proliferation resembling that found in the ageing

process [42]. Proliferative stress may also be triggered by infections (bacterial, viral or fungal) through stimulation of Toll-like receptors (TLR) on HSC's or respective receptors for certain proinflammatory cytokines [43] but this is rather acute stress and usually is promptly resolved and does not lead to HSC exhaustion [44]. One of the probable reasons that acute stress may be resolved with little loss/damage of HSC's, may be the innate immune system's dominant role in response to acute stimuli [45].

Therefore, HSCT, which induces prolonged proliferative stress, might be a good model for studying hematopoietic cell senescence. Transplanted HSC's undergo extensive proliferative stress for a span of a few months after transplantation (Tx) [46]. In addition, transplant recipients underwent chronic GvHD and experienced increased incidence of infections, when compared to healthy population, due to immune suppression after transplantation. It is a well-established fact that allo-HCT leads to telomeric shortening in recipients compared to their donors and that this phenomenon persists even after decades after transplantation, as proven in humans by Mathioudakis et al., de Pauw et al. and Wynn et al. [47–49] and in canines by Zaucha et al. [50]. In turn, telomeric attrition results in a similar phenotype to that occuring in the cellular senescence [51]. We recently asked a question whether the senescence of the immune system in allo-HCT recipients is increased compared to the senescence of their respective family donors. We have compared the immune parameters such as telomeric length in main lymphocyte subsets, immunophenotype, and proinflammatory cytokines concentrations between recipients and donors of allo-HCT after more than a decade after transplantation. Our results were not clearly conclusive to support the hypothesis of faster senescence of the immune system in transplant recipients. We found shorter telomeres in recipients but only in $TCD8^+$ subpopulation and subtle changes in the numbers of certain immune cells — $TCD8^+$, B-cells, and $TCD4^+/TCD8^+$ ratio [52]. All those changes resembled an ageing immune phenotype but do not clearly indicate that the immune system of allo-HCT recipients ages faster compared to their respective donors [52].

Summary

Successful ageing is complex and still not a well-understood phenomenon. Ageing of the immune system includes two mutually interconnected phenomena: inflammageing and immunosenescence. The common denominator of the ageing of the immune system is chronic proliferative stress which results in the shortening of telomeres, qualitative and quantitative changes in the immune cells, and shift to the proinflammatory phenotype of the immune cells. The allo-HCT was thought to be an excellent platform for studying the ageing of the immune system. However, our recently published findings indicate the presence of only few quantitative changes in lymphocyte subpopulations in long-term allo-HCT survivors when compared to their donors, which resemble those found in aged individuals. This indirectly indicates that the elasticity of the immune system exposed to the immense proliferative stress at the time of allo-HCT is big enough to prevent the significant and clinically relevant acceleration of the immune system's ageing.

Conflict of interest: none declared

References

1. Fulop T, Larbi A, Hirokawa K, et al. Immunosenescence is both functional/adaptive and dysfunctional/maladaptive. Semin Immunopathol. 2020; 42(5): 521–536, doi: 10.1007/s00281-020-00818-9, indexed in Pubmed: 32930852.
2. Fulop T, Larbi A, Dupuis G, et al. Immunosenescence and inflamm-aging as two sides of the same coin: friends or foes? Front Immunol. 2017; 8: 1960, doi: 10.3389/fimmu.2017.01960, indexed in Pubmed: 29375577.
3. Blackburn EH, Epel ES, Lin J. Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection. Science. 2015; 350(6265): 1193–1198, doi: 10.1126/science.aab3389, indexed in Pubmed: 26785477.
4. Blackburn EH. The molecular structure of centromeres and telomeres. Annu Rev Biochem. 1984; 53: 163–194, doi: 10.1146/annurev.bi.53.070184.001115, indexed in Pubmed: 6383193.
5. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961; 25: 585–621, doi: 10.1016/0014-4827(61)90192-6, indexed in Pubmed: 13905658.
6. Olovnikov AM. The role of incomplete terminal repair of chromosomal DNA in the aging of neurons and postmitotic organisms. Izv Akad Nauk Ser Biol. 1995(4): 504–507, indexed in Pubmed: 7496320.
7. Franceschi C, Bonafè M, Valensin S, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000; 908: 244–254, doi: 10.1111/j.1749-6632.2000.tb06651.x, indexed in Pubmed: 10911963.
8. Bektas A, Schurman SH, Sen R, et al. Human T cell immunosenescence and inflammation in aging. J Leukoc Biol. 2017; 102(4): 977–988, doi: 10.1189/jlb.3RI0716-335R, indexed in Pubmed: 28733462.
9. Fulop T, Witkowski JM, Olivieri F, et al. The integration of inflammaging in age-related diseases. Semin Immunol. 2018; 40: 17–35, doi: 10.1016/j.smim.2018.09.003, indexed in Pubmed: 30287177.

