Changes occurring in the immune system of ageing humans, known as ‘immunosenescence’, have huge consequences on lifespan, with a major impact on public health, especially as the demography of population shifts toward increased age. So far, few studies evaluated the differences of the observed phenotypic variability during ageing. The simultaneous study of the changes in levels of circulating immune cells during life, the genetic variants regulating them and their quantitative modification due to environmental factors, will allow a better understanding of mechanisms underlying immunosenescence and related immune-mediated pathology in the elderly.

With these aims, we evaluated the quantitative modifications of the immune system in the SardiNIA general population ageing cohort on up to 3,757 individuals, ranging from 18 to 103 years. We studied 731 immune cell traits belonging to the lymphoid and myeloid compartments through seven multicolor antibody panels assessed by flow cytometry on fresh blood. These traits included 118 absolute and 192 relative cell counts, 32 morphological parameters and 389 expression level of surface markers (MFIs).

On this dataset, we estimated changes of the cross-sectional trajectories during ageing overall and in specific periods of time, which, if corresponding to age of maximum incidence of a disease, could inform about specific traits potentially implicated in disease predisposition. We also evaluated the interaction of ageing with sex and with genetic variants regulating immune traits.

At a Bonferroni-adjusted threshold of $P<2.3 \times 10^{-5}$, we observed that more than 80% of the actual counts vary significantly with ageing, compared to the 47% of the MFI, indicating a more stable behavior of the last in immunosenescence. Interestingly, we observed that both the lymphoid and myeloid compartment are affected by ageing, with lymphoid cells generally decreasing and myeloid increasing in elderly.

We observed significant sex differences, which were more marked in myeloid (70%) than in lymphoid (33%) cell counts. Interestingly, our data indicate that 17% of the immune cell counts show different trajectories during ageing in males and females, especially in B cells. In fact, males and females show different trajectory-change time points in 19% and 13% of the actual counts, respectively, with an overlap of only 2% of traits. In lymphoid cells, for example, the mean age of change is 56y in males and 52y in females (and 49y vs 54y in the myeloid compartment): this sex-specific information could be particularly relevant, especially when the immune traits are causally involved in predisposition for diseases such as infectious diseases, more severe in males compared to females especially in the elderly.

Our genetically-characterized sample set allow us to dissect the interaction between the phenotypic and genetic variability acting during ageing, which are both of notable influence for the shape and capabilities of the immune system, likely affecting its decline with senescence. Indeed, we identified a subset of variants regulating immune cell levels significantly interacting with ageing, thus, highlighting a different behavior of some immune features in a genotype-dependent manner.

This project is ongoing with the estimation of the impact of several environmental factors (cytomegalovirus titers and vaccination titers against poliomyelitis, diphtheria and hepatitis B), and lifestyles (smoke, alcohol consumption or physical activity) on ageing, together with their genetic regulation.
References:

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