The role of immune response in ageing and longevity. A focus on B cell compartment

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Abstract

The improvement of the quality of life of elderly people is going to become a priority because of the continuous increase in the number of centenarians. This render the studies of the processes involved in ageing of critical importance. Centenarians are a widely accepted model of successful ageing, a complex process which is influenced by several biological, environmental and lifestyle factors, because they have reached the extreme limits of life span overcoming the major age-related diseases. In centenarians model, several aspects have been studied, as inflammation, immune system, genetics and metabolism, to understand the secret of their long survival. It has been proposed that centenarians are characterized by more efficient protective molecules and biochemical pathways, and show well preserved immune functions. But a complication in the studies of centenarians is their

extremely variable clinical conditions. Indeed, among centenarians, there are both frail individuals with multiple pathologies, and healthy subjects, though some of them present signs of the advanced ageing process. Concerning the B cell compartment, centenarians seem to show the typical age-related changes observed in the elderly, but, surprisingly, their offspring present a well-preserved humeral immunity. These findings support the hypothesis that centenarian offspring are predisposed to healthy aging and longer survival, making them a suitable target of ageing studies.

Key Words

B cells, Centenarian Offspring, Inflamm-ageing, Immunosenescence.

State of the art

The role of inflammation on immunosenescence

Ageing is characterized by a general decline in physiological functions with an increasing morbidity and mortality, and it has been well established that is the major risk factor for all chronic diseases and geriatric syndromes, which negatively affect health span and longevity [Franceschi et al., 2017]. It is well known that ageing is accompanied by a complex remodelling of tissues and organs, in order to contrast the time-enduring exposure to biological and environmental stressors, whereby longevity depends on efficient mechanisms of adaption capacity [Baluster et al., 2014; Bucky et al., 2014; Candour et al., 2010; Capri et al., 2008]. The most important aspect of ageing is "inflamm-ageing", a chronic low-grade inflammatory status. Given that inflammation is essential for survival, the development of inflamm-ageing can only be explained with the "antagonistic pleiotropic theory", that, in other words, it asserts that inflammation, important for survival in the earlier stage of life to fight infections and for the tissues repair, have adverse and detrimental effects on aged individuals [Goto, 2008]. An opposing mechanism is strictly associated with inflammation, indicated as anti-inflammation, which is its inhibitory counterpart and that have the role to resolve the inflammatory processes. Lifelong depends on the balance between "inflammation" and "anti-inflammation" [Franceschi et al., 2017]. In this way, an important role is played by genetic background, as demonstrated in a large number of studies which have shown that the frequency of several polymorphism involved in inflammation are different between elderly and successfully aged people, as centenarians [Reviewed by Larbi et al., 2008]. As it is known, centenarians show a complex and heterogeneous phenotype, which seems to be the result of the capacity to adapt and remodel their body in response to stressors, that makes them able to delay the ageing process and to escape the major age-related diseases. Moreover, it has been demonstrated that longevity has a strong familial component [Passarino et al., 2016], indeed centenarian offspring, like their centenarian parents, have a significant advantage for longer survival together with a lower risk to develop age-related diseases [Balistreri et al., 2014].

The phenomenon of inflamm-ageing is strictly associated with the deterioration of the immune function, termed "immunosenescence", which is the cause of the increased susceptibility to infectious diseases, cancer, dementia, cardiovascular diseases and autoimmunity, and of the decreased response to vaccination, which characterize elderly people [Bucci et al., 2014; Derhovanessian et al., 2010, 2013; Fulop et al., 2016; Grasse et al., 2016; Pawelec 2014a, b; Salvioli et al., 2013; Strindhall et al., 2007]. The condition of inflamm-ageing provides a continuous mild antigenic challenge that leads to a progressive stimulation, or depletion, of the immune system cells and the filling of the immunological space by activated/exhausted lymphocytes with altered functions [Bulati et al., 2011, 2014; Fulop et al., 2017; Larbi & Fulop, 2014; Naradikian et al., 2016; Pawelec, 2014a,b; Pinti et al., 2016; Rubtsova et al., 2015]. Although T cell compartment has been more extensively studied [Di Benedetto et al., 2015; Wistuba-Hamprecht et al., 2016], age-related changes in B cell number and repertoire have also been described, and data in literature demonstrate that elderly, frequently, do not have protective antibody against recall antigens or newly encountered antigens, so suggesting the impairment of B cell branch [Aberle et al., 2013; Bulati et al., 2011, 2014, 2015, 2017; Cancro et al., 2009; Colonna-Romano et al., 2009; Dunn-Walters & Ademokun, 2010; Frasca & Blomberg, 2016; Naradikian et al., 2016].