10. Franceschi C, Monti D, Sansoni P, et al. The immunology of exceptional individuals: the lesson of centenarians. Immunol Today. 1995; 16(1): 12–16, doi: 10.1016/0167-5699(95)80064-6, indexed in Pubmed: 7880382.
11. Schwarz TF, Volpe S, Catteau G, et al. Persistence of immune response to an adjuvanted varicella-zoster virus subunit vaccine for up to year nine in older adults. Hum Vaccin Immunother. 2018; 14(6): 1370–1377, doi: 10.1080/21645515.2018.1442162, indexed in Pubmed: 29461919.
12. Daste A, Domblides C, Gross-Goupil M, et al. Immune checkpoint inhibitors and elderly people: A review. Eur J Cancer. 2017; 82: 155–166, doi: 10.1016/j.ejca.2017.05.044, indexed in Pubmed: 28689093.
13. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: A systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev. 2007;128(1):92–105, doi: 10.1016/j.mad.2006.11.016, indexed in Pubmed: 17116321.
14. Morrisette-Thomas V, Cohen AA, Fülöp T, et al. Inflamm--aging does not simply reflect increases in pro-inflammatory markers. Mech Ageing Dev. 2014; 139: 49–57, doi: 10.1016/j.mad.2014.06.005, indexed in Pubmed: 25011077.
15. Arai Y, Martin-Ruiz CM, Takayama M, et al. Inflammation, but not telomere length, predicts successful ageing at extreme old age: a longitudinal study of semi-supercentenarians. EBioMedicine. 2015; 2(10): 1549–1558, doi: 10.1016/j.ebiom.2015.07.029, indexed in Pubmed: 26629551.
16. Witkowski JM. Immune system aging and the aging-related diseases in the COVID-19 era. Immunol Lett 2022;243:19–27. , doi: 10.1016/j.imlet.2022.01.005, indexed in Pubmed: 35108570.
17. Fulop T, Larbi A, Pawelec G, et al. Immunology of aging: the birth of inflammaging. Clin Rev Allergy Immunol. 2023; 64(2): 109–122, doi: 10.1007/s12016-021-08899-6, indexed in Pubmed: 34536213.
18. Horvath S, Pirazzini C, Bacalini MG, et al. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. Aging (Albany NY). 2015; 7(12): 1159–1170, doi: 10.18632/aging.100861, indexed in Pubmed: 26678252.
19. Fulop T, Dupuis G, Baehl S, et al. From inflamm-aging to immune-paralysis: a slippery slope during aging for immune-adaptation. Biogerontology. 2016; 17(1): 147–157, doi: 10.1007/s10522-015-9615-7, indexed in Pubmed: 26472173.
20. Geeraerts X, Bolli E, Fendt SM, et al. Macrophage metabolism as therapeutic target for cancer, atherosclerosis, and obesity. Front Immunol. 2017; 8: 289, doi: 10.3389/fimmu.2017.00289, indexed in Pubmed: 28360914.
21. Magrone T, Jirillo E. Disorders of innate immunity in human ageing and effects of nutraceutical administration. Endocr Metab Immune Disord Drug Targets. 2014; 14(4): 272–282, doi: 10.2174/1871530314666141010105540, indexed in Pubmed: 25307109.
22. Fulop T, Larbi A, Douziech N, et al. Signal transduction and functional changes in neutrophils with aging. Aging Cell. 2004. ; 3(4): 217–226, doi: 10.1111/j.1474-9728.2004.00110.x, indexed in Pubmed: 15268755.
23. Bryl E, Witkowski JM. Decreased proliferative capability of CD4(+) cells of elderly people is associated with faster loss of activation-related antigens and accumulation of regulatory T cells. Exp Gerontol. 2004; 39(4): 587–595, doi: 10.1016/j.exger.2003.10.029, indexed in Pubmed: 15050294.
