Efficacy of Vaccines

Subjects: Immunology

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Vaccination is one of the most effective medical procedures with a significant impact on quality of life. The elderly and the immune-suppressed people are at risk to develop side effects or not respond. Elderly people present an altered immune response, known as immunosenescence. Immunosenescence involves mainly the adaptive immune system, with a reduced ability to respond to new antigens, accumulation of memory T cells and the constant presence of low-grade inflammation, known as inflammaging. Many alterations of adaptive immunity system have been observed and are probably central in the development of immunosenescence and possibly in the deficient response to vaccines in the elderly population. In this review, we discuss the role of immunosenescence as the result of alterations in the function of all the branches of the human immune response, which causes a defect in the normal homeostasis of the immune system, resulting probably in a major susceptibility of infections and a poorer response to vaccinations.

Keywords: Imflammaging, immunesenescence, ; innate and adaptive immunity

1. Intoduction

Vaccination is one of the most effective medical procedures and has had a significant impact on both quality of life and life expectation of people[1]. Yet, certain populations are at a risk of developing side effects from the administration of vaccines or not respond. Even though children are usually viewed as at risk of developing such side effects, it is actually the elderly and the immune-suppressed people who are at danger. The elderly population and persons who are immune-suppressed are also at a risk of developing potentially lethal infections, take longer to recover and often face long lasting sequelae.

Particular vaccination protocols have indeed been designed for these populations and live-vaccines are very rarely used, because of the risk of developing infections following the vaccination itself[2]. On the other hand, these populations have also a worse and less effective response to non-live-vaccinations: the use of immunity-boosters is mandatory to obtain any kind of response.

Immune-suppression in itself determines an altered response to vaccinations and elderly people often fall into this group, due mainly to malnutrition[3]. Yet, even those elderly persons who do not meet the requirements to be conventionally considered immune-suppressed, present an altered immune response, a condition known as immunosenescence [4] Immunosenescence involves mainly the adaptive immune system, with a reduced ability to respond to new antigens, accumulation of memory T cells and the constant presence of low-grade inflammation, so called inflammaging. Furthermore, innate response undergoes some changes, particularly in terms of signal-transduction, but they are not as relevant[5]. Even though some of these changes could be partly explained by cellular senescence, there still is a lack of understanding of immunosenescence.

2. Immunosenescence

Immunosenescence can be defined as the physiological age-associated changes of the immune system that determine an increased susceptibility to infectious pathogens and poor vaccine responses[6]. Immunosenescence, aggravated by co-morbidities, varies with age, becoming apparent after 60–65 years and more important after 85 years of age[7]. The underlying mechanisms though are not clear. Both qualitative and quantitative alterations concerning innate and adaptive immunity have been observed. Furthermore, in older adults a state of a systemic chronic low-grade inflammation, defined inflammaging by some authors, can be observed and seemingly contributes to the dysregulation of the immune systems[8]. Inflammaging can be influenced by many factors such as environmental and metabolic factors, diet, nutrition and gut microbiota[9].

3. Innate Immune Response

Regarding the alterations observed in innate immune response, with advanced age, neutrophils reduce their ability to migrate to infection sites. This has been mainly linked to the development of signal transduction defects. Specifically, a fundamental pathway is the phosphatidylinositol-3 kinase (PI3K) pathway which is normally activated by chemokines. The aberrant activation of this signaling cascade would cause altered neutrophil migration to the infection site[10]. Furthermore, the activity of phagocytosis also appeared to be reduced both because of the reduced expression of the Fcγ receptor CD16[11][12] and the lower production capacity of reactive oxygen species[13].

There are also changes in the activity of macrophages: in advanced age, a reduction in the production capacity of cytokines (mostly IL6 and TNF alpha) is observable, probably due to an altered expression of Toll like receptors (TLRs)[14]. The mechanisms underlying this altered production are complex and not entirely clear[9]. At the same time, with aging, macrophages develop a defect in macro-autophagy[15]. This defect causes an accumulation of macrophages and consequentially inflammatory cytokines, which contributes to the previously mentioned inflammaging [9]. Macrophages reduce the ability to respond to IFN-γ with a simultaneous reduction in the phosphorylation of the STAT-1alfa pathway[16]. This pathway is fundamental for macrophage activation and for IFN-dependent production of superoxide anion. Finally, monocytes and macrophages appear to express lower levels of HLA and MHC class II with age on their surface[17][18].

