Published in final edited form as:

Nat Med. 2019 March ; 25(3): 362–364. doi:10.1038/s41591-019-0387-5.

Immunoprofiling comes of age

Soumya Raychaudhuri^{1,2,3,4,5,6,*} and **Rajat M. Gupta**^{4,7}

¹Center for Data Sciences, Brigham and Women's Hospital, Boston, MA, USA.

²Division of Rheumatology and Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA.

³Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.

⁴Broad Institute of Massachusetts Institute of Technology and Harvard University, Cambridge, MA, USA.

⁵Division of Rheumatology, Immunology, Allergy, Brigham and Women's Hospital and Harvard Medical School, Brookline, MA, USA.

⁶Arthritis Research UK Centre for Genetics and Genomics, Centre for Musculoskeletal Research, The University of Manchester, Oxford Road, Manchester, UK.

⁷Divisions of Cardiovascular Medicine and Genetics, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA.

Abstract

Application of immunoprofiling of human peripheral blood samples from an aging cohort identifies changes in the immune system that inform our understanding of age-associated complex diseases.

As individuals age, almost every component of the immune system is affected, and these changes are collectively called 'immunosenescence'¹. For example, with aging, the number of naive CD8⁺ T cells decreases and there is a moderate reduction in the TCR repertoire. In parallel, function of dendritic cells also becomes impaired. The consequence is that as they age, individuals become susceptible to a whole range of infectious pathogens. Aging is also a unifying risk factor for many other complex diseases in which the immune system may play important roles. However, disentangling the role that it plays in disease pathogenesis is often difficult because of its widespread effects. In this issue, Alpert, Davis, Shen-Orr and colleagues² use immunoprofiling strategies in an aging cohort of humans to get a very broad understanding of the changes in the aging immune system. Not only do they quantify some of the major changes in immune population frequencies in human peripheral blood, but they also provide important universal tools to assign an immunological age to humans based on peripheral blood expression profiling. The authors use this approach to explore the link between inflammation and cardiovascular disease.

* soumya@broadinstitute.org.

Competing interests

The authors declare no competing interests

The existence of a link between inflammation and complex disease has long been suggested, as the role of inflammation in atherosclerosis and subsequent cardiovascular disease is well-described³. Both adaptive and innate immune mechanisms have been implicated in mouse models of atherosclerosis. However, the question remains whether inflammation and atherosclerosis are causally linked in humans. Clinical trials of anti-inflammatory medications have delivered mixed results. Canakinumab, a monoclonal antibody that inhibits interleukin-1 β , resulted in a lower rate of cardiovascular events in the recent Canakinumab Antiinflammatory Thrombosis Outcome Study (CANTOS) trial⁴. Conversely, treatment with low-dose methotrexate did not reduce cardiovascular events⁵. These observations do not exclude the possibility that aging and its associated immunological changes are the drivers of cardiovascular disease risk.

It may be possible to clarify the immunologic component that links aging and complex diseases, such as atherosclerosis, using human immunoprofiling. Application of immunoprofiling in the context of clinical studies can allow investigators to understand what immune changes happen in healthy individuals, the changes that occur with environmental exposures, and the connection between the human immune system and disease. The last decade has seen an explosion in high-dimensional technologies to quantify the immune system in health and disease. The emergence of mass cytometry has enabled quantification of >30 markers at the single-cell level⁶. Most recently, droplet-based RNA-seq technologies can be combined with sequencing of oligonucleotide-labeled antibodies to generate parallel surface marker and transcriptional measurements simultaneously^{7,8}. These approaches can be used to quantify immune parameters broadly in clinical studies⁹.

