REVISÃO/REVIEW

IMUNOSENESCÊNCIA E SEU IMPACTO NA PRÁTICA MÉDICA. UM NOVO OLHAR PARA UM VELHO PROBLEMA.

IMMUNOSENESCENCE AND ITS IMPACT ON MEDICAL PRACTICE. A NEW LOOK AT AN OLD PROBLEM.

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RESUMO

Introdução:O envelhecimento é um processo complexo que influencia todos os sistemas do corpo humano e seu impacto no sistema imune é chamado Imunosenescência. Essa condição é resultado de várias modulações imunológicas causadas por interações entre fatores genéticos e ambientais e é responsável por importantes condições clínicas em indivíduos idosos como alta prevalência de doenças infecciosas e autoimunes, neoplasias e menor eficácia de vacinas. Objetivo: Nesta revisão serão discutidos os problemas clínicos mais comuns na população idosa relacionados a Imunosenescência, e os novos achados da ciência básica relevantes a este tópico. Conclusão: A melhor compreensão da Imunosenescência é importante para prevenção de doenças comuns relacionadas à idade e para a promoção de um envelhecimento saudável.

Palavras chaves: Imunologia, Envelhecimento, Envelhecimento Celular.

ABSTRACT

Background: Ageing is a very complex process that modulates all the organ systems of the human body, and its impact on the immune system is called Immunosenescence. This condition is the result of several immune modulations due to genetic and environmental interactions and is responsible for important clinical conditions in elderly subjects, such as a higher incidence of infectious and autoimmune diseases, neoplasias and decreased vaccine efficacy. Objective: In this current review we will discuss the most common clinical problems in the elderly population related to Immunosenescence and new findings in basic science relevant to this topic. Conclusion: A better understanding of Imunosenescence is important to prevention of common age related diseases and for the promotion of healthy ageing.

Key words: Immunology, Aging, Cell Aging.

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INTRODUCTION

One way to measure the quality and success of a society is the life expectancy or in other words, life and health span. The recent social, economic and technological development is causing a fast ageing of the world population, especially in developed countries. Brazil being a developing country, is facing a rapid increase of its elderly population. Currently, 11% of the Brazilian population is composed of subjects older than 60 [1]. This demographical transition implies a great change in social structures, such as the health care system. The elderly population demands a different and specialized care with focus on treatment of chronic and degenerative diseases, prevention of disability, frailty and infectious diseases.

From a biological point of view, ageing is a very complex process that modulates all the organ systems of the human body, and its impact on the immune system is called Immunosenescence. Franceschi et.al[2]. proposed a simple equation to better understand the interaction between ageing and the immune system : *Stress resistance = Ability to survive*. Adopting an evolutionary point of view, the capacity to deal with environmental and physiological challenges prolongs survivability and as a result expose organisms once more to new stressors, promoting an endless selection process. In other words, the evolution of the immune system resulted in lifespan extension and ageing in its own way modulates the defense mechanisms based on the new environment and physiologic demands. The human innate and adaptive immune responses thus pass through several changes dictate by different challenges during ageing.

The immune system ageing is characterized by a decrease of hematopoietic stem cells and thymus involution, leading to a decline in the replenishment of naïve T and B cells. Interaction with environmental triggers leads to a shift from naïve to memory cells, an expansion of oligoclonal memory cells related to cytomegalovirus (CMV), and a low grade and persistent inflammatory state[2-5]. The ageing phenotype is a result of the sum of all these immune modulations and has been correlated with several clinical conditions such as increased incidence of inflammatory, neurodegenerative and infectious diseases, frailty, decreased vaccine efficacy and occurrence of some age-related neoplasms[6-11].

In this current review we will discuss the most common clinical problems in the elderly population related to Immunosenescence and new findings in basic science relevant to this topic.

TITULO??

Is there a maker of immune ageing? - The immune risk profile.

Humans have always pursued the secret of longevity. Despite intense investigation, only recently some studies identified certain immune characteristics able to predict mortality in elderly populations. The sum of these immune factors is called “Immune Risk Profile” (IRP), and were identified for the first time in the large *Swedish OCTO/NONA*[12,13] cohort study. It was observed that elderly subjects with a CD4/CD8 ratio < 1, CMV IgG serum positivity, and expansion of $CD8^+$ $CD28^-$ cell population exhibited higher mortality irrespective of health status. An extension of this study has found that CD4/CD8 ratio <1 was in fact the best independent predictor of mortality and ratios >1 were correlated with successful ageing[14,15]. Despite the robust evidence, further studies did not confirm the same IRP variables in different elderly populations around the world, suggesting that immune ageing can be a heterogeneous process.

An interesting note covered in the original IRP was the identification of a viral infection playing a role in the ageing process. Further studies documented a close relationship between CMV chronic infection and modulations of T cell subsets. The CMV IgG serum positivity has been correlated with accumulation of highly differentiated effector T cells[16]. This cell subset is characterized by an impaired capacity to migrate to lymph nodes, decreased ability to being stimulated by APC and higher production of pro inflammatory cytokines.

In summary, there is not a robust marker of immune ageing. The decline of CD8 naïve T cells and the occurrence of $CD28^-$ T cells are the most common and reproducible findings in different elderly populations, but its impact in healthy ageing and disease development is not clear yet.

Sometimes more is less. - Inflammageing a silent killer.