B cell and Ageing

It is well known that, with ageing, there is a significant decrease in circulating B lymphocytes [Bulati M et al., 2011; Colonna-Romano G et al., 2009; Pinti M et al., 2016; Strindhall et al., 2007] and a shift from naïve (IgD, IgM) to memory (IgG, IgA) immunoglobulins production [Listì et al., 2006], accompanied by an impaired ability to produce high affinity protective antibodies against infectious agents [Frasca & Blomberg, 2016; Frasca et al., 2017] and the shrinkage of the repertoire diversity [Dunn-Walters, 2016; Gibson et al., 2009]. Moreover, in elderly, it has been demonstrated the increase of a senescent B cell subpopulation, namely DN late memory B cells, at the expense of naïve B cells [Bulati et al., 2011, 2014, 2015, 2017; Colonna-Romano et al., 2009; Frasca et al., 2017]. $IgD^{-}CD27^{-}$ DN late memory B cells have been also reported to be expanded in patients affected by autoimmune diseases, as Systemic Lupus Erythematosus or Rheumatoid

Arthritis, and in HIV-infected people [Fecteau et al., 2006; Mahmood et al., 2015; Palma et al., 2014; Sanz et al., 2008; Wei et al., 2007], suggesting the pivotal role of inflammation as the cause of this increase.

B cell in centenarian offspring, a model of successful ageing

As known, centenarians are able to reach the extreme limits of life slowing down aging processes and are characterized by a lower prevalence of cancer, cardio- and cerebral-vascular diseases and most of the metabolic age-associated diseases, as insulin resistance or diabetes [Caruso et al., 2012]. Moreover, many of them show optimal metabolic (cholesterol, LDL-C, HDL-C, triglycerides), anthropometric (Body Mass Index) and cardiovascular (blood pressure) parameters for their age [Kolovou et al., 2014]. Nonetheless, the study of these exceptional individuals has highlighted several methodological problems. First of all, the difficulty in their recruitment due to their low frequency in the population. Besides, it is not easy to perform population-based cross-sectional studies on centenarians, because of the very high mortality rate at extremely advanced age.

Last but not least, a complication in the studies of centenarians is their extremely variable clinical conditions, as, among centenarians, there are both frail individuals with multiple pathologies, and healthy subjects, though some of them present signs of the advanced ageing process [Arai et al., 2015; Bucci et al., 2014; Gueresi et al., 2013; Salvioli et al., 2013; Strindhall et al., 2007]. It is also known that longevity have a strong familial component and recent studies have suggested that centenarian offspring, like their centenarian parents, have a significant advantage for longer survival together with a lower risk to develop age-related diseases [Balistreri et al., 2014]. At the same time, the study of centenarian offspring resolves the problems occurring with their parents, as being younger, they are easier to recruit, are less frail and less likely to die within a short time. Finally, they can be compared with an appropriate control group, consisting of age-matched elderly people whose parents died at an average life expectancy. For these reasons, offspring of long lived subjects, represent the appropriate model to analyse successful ageing and, consequently, to understand the advantage of centenarian phenotype [Capri et al., 2008; Cevenini et al., 2008; Rea et al., 2005], as centenarian offspring show a favourable lipid, immunological and cardiovascular profile, a

decreased cognitive decline and a protective genetic background [Balistreri et al., 2014]. So, it can be stated that it exists a potential transmission from centenarians to their offspring of the ability to escape or postpone the major age-related disease.

Concerning the B cell compartment, its study in centenarian offspring, has shown that, although there is a reduction in the B cell count, typical of elderly people, they do not present the typical naïve-memory shift observed in the elderly [Balistreri et al., 2014; Buffa et al., 2013; Colonna-Romano et al., 2010]. Indeed, centenarian offspring do not show neither the reduction of $IgD^{+}CD27^{-}$ naïve nor the increase of the $IgD^{-}CD27^{-}$ DN late memory B cells observed in the average elderly population, but it look similar to young people [Colonna-Romano et al., 2010].

This failed age-associated increase of DN B cells, observed in the general elderly population, suggest that in centenarian offspring there is not an exhaustion of the B cell compartment. Furthermore, the evaluation of IgM of centenarian offspring serum shows values that are within the range of the levels observed in young subjects [Colonna-Romano et al., 2010].

These data, together with the increased number of naïve B cell, suggest a good bone marrow cell reservoir in centenarian offspring. This is an interesting observation, as it has been demonstrated [Cancro et al., 2009] that the bone marrow ability to generate B cells is impaired with age. The "younger" immune profile of centenarian offspring is also supported by data obtained from T cell compartment of these subjects, in which it was not observed the typical shift from naïve to exhausted memory T cells that are a typical feature of immune system ageing [Pellicanò et al., 2014].