Alpert et. al. sought to define the changes in the immune system that tracked with aging. They collected peripheral blood from 135 individuals between 2007–2015 as they aged, as part of the Stanford-Ellison longitudinal aging study. They carried out a deep examination of cellular frequencies and how they are modified by aging, seeking to model changes over time. At early time points, the authors obtained a ‘snapshot’ of 73 immune cell subsets for each of 19 individuals, and they applied cell subset analysis and gene expression profiling to the larger set of 135 individuals. Strikingly, they observed that 33 cellular subsets were influenced by aging, including CD8⁺ T cell, monocytes, natural killer (NK) cells, B cells, and CD4⁺T cell subsets. For some of these populations, they were able to model the changes as either asymptotic (where frequencies hovered towards a stable value in old age) or linear (where frequencies steadily increased or decreased), and some populations did not have clear, regular changes in baseline over time. To simplify the trends that they observed, the authors applied a diffusion pseudotime algorithm to define an aging trajectory (Fig. 1). In doing this, the authors assigned what they called an IMM-AGE score and argue that it captures essential aspects of immune aging.

The authors also found that individual cytokine response was more statistically significantly associated with IMM-AGE score than with actual age. In order to generalize their score, they took advantage of their genome-wide gene expression dataset to define a set of 121 genes that correlated with the IMM-AGE score. To understand whether these changes influence human disease, they examined cardiac risk. A subset of 57 of these 121 genes was then used to test the clinical relevance of the IMM-AGE score in the Framingham Heart

Study Offspring cohort, a population-based cohort recruited in eastern Massachusetts, to track cardiovascular outcomes. The authors found that this score, even after adjusting for age, gender and traditional cardiac risk factors (total and HDL cholesterol, diabetes, smoking and blood pressure), resulted in an association with cardiovascular disease diagnosis.

These findings suggest that the IMM-AGE score may serve as an independent risk factor for cardiovascular disease risk and help identify patients who can benefit from anti-inflammatory treatment. Many important questions remain, however. First, it will be important to reproduce the observed signal in independent cohorts. Second, it will be important to understand how this measurement of immunological age differs from other serum markers, such as C-reactive protein (CRP), that are known to be correlated with cardiovascular risk. Third, it will be important to conduct a more direct analysis of cell frequencies in cardiovascular disease cohorts to directly assess the association of specific cellular components cardiovascular risk. Finally, it must be determined whether observed associations represent a proxy for aging or whether there are specific causal immune mechanisms that underlie cardiovascular risk that can be seen by immunoprofiling.

This study adds to accumulating evidence that drug trials and other clinical studies of aging, cardiovascular disease, autoimmune, and infectious diseases would benefit from have an immunoprofiling component. Determining the expression of preselected genes from peripheral blood and flow cytometry on a limited number of markers is the most basic level of immunoprofiling that can be obtained. But far more comprehensive technologies are now available and can be applied when paired with thoughtful sample handling. As this study demonstrates, application of immunoprofiling in these contexts may lead to powerful disease insights. Ultimately, some of these insights may lead to targeted immune modulatory therapeutics in a range of complex diseases.

References

1. Nikolich-Zugich J. Nat. Immunol. 19, 10–19 (2018). [PubMed: 29242543]
2. Alpert A et al. Nat. Med. 10.1038/s41591-019-0381-y (2019).
3. Libby P Nature 420, 868–874 (2002). [PubMed: 12490960]
4. Ridker PM et al. N. Engl. J. Med. 377, 1119–1131 (2017). [PubMed: 28845751]
5. Ridker PM et al. N. Engl. J. Med. 10.1056/NEJMoal809798 (2018).
6. Bendall SC et al. Science 332, 687–696 (2011). [PubMed: 21551058]
7. Stoeckius M et al. Nat. Methods 14, 865–868 (2017). [PubMed: 28759029]
8. Peterson VM et al. Nat. Biotech. 35, 936–939 (2017).
9. Fonseka CY et al. Sci. Transl. Med. 10, eaaq0305 (2018). [PubMed: 30333237]

Fig. 1 | Identifying a measure of immune aging.

Alpert et al.² analyzed the immune cell composition (shown by the clusters in the plots on the left and right) and interpreted the data using multidimensional trajectory analysis between 2007 and 2013, as indicated by the arrows. Their resultant score named IMM-AGE, representing the distance along the trajectory, is derived from many different immune measurements aggregated into a single number.