Comments on the evaluation of lymphocyte levels in a random sample of 218 elderly individuals from São Paulo city

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In the article, "Evaluation of lymphocyte levels in a random sample of 218 elderly individuals from São Paulo city" by Teixeira et al.,[1] the authors measured percentages of CD4, CD8 and CD19 in blood from a population of 218 randomly selected elderly individuals of both genders aged between 60 and 101 years from Sao Paulo, Brazil. Participants were grouped according to their ages. Results showed significant differences in all age groups between males and females, especially in respect to the CD4/CD8 ratio which was significantly higher in females. No significant differences among age groups were found, except for the CD19 percentage in men which was lower in some elderly. The major point of the paper is that elderly men showed more changes in lymphocyte subsets than elderly women, in particular lower CD4 and higher CD8 percentages in all age groups. The authors suggest that the lower CD4 percentages in elderly men may account for reduced T cell help to B cells, whereas higher CD8 percentages may be a consequence of increased chronic inflammation observed during aging.

These suggestions may be very relevant to health conditions but would need to be supported with functional experimental results. It will be interesting in future studies, to better characterize the lower CD4/CD8 ratio in elderly men, to investigate if CD* T cell homeostatic proliferation occurs in this population of very elderly individuals and if it is associated with lymphocyte activation and subpopulation changes, e.g. the $CD8^{+}CD28^{-}$ population, which has been shown to increase with age but is associated with less function.[2,3]

The lower CD4/CD8 ratio was described years ago associated with persistent cytomegalovirus (CMV) infection and increases in the numbers of $CD3^{+}CD8^{+}CD28^{-}$ cells.[4,5] These measures were used to identify the immune risk profile (IRP) of very old individuals between 86 and 94 years of age[6] and predicted shorter survival in elderly patients. In the Swedish studies, OCTO[7] and NONA,[8] the prevalence of individuals with a lower CD4/CD8 ratio increased from 8% in under 60-year-old individuals to 16% in over 60-year olds. The mortality rate in individuals with a lower CD4/CD8 ratio also increased significantly in over 60-year old individuals as compared to younger controls. Interestingly, the proportion of individuals with a lower CD4/CD8 ratio was found to be significantly higher in men[9] as shown in the current paper from the Brazilian group. One importance of this paper is the relevance for the whole human population; data collected from populations in different geographical areas are comparable.

The Brazil study, like the Swedish NONA study, did not exclude individuals with reduced health. In the NONA study, this was justified by the need to achieve equal numbers of participating individuals in the 86, 90, and 94 age categories. In particular, only 9% of the individuals in the NONA study met the SENIEUR protocol criteria, a very strict protocol to exclude all diseases affecting the immune system.[10] Conversely, 35% of the individuals met the criteria used in the previous OCTO study[11] in which participants were included even though they had mild cognitive dysfunction as long as they did not have malnutrition and were not on anti-inflammatory, anti-viral or immunosuppressive drugs. Although the OCTO/NONA Swedish studies showed no significantly different results among non-selected, SENIEUR-selected or OCTO-selected individuals, it would be helpful to know the health conditions of those included in this work for future studies on this important population.

Populations selected based on clinical information and laboratory data would also help to resolve different immunogerontological studies in human beings which have led to conflicting results. Moreover, the use of admission selection criteria minimizes the risk of including individuals with diseases that could influence the results by introducing exogenous variables.

The Brazilian study also showed that B cells are significantly decreased in men and not in women. This result suggests that men could be more susceptible to infections or produce less protective antibodies after vaccination. Others have also shown decreases in

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B cell percentages and numbers with age, but to our knowledge no differences between genders.[11-15] Not only do the percentages of B cells change with age, but also the ratio among the different subsets in the CD19 pool changes[13,14,16] and this can help to explain why elderly individuals respond poorly to vaccination.

The current study is an important study on human aging, with a unique population to establish the baseline values of lymphocyte percentages as affected by age. For the future it will be important to extend these studies to establish further information about either exclusion criteria for enrollment, and/or more detailed health information on participants, increased cell surface markers previously shown to be affected by aging, i.e. CD28 in T cells and IgG/IgA/CD27 in B cells (Figure 1), and further functional data, e.g. vaccine responsiveness, such as to the influenza vaccine. It would also be important to follow up with participants to track whether the decreased CD4/CD8 in males correlates with infectious disease, frailty, cancer, etc.

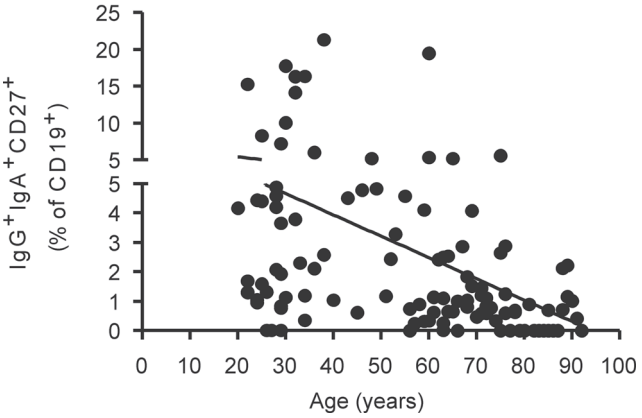

Figure 1 – The percentage of switch memory B cells $IgG^{+}IgA^{+}CD27^{+}$ decreases with age. One hundred µL of blood from each subject were stained for 20 min at 4°C with anti-CD19, anti-IgG, anti-IgA, and anti-CD72 antibodies. After staining, red blood cells were lysed. The blood from 112 healthy individuals was analyzed; Young: 66 (20-64 years of age) and elderly: 46 (≥ 65 years).

Developing and implementing vaccines to control infectious diseases in the elderly will require a more thorough understanding of the immunological mechanisms underlying the immune senescence across different populations, and how this is modulated by environmental parameters such as exposure to infectious agents. The discovery of biomarkers of aging will help predict which individuals will be able to respond to vaccination and design better adjuvants to improve vaccine responses and ensure effective disease prevention.

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