

wFading immunoprotection in humans : vaccination in elderly

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Summary

The function of the immune system declines with age, causing an increased occurrence and severity of infectious diseases and a decreased response to vaccines (Grubeck-Loebenstern et al., 2009). As the thymus gradually loses its ability to replenish the population of naïve T cells, the memory and effector T cells increase in number and dominate the repertoire. The changes in the naïve and memory T cell pool that occur with aging in humans are discussed here, along with a brief update of the knowledge of B cell populations in the elderly.

Naïve T cells in elderly persons

Upon presentation of a specific antigen, naïve T cells¹ will be stimulated and differentiated into an effector or a memory T cell. Studies have shown that the number of naïve T cell population is extremely small in elderly persons (over 65 years of age), as compared to younger persons (below 30 years old) (Fagnoni et al., 2000). This is true for the peripheral blood, but has also recently been confirmed for lymph node tissue (Lazuardi et al., 2005). This is mainly due to thymic involution.

The question remains whether the residual naïve T cells in elderly people are still functional. In theory, a very limited number of functional naïve T cells would be enough to guarantee a good immune response. A large amount of data is available on this subject, allowing to state that the T cell receptor (TCR) repertoire is strongly reduced among the residual naïve T cells of elderly persons (Pfister et al., 2006).

The ‘immunoscope’ technique reveals that some TCR (or, more precisely V β) ‘families’ in elderly people are dominated by large expanded clones, while other clones are completely depleted (see figure 1). The mechanism of this phenomenon remains to be explained. All these age-related changes taken together may pose a problem for the health of elderly persons exposed to neoantigens, such as travel vaccines (i.e. rabies or yellow fever) or pandemic flu.

Memory T cells: two types of elderly persons

A striking observation is that the memory/effector CD8⁺ cells ratio varies in elderly persons, and two types of subjects can be differentiated.

So-called **type 1** elderly people have a relatively large number of CD28⁺ CD25⁺ central memory T cells² and relatively few CD28⁻ (effector) T cells.

The **type 2** group of elderly people is characterised by a limited number of memory T cells and a larger number of effector cells.

The CD28⁺ CD25⁺ cells were found to be memory cells, not regulatory or recently activated cells (Herndler-Brandstetter et al., 2005). They produce a significant level of interleukin 2 (IL-2), which is unusual among CD8⁺ cells, and also, to a lesser extent, interleukin 4 (IL-4) and interferon gamma (IFN γ).

Contrary to naïve T cells in the elderly, these CD28⁺ memory cells are very diverse. It has been observed that type 1 elderly people with abundant memory cells produce a significant immune response following seasonal flu vaccination, above the protective titres (see figure 2). However, this response is lower than the one observed in the group of young people. On the

¹ The phenotype of a naïve T cell is defined as CD8⁺CD45RA⁺CD28⁺.

² The phenotype of an IL-4 producing central memory T cell is defined as CD8⁺CD25⁺CD28⁺CD45RA⁻, while the phenotype of an effector T cell is defined as CD8⁺CD25⁻CD28⁻CD45RA⁻.

other hand, a very large proportion of the subjects in the type 2 group did not raise any humoral response at all (so-called ‘non responders’). The proportion of ‘non-responders’ among the elderly varies among studies between 30 and 70% of the elderly persons.

Effector CD28⁻ T cells accumulate in elderly non-responders

When purified, the effector (CD8⁺CD28⁻) T cells from the blood of non-responders produce no IL-2 or IL-4, but secrete high quantities of IFN γ . They are highly pro-inflammatory, and probably contribute to both the ‘inflamm-aging’ phenomenon and to immune senescence, inhibiting antibody production. They are also very restricted, and dominated by a few large clones. A large proportion of these effector T cells is specific to the cytomegalovirus (CMV), and in particular to one of its proteins, pp65 (Almanzar et al., 2005; Weinberger et al., 2007). So far, they have not been found in lymph node tissue. The presence of these effector T cells at the site of CMV infection may suggest a deleterious regulatory role. For these reasons, the elimination of these cells might be a goal for medical development.

As a first step, however, it should be determined whether the dominating clones from this subpopulation are dispensable. This was investigated after the culture and purification of CMV-pp65 specific cells (Schwanninger et al., 2008; Weinberger et al., 2009). Results show that there is a preferential use of both V β 8 and V β 13 on the β chain of the TCR – irrespective of the donor’s age. Furthermore, the same V β 8 and V β 13 sequences were present in both CD28⁻ and CD28⁺ T cells with specificity for the pp65 peptide (NLVPMVATV). In other words, even if an aged subject would lose all its CD28⁻ clones at once, upon specific stimulation, he would still be able to generate the same clonotypes through the expansion of CD28⁺ cells. This suggests that these CD28⁻ CMV-specific cells are probably dispensable.