24. Akbar AN, Terry L, Timms A, et al. Loss of CD45R and gain of UCHL1 reactivity is a feature of primed T cells. J Immunol. 1988; 140(7): 2171–2178, doi: 10.4049/jimmunol.140.7.2171.
25. Willinger T, Freeman T, Hasegawa H, et al. Molecular signatures distinguish human central memory from effector memory CD8 T cell subsets. J Immunol. 2005; 175(9): 5895–5903, doi: 10.4049/jimmunol.175.9.5895, indexed in Pubmed: 16237082.
26. Fülöp T, Larbi A, Pawelec G. Human T cell aging and the impact of persistent viral infections. Front Immunol. 2013; 4: 271, doi: 10.3389/fimmu.2013.00271, indexed in Pubmed: 24062739.
27. Muller GC, Gottlieb MGV, Correa BL et al. The inverted CD4:CD8 ratio is associated with gender-related changes in oxidative stress during aging. Cell Immunol 2015;296(2):149–154, doi: 10.1016/j.cellimm.2015.05.006, indexed in Pubmed: 26051633.
28. Sainz T, Serrano-Villar S, Díaz L, et al. The CD4/CD8 ratio as a marker T-cell activation, senescence and activation/exhaustion in treated HIV-infected children and young adults. AIDS. 2013; 27(9): 1513–1516, doi: 10.1097/QAD.0b013e32835faa72, indexed in Pubmed: 23435292.
29. Gui J, Mustachio LM, Su D-M, et al. Thymus size and age-related thymic involution: early programming, sexual dimorphism, progenitors and stroma. Aging Dis. 2012; 3(3): 280–290, indexed in Pubmed: 22724086.
30. Aspinall R, Andrew D. Thymic involution in aging. J Clin Immunol. 2000; 20(4): 250–256, doi: 10.1023/a:1006611518223, indexed in Pubmed: 10939712.
31. Goronzy JJ, Fang F, Cavanagh MM, et al. Naive T cell maintenance and function in human aging. J Immunol. 2015; 194(9): 4073–4080, doi: 10.4049/jimmunol.1500046, indexed in Pubmed: 25888703.
32. Pawelec G. Immunosenescence and cancer. Biogerontology. 2017; 18(4): 717–721, doi: 10.1007/s10522-017-9682-z, indexed in Pubmed: 28220304.
33. Saule P, Trauet J, Dutriez V et al. Accumulation of memory T cells from childhood to old age: Central and effector memory cells in CD4+ versus effector memory and terminally differentiated memory cells in CD8+ compartment. Mech Ageing Dev 2006;127(3):274–281, doi: 10.1016/j.mad.2005.11.001, indexed in Pubmed: 16352331.
34. Derhovanessian E, Maier AB, Hähnel K, et al. Lower proportion of naïve peripheral CD8+ T cells and an unopposed pro-inflammatory response to human Cytomegalovirus proteins in vitro are associated with longer survival in very elderly people. Age (Dordr). 2013; 35(4): 1387–99, doi: 10.1007/s11357-012-9425-7, indexed in Pubmed: 22661297.
35. McElhaney JE, Garneau H, Camous X, et al. Predictors of the antibody response to influenza vaccination in older adults with type 2 diabetes. BMJ Open Diabetes Res Care. 2015; 3(1): e000140, doi: 10.1136/bmjdrc-2015-000140, indexed in Pubmed: 26504526.
36. Sansoni P, Vescovini R, Fagnoni FF, et al. New advances in CMV and immunosenescence. Exp Gerontol. 2014; 55: 54–62, doi: 10.1016/j.exger.2014.03.020, indexed in Pubmed: 24703889.
37. Cuollo L, Antonangeli F, Santoni A, et al. The Senescence-Associated Secretory Phenotype (SASP) in the Challenging Future of Cancer Therapy and Age-Related Diseases. Vol. Biology (Basel). 2020; 9(12): 485, doi: 10.3390/biology9120485, indexed in Pubmed: 33371508.
38. Coppé JP, Patil CK, Rodier F, et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of on-