The inflammatory response is the crucial physiological response to the constant immunological challenges that we are exposed to in daily life. Several studies have observed a progressive low-grade inflammation that follows the ageing process termed Inflammageing. Inflammageing has been characterized as an unbalance between pro and anti-inflammatory factors resulting in increased serum levels of IL-6, TNF-α and acute phase proteins such as CRP[2]. This condition has been correlated with the development of important clinical conditions such as frailty, cancer and cardiovascular diseases [17-19]. Although several transversal studies correlated CMV infection with Inflammageing, a recent longitudinal study did not find any association between this viral infection and an increase of inflammatory cytokines[20].

In healthy centenarians it has been observed that higher production of anti-inflammatory factors is protective and contributes to longer survival. Lio et.al[21].found that healthy centenarians have higher serum levels of TGF- β and carry a higher frequency of an IL-10 gene polymorphism that promotes higher IL-10 production when compared to controls. The Leiden 85+ cohort study[22] also revealed that individuals with higher IL-10 serum levels presented lower cardiovascular mortality when compared with subjects with lower levels of IL-10.

The Groningen Research Initiative on Healthy Ageing and Immune Longevity (GRAIL) group is conducting several research projects related to Inflammageing. Based on the evidence that B cells can present pro and anti-inflammatory roles through their cytokine production profile, our group explored the impact of ageing on cytokine producing B cells. The population of effector B cells is characterized by production of TNF-α and IL-6, promoting inflammation, and disturbances in this subset have been reported in diseases such as rheumatoid arthritis, giant cell arteritis and polymyalgia rheumatica[23,24]. On the other hand, B cells can block the inflammatory response inhibiting TNF-α and IFN-γ production by T cells in an IL-10 dependent way. IL-10 producing B cells are termed B regulatory cells (Breg). Decreased numbers of Breg have been correlated with several inflammatory diseases such as systemic lupus erythematous, multiple sclerosis and rheumatoid arthtritis[25-27]. In a cross sectional study we have found that regulatory B cells numbers tends to decrease with ageing whereas we did not find any modulation of the effector B cell subset. Thus, ratio's of Beff/Breg increase with ageing thereby favoring pro-inflammation. Our findings suggest a new players in Inflammageing: the B effectors and the Bregs (unpublished data).

Preventing severe complications of common diseases -Vaccination response in elderly.

Vaccination should be regarded as a milestone in the quest for extension of life expectancy for mankind, making prevention of several life threatening infectious diseases possible. A particular health issue is the vaccination of the elderly population since infectious diseases incidence increases with age[6]. Several clinical and epidemiological studies have shown a decreased vaccine response in older subjects. Both the innate and the adaptive immune system are involved in this process. The aged innate response displays diminished migration and phagocytic activity of neutrophils and macrophages summed to decreased numbers of APC cells and reduced expression of MHC I and II as well[28,29]. On the other hand, the aged adaptive response is impaired due to decreased numbers of naïve T and B cells, accumulation of highly differentiated effector T cells, decreased expression of CD40-ligand by $CD4^+$ cells, defects in isotype switching and somatic mutation in B cells[30-35]. This highly disturbed immune response contributes to increased susceptibility to infectious diseases and is a challenge to be overtaken by the development of new vaccines.

Changing old for new – The challenge of transplantation medicine in elderly subjects.

The improvement of chronic diseases care is leading to an increase in the prevalence of end stage organ failures. Since regenerative medicine and stem cells therapy are not feasible treatments yet, organ transplantation is the best alternative for these conditions. Age is one of the most important factors in transplant outcome and Immunosenescence plays an important role in this clinical scenario. Several epidemiological studies have reported lower incidences of acute graft rejection in elderly recipients[36-38], however the mortality and chronic rejection are still higher in this population[39,40]. Most of the authors attributes

this different clinical outcome to the same immune changes that also determine/impact the impaired vaccine response.

Autoimmune diseases: Age marked pathologies.

The correlation between Immunosenescence and autoimmune diseases is based on several epidemiological and laboratory data. It is important to note that autoimmune disorders are more prevalent in older subjects particularly with rheumatoid arthritis, giant cell arteritis and polymyalgia rheumatica[6]. This fact can be explained by a breach of tolerance that follows ageing. The low naïve T cell output due to thymus involution may induce an intense proliferation of peripheral naïve T cells, resulting in impaired selection and replication of naïve and memory self-reactive T cells. Insufficiency of telomerase activity, deficiency of DNA repair mechanisms and accumulation of $CD28^-$ cells may also contribute to the pathogenesis, promoting inflammation and impaired regulatory capacity[41-43]. Noteworthy, several of these characteristics can be observed in RA patients, despite disease duration and treatment, suggesting that these subjects present with a premature ageing of the immune system.

CONCLUSIONS

Immunosenescence is a complex phenomenon that affects all the components of the immune system and depends on genetic and environmental factors. Accumulation of oligoclonal highly differentiated T cells and increasing serum levels of pro inflammatory cytokines might be main events responsible for the immune impairment in elderly subjects. Healthy centenarians provide living proof that effective immune responses can be maintained for decades, even after thymus involution. More immunogerontology studies are required to understand immune competence and immune dysfunction with ageing. A better understanding may hold promise for future clinical studies for the prevention of common age related diseases and promotion of healthy ageing.

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