Age-related impairments of B cells

B cells are generated in the bone marrow, and after being transported by lymph and blood, they return to the bone marrow, either as plasma cells or as memory cells. The decrease of B lymphocyte production begins early in adult life, but is more marked in the elderly (Signer et al., 2007). This occurs through a blockage of early hematopoietic progenitors and B cell precursor maturation, leading to an age-dependant decrease of mature B2 cells (naïve cells) (Signer et al, 2007). The nature of these blocks is not yet understood.

Regarding memory and plasma cells, the literature regarding their fate and interactions within the bone marrow in ageing individuals is limited. Impairments of the B cell pool in the elderly are numerous, with a decreased generation of B cell precursors, loss of diversity of the B cell repertoire, reduced size and number of germinal centres, a lower number of mature (memory) B cells in the bone marrow and less serum antibodies specific for foreign antigens. These impairments contribute to the poor vaccine uptake observed in aged populations.

Problematic vaccine uptake in aged persons

The limited response to vaccination is not restricted to seasonal flu vaccination. A previous work related to tetanus toxoid vaccine (300 young and 300 old persons) revealed that the time of the last vaccination as well as age had highly significant effects on tetanus protection ($p < 0.001$, Hainz et al., 2005). A strong decline in post-vaccination antibody concentrations is observed in relation with age, with an onset at the age of 40. Persons over 60 years of age frequently have no protective antibody levels, and some even do not have any detectable titres (Hainz et al., 2002).

Following a booster vaccination using a multivalent vaccine containing tetanus, diphtheria, pertussis and polio in 252 healthy persons of over 65 years of age, a significant correlation was observed with pre-booster titres ($R^2 = 0.39$; $p < 0.0001$): booster vaccinations have a better effect if the pre-vaccination antibody concentrations are high (Kaml et al., 2006). While there

was generally a booster effect in response to the tetanus toxoid component of the vaccine, some subjects that had very low pre-booster titres of antibodies against diphtheria did not raise any response following booster injection. This phenomenon has also been observed with the tick-borne encephalopathy (TBE) vaccine used in Austria (Hainz et al., 2005).

Conclusion

The immune response to vaccination seems to decrease throughout adult life, and vaccination strategies in elderly need to be improved. One of the options might be to carry out regular booster vaccinations in order to elicit a good memory pool as early as possible. Shorter vaccination intervals might also be considered with advancing age. Post-vaccination antibody levels should also be checked on a more regular basis. But most important of all, there is an urgent need to develop new vaccines, that are adjusted to the requirements of the aging immune system.

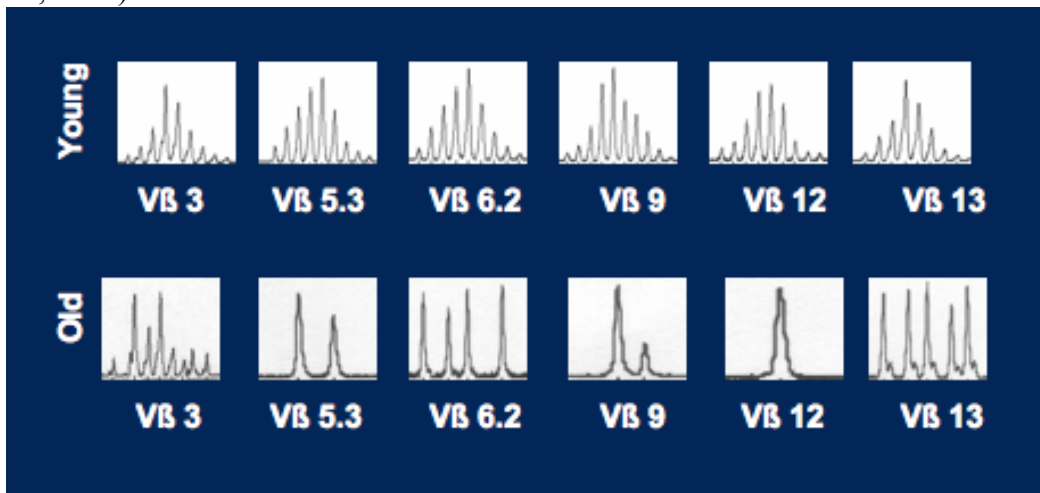
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Caption of figure 1:

Naïve T cells (CD8+45RA+CD28+) lose their diversity in elderly persons (from Pfister et al., 2006).



Caption of figure 2: Comparative humoral response (HI titres, geometric means, 4 weeks after vaccination) to seasonal flu vaccination among young, old 'type 1' and old 'type 2' persons (from Herndler-Brandstetter et al., 2005).

