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REVIEW ARTICLE

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

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. This is caused by 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 well-established explanations of this phenomenon may be the impaired repair of telomeric DNA, due to high demand on the repair machinery, caused by damage to DNA by ROS. This is consistent with the assumption of Olovnikov [6] who proposed the "theory of marginotomy" which postulates shortening of the replica as compared to the DNA template. This has directly led to the discovery of telomeres. The two studies were 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 for adjustment of 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 characteristic for 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 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 of the elderly remains adequate when compared with young subjects [11] as well as response to 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, as 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 emphasizes the aforementioned relationship between immunosenescence and inflammageing.

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

Chronic stress (eg. serial bone marrow transplantations (BMT's)) may lead to the decline of function of hematopoietic stem cells (HSC's) and exhaustion [41]. In the murine model, the use 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]. This however, is acute stress usually promptly resolved and does not lead to HSC exhaustion [44]. One of the likely reasons of resolving acute stress   at only slight loss of HSC, 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' undergo extensive proliferative stress for a span of a few months after transplantation (Tx) [46]. In addition, transplant recipients may suffer from chronic GvHD and increased incidence of infections, due to immune suppression after transplantation. It is a well-established fact that allo-HCT leads to telomeric shortening in recipients as compared to their donors and that this phenomenon persists 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 enquired whether the senescence of the immune system in allo-HCT recipients is higher 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 following 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

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