cogenic RAS and the p53 tumor suppressor. PLoS Biol. 2008; 6(12): 2853–2868, doi: 10.1371/journal.pbio.0060301, indexed in Pubmed: 19053174.
39. Campisi J. Cellular senescence and lung function during aging. Yin and Yang. Ann Am Thorac Soc. 2016; 13 Suppl 5(Suppl 5): S402–S406, doi: 10.1513/AnnalsATS.201609-703AW, indexed in Pubmed: 28005423.
40. Akbar AN, Henson SM, Lanna A. Senescence of T lymphocytes: implications for enhancing human immunity. Trends Immunol. 2016; 37(12): 866–876, doi: 10.1016/j.it.2016.09.002, indexed in Pubmed: 27720177.
41. Rossi DJ, Jamieson CHM, Weissman IL. Stems cells and the pathways to aging and cancer. Cell. 2008; 132(4): 681–696, doi: 10.1016/j.cell.2008.01.036, indexed in Pubmed: 18295583.
42. Schoedel KB, Morcos MNF, Zerjatke T, et al. The bulk of the hematopoietic stem cell population is dispensable for murine steady-state and stress hematopoiesis. Blood. 2016; 128(19): 2285–2296, doi: 10.1182/blood-2016-03-706010, indexed in Pubmed: 27357698.
43. Schuettpelz LG, Link DC. Regulation of hematopoietic stem cell activity by inflammation. Front Immunol. 2013; 4: 204, doi: 10.3389/fimmu.2013.00204, indexed in Pubmed: 23882270.
44. Singh S, Jakubison B, Keller JR. Protection of hematopoietic stem cells from stress-induced exhaustion and aging. Curr Opin Hematol. 2020; 27(4): 225–231, doi: 10.1097/MOH.0000000000000586, indexed in Pubmed: 32398455.
45. Baldridge MT, King KY, Goodell MA. Inflammatory signals regulate hematopoietic stem cells. Trends Immunol. 2011; 32(2): 57–65, doi: 10.1016/j.it.2010.12.003, indexed in Pubmed: 21233016.
46. Rodrigues-Moreira S, Moreno SG, Ghinatti G, et al. Low-dose irradiation promotes persistent oxidative stress and decreases self-renewal in hematopoietic stem cells. Cell Rep. 2017; 20(13): 3199–3211, doi: 10.1016/j.celrep.2017.09.013, indexed in Pubmed: 28954235.
47. Mathioudakis G, Storb R, McSweeney P, et al. Polyclonal hematopoiesis with variable telomere shortening in human long-term allogeneic marrow graft recipients. Blood. 2000; 96(12): 3991–3994, doi: 10.1182/blood.v96.12.3991.
48. Pauw EDe, Otto S, Wijnen J, et al. Long-term follow-up of recipients of allogeneic bone marrow grafts reveals no progressive telomere shortening and provides no evidence for haematopoietic stem cell exhaustion. Br J Haematol. 2002; 116(2): 491–496, doi: 10.1046/j.1365-2141.2002.03283.x.
49. Wynn R, Thornley I, Freedman M, et al. Telomere shortening in leucocyte subsets of long-term survivors of allogeneic bone marrow transplantation. Br J Haematol. 1999; 105(4): 997–1001, doi: 10.1046/j.1365-2141.1999.01450.x, indexed in Pubmed: 10554813.
50. Zaucha JM, Yu C, Mathioudakis G, et al. Hematopoietic responses to stress conditions in young dogs compared with elderly dogs. Blood. 2001; 98(2): 322–327, doi: 10.1182/blood.v98.2.322, indexed in Pubmed: 11435299.
51. Hewitt G, Jurk D, Marques FDM, et al. Telomeres are favoured targets of a persistent DNA damage response in ageing and stress-induced senescence. Nat Commun. 2012; 3: 708, doi: 10.1038/ncomms1708, indexed in Pubmed: 22426229.
52. Czarnogórski MC, Sakowska J, Maziewski M, et al. Ageing-resembling phenotype of long-term allogeneic hematopoietic cells recipients compared to their donors. Immun Ageing. 2022; 19(1): 51, doi: 10.1186/s12979-022-00308-6, indexed in Pubmed: 36324179.