Discussion

Aged people are characterized by a chronic inflammatory status, named "inflamm-ageing", which is strictly associated with the deterioration of the immune function, defined as "immunosenescence" [Salvioli et al., 2013]. These events are cause of the increased susceptibility of elderly to infectious diseases, cancer, dementia, cardiovascular diseases, autoimmunity and of the decreased response to vaccination [Bucci et al., 2014; Derhovanessian et al., 2010, 2013; Fulop et al., 2017; Grasse et al., 2016; Pawelec 2014a,b; Salvioli et al., 2013; Strindhall et al., 2007]. It has been widely demonstrated that ageing have a strong impact on the

remodelling of the B cell branch of immune system. Indeed, together with the reduced number of circulating B lymphocytes, the reduction of $IgD^{+}CD27^{-}$ naïve and the simultaneous increase of $IgD^{-}CD27^{-}$ late memory DN B cells have been reported [Bulati et al., 2011, 2014, 2015, 2017; Colonna-Romano et al., 2009; Frasca et al., 2017]. A crucial role in the impairment of B cell branch of the immune system is played by senescent/exhausted $IgD^{-}CD27^{-}$ DN B cells. Indeed, these cells are also increased in other models of chronic inflammation, and they shown a pro-inflammatory trafficking and a senescent associated secretory phenotype [Bulati et al., 2011, 2014, 2015, 2017; Colonna-Romano et al., 2009; Frasca et al., 2017]. Moreover it is also known that there is a considerable variation in the rate of progression of ageing that it has led to make a distinction between successful and unsuccessful ageing. Centenarian offspring, a model of successful ageing, seem to show an optimal B cell profile, which is comparable for several aspects, to that of young subjects [Balistreri et al., 2014; Buffa et al., 2013; Colonna-Romano et al., 2010; Derhovanessian et al., 2010; Pellicanò et al., 2014]. In this way, centenarian offspring behave as the young people, maintaining the ability to respond to new infections and responding to vaccination, differently from their parents [Derhovanessian et al. 2010]. This condition determines a better control of inflammatory response with a reduction of the risk for the major age-associated diseases. All together these factors described, suggest that the positive ageing phenotype of centenarian offspring might be the result of an efficient physical performance. This allows them to have a major chance to extend survival, not only in chronological age, but also in a health and well-being ageing [Balistreri et al., 2014].

Conclusion

The most studies focusing on the "successful pattern of centenarians", reveal that they may easily fail to be considered as successful agers, when objective criteria are applied. Indeed, although they are in relatively good conditions, many centenarians show signs of frailty, due to their extreme age, and present a great heterogeneity in their health and functional status. Nonetheless, these long-lived exceptional individuals have delayed the ageing processes and have escaped the major age-related diseases, probably because they have a favourable genetic background and good metabolic parameters [Paolisso et al., 2001; Motta et al., 2005; Bucci et al.,

2014]. Moreover, it has been widely demonstrated that "IRP" is a real predictor of mortality in elderly individuals and that the survival of centenarians is due to the selection of octo- and nonagenarians without IRP [Stridhall et al., 2007]. All together, these data, led to speculate that centenarians spent the most of their life in good health conditions, but, having overcome the "biological barriers", they are extremely fragile, show rapid evolution of cellular and tissues degeneration, with a compression of their disability into a relatively short period at the end of their exceptional long life. For these reasons, the synonymous "centenarian-successful ageing" somehow collapses, and it becomes of crucial importance to study the differences among individuals which are in the "critical age" in which the physiological decline and the onset of the major age-related diseases occur. This statement is supported by some fundamental concepts. First of all, it has been demonstrated the existence of strong genetic determinants for longevity and also that the favourable modulation of diseases susceptibility is strongly inherited in families with exceptional longevity [Balistreri et al., 2014]. Indeed, offspring of long lived subjects, like their centenarian parents, show a favourable lipid, immunological and cardiovascular profile, associated with decreased cognitive decline and a protective genetic background. So, it exist a potential transmission from centenarians to their offspring of the capacity to escape or postpone the major age-related diseases. Moreover, it has been also demonstrated that the state of health of elderly people, without long-lived parents, is worse compared to that of subjects with at least one centenarian parent [Gueresi et al., 2013], confirming the hypothesis that longevity is a familial genetic trait. So their survival advantage, the higher probability to become long-lived and the lower risk to undergo to major age-related diseases, render centenarian offspring, who are one generation younger than centenarians, the best model for the studies on healthy ageing.

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