Age-associated alterations in Natural Killer (NK) cells consist of a progressive reduction of expression of the $CD56^{bright}$ receptor, which has a mainly immunoregulatory function, with a simultaneous increase in NK cells expressing the $CD56^{dim}$ receptor, that provides cytotoxic actions. This results in a reduced responsiveness to cytokine signaling[19]. The remaining $CD56^{bright}$ cells develop a greater capacity to the response to INF-γ but this phenomenon has not been noticed for the other cytokines[20][21].

During immunosenescence a defect in the connection between innate and adaptive immune responses occurs. Plasmacytoid dendritic cells and myeloid dendritic cells in older adults reduce their ability to present antigen and to stimulate $CD4^+$ and $CD8^+$ T-cell activation[22]. Moreover, follicular dendritic cells develop an age-related reduction in Fcγ RII receptor expression which causes a defect in the formation of germination centers. This causes an overall alteration in B-cell proliferation and antibody production[23].

4. Adaptive Immune Response

Concerning adaptive immunity system, many alterations have been observed and are probably central in the development of immunosenescence and possibly in the deficient response to vaccines in the elderly population.

B cells play a pivotal role in the humoral component of the adaptive immune system, secreting antibodies, with their activity of antigen-presenting and secreting cytokines. With aging, maturation of B cells in bone marrow is impaired due to a reduced production by stromal cells of IL-7, which is an important growth factor for maturing B cells; B cell progenitors also appear to be less responsive to IL-7[24]. Studies conducted in mice linked this impairment with a state of chronic inflammation in the bone marrow[25]. However, human studies about this defect are limited. Interestingly, a reduced serum level of B-cell activating factor (BAFF) has been found in studies conducted in humans. BAFF is an important factor connected to the survival of B-cells[26]. However, the total number of B cells remains stable with age[27], which suggests that there is a reduced cellular turnover with a simultaneous accumulation of aged B cells that present defects in normal functions, such as the ability to recognize and respond to new antigens. Specifically, aged B cells have a reduced diversity of B-cell receptor (BCR) [28]. An intrinsic defect in class-switch recombination also contributes to the reduced responsiveness to new antigens. This defect seems to be related to the altered transcription of the E47 factor, with a consequent dysregulation in the expression of the activation-induced cytidine deaminase (AID), essential for the recombination process[29]. Furthermore, aged B cells show a reduced ability in differentiating into plasma cells and therefore in the ability to produce antibodies[30], and at the same time a spontaneous and unmotivated production of TNF-α can also be observed and contributes to the previously mentioned inflammaging[31].

Regarding T cells, similarly to B cells, their total number does not vary with age[32]. However, there are intrinsic changes in T cells, which modify the cellular immune response. The physiological defect of production of cytokines and growth factors by thymic cells, caused by thymic involution, determines a reduction in circulating naive T cells [33]. It has been hypothesized that chronic infective states play a role in the altered immune response mediated by CD8 + T cells[9]. This has been supposed observing results from studies in older adults with CMV infection. Specifically, it was observed that chronic CMV infection causes oligoclonal expansion of CMV-specific memory CD8 + T cells; this causes a red[34]uction in the CD8 + T cell repertoire in the periphery capable of responding to other antigenic stimuli [In addition, aged T cells reduce their expression of the costimulatory regulator CD28, which is fundamental for a complete activation of T cells[35],

with a not entirely clear mechanism; TNF-α seems to play a role in this defect, as it is able to inhibit the transcription of CD28[36]. Furthermore, studies conducted in mice and humans show an altered production of cytokines in T cells. More specifically, effector memory cells have a reduced production of cytokines in response to the antigen[37][38], while terminally differentiated senescent CD4 + T cells show a higher secretory activity contributing to the already mentioned inflammaging[39]. In conclusion, immunosenescence can be defined as the result of alterations in the function of all the branches of the human immune response, which causes a defect in the normal homeostasis of the immune system, resulting probably in a major susceptibility of infections and a poorer response to vaccinations.

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