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Human lymphocyte repertoires in ageing

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Deterioration of adaptive immunity with ageing may reflect changes in the repertoire of T cells and B cells available to respond to antigenic challenges, due to altered proportions and absolute numbers of lymphocyte subpopulations as well as changes in the repertoire of antigen receptor genes expressed by these cells. High-throughput DNA sequencing (HTS) now facilitates examination of immunoglobulin and T cell receptor gene rearrangements, and initial studies using these methods to study immune system ageing in humans have demonstrated age-related alterations in the receptor populations within lymphocyte subsets, as well as in repertoires responding to vaccination. Accurate measurement of repertoire diversity remains an experimental challenge. Studies of larger numbers of human subjects, analysis of defined lymphocyte subpopulations including antigen-specific populations, and controlling for factors such as chronic viral infections, will be important for gaining additional understanding of the impact of ageing on human lymphocyte populations.

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Introduction

A highly diverse repertoire of lymphocytes facilitates adaptive immunity by providing a sufficiently varied selection of specificities to meet immunological challenges. Diversity is achieved by way of genomic rearrangements, combining variable (V) diversity (D) and joining (J) gene segments to create the antigen binding regions of immunoglobulin (Ig) heavy chains (VDJ), light chains (VJ) and T cell receptor (TCR) alpha or gamma chains (VJ) and beta or delta chains (VDJ). The junctional regions of these gene segment rearrangements are particularly diverse due to variable exonuclease shortening of segment ends, and random addition of additional junctional nucleotides by terminal deoxynucleotidyl transferase. These regions encode areas of the Ig or TCR that are particularly important for antigen binding and are known as complementarity determining region 3 (CDR3). Further diversity is attained by assortment of the products of rearranged genes into the final molecule; Ig/B cell receptor (BCR) consisting of 2 identical heavy chains and 2 identical light chains and the TCR consisting of either a gamma and delta chain or, more commonly, an alpha and beta chain. The gene rearrangements encoding Ig and TCR molecules represent highly informative markers of individual clonal lineages of B cells and T cells.

The lymphocyte repertoire as a whole can be characterised by sequence features (such as V, D and J gene segment usage, and CDR3 physicochemical properties) and is shaped by a number of factors. Initial gene rearrangement may not be completely random and may be affected by preferences of the recombination activation enzymes (RAG1 and RAG2) for differing recombination signal sequences (RSS) that flank the genes in their germline configuration, or by the proximity of different gene segments to each other in the germline. In addition to this there are powerful selective forces that alter repertoire composition. In early development in the bone marrow (B cells) or the thymus (T cells) there is positive selection for receptors that are functional and negative selection to remove receptors that have high affinity for self-antigen. Thus the mature naïve lymphocyte populations consist of cells with functional receptors that do not have high affinity for autoantigen. Antigen encounter and a subsequent immune response will skew the repertoire towards having cells with affinity for the challenging antigens. Hence the memory lymphocyte repertoires will reflect the antigen response history of the individual.

In old age there appears to be a breakdown of the immune system on two fronts. In the first instance there is a decreased ability to respond to challenge, as evidenced by poor responses to vaccination and increased susceptibility to infection. Secondly, there is increased evidence of inappropriate immune activation. The level of autoantibodies in the serum is increased and there is a general increase in inflammatory mediators. In terms of repertoire one could hypothesise that these two failures reflect changes in positive selection and negative selection respectively.

Changes in lymphocyte subpopulations with ageing

Changes in the proportions and absolute numbers of different lymphocyte subsets could account for some of the age-related impairments of the immune system. In particular, reduction in naïve lymphocyte output accompanied by increases in clonally expanded memory cells could skew the repertoire in favour of cells that have been positively selected by antigen, decreasing the ability to respond to new antigenic challenges. During ageing, thymic involution occurs, resulting in altered tissue architecture, decreased tissue mass and a reduction in CD3+ T cell production [1–5]. Similarly, it has been shown in mice that there is a reduced output of B cells from the bone marrow in old mice [6]. However, the situation may not be so simple. The thymus involutes at a very early age and yet the size and quality of the naïve T cell repertoire can be maintained until well past the 5th decade in life [7]. Some maintenance is provided by homeostatic turnover, but a recent TREC analysis of a large number of blood samples to measure recent thymic emigrants did not show any significant decrease until the 9th decade of life [2]. Data on B cell production from human bone marrow are limited, but output is sufficient to reconstitute the repertoire within a year of B cell depletion by Rituximab in patients as old as 80 [8]. That said, it is clear that the older repertoire contains more memory cells. Despite there being different ways of measuring T cell memory [9], an age related increase in effector memory T cells is well established [10–12]. There is a significant decrease in CD3+CD45RA+CCR7+ naive cells and an increase in CD3+CD45RA− and CCR7− effector memory cells [12], changes that are more apparent in CD8+ than CD4+ T cells. CD4+ T cells seem to maintain their number and diversity to a much later age before changing suddenly in the 7th decade [7]. CD8+ T cell populations are dysregulated earlier, with an increase in numbers (likely exacerbated by chronic infection with viruses such as cytomegalovirus (CMV) and Epstein–Barr virus (EBV)) resulting in a decreased CD4+:CD8+ ratio [4,10,13–15]. Within the CD4 and CD8 populations there are further subpopulations that are changed with age, for example with respect to relative proportions of TCRαβ and TCRγδ [12,14,15], and an age related increase in CD4+FoxP3+ Tregs [15–18]. T cell populations in ageing rhesus macaques show similar features, with decreased naïve CD4 and CD8 T cell numbers and persistent oligoclonal T cell expansions correlated with poor vaccination responses measured by CD8 T cell and antibody response [15].

Within aged B cell populations, it is also thought that naive B cells decrease in proportion to memory cells. However, there are conflicting reports in the literature, potentially related to the markers used to define B cell subsets [15,19–22]. Two distinct combinations of markers, CD27/IgD and CD24/CD38, have been used to define B cell populations, but the populations defined by these markers do not easily map onto each other (Figure 1). To complicate this further, different isotypes, for example IgM, IgG, and IgA, exist within many of the memory populations and older papers defining memory by class switching therefore will have missed a large proportion of IgM+ memory cells. Furthermore, CD27 was until recently considered to be a memory B cell marker but reliance on this alone would fail to take account of CD27− cells with memory characteristics [23]. Although they only comprise a small subset of total B cells, the proportion of CD27−IgD− memory cells increases with age [24]. CD27+IgD+ (IgM memory) cells have been reported to decrease, or remain unchanged, with age. Some groups have also reported a decrease in CD27+IgD− (Switched Memory) cells [20,25–27]. A decrease in the absolute number and proportion of plasma cells (IgG, IgM and IgA) [28] as well as a decrease in the generation of plasmablasts in response to influenza vaccine [29] has also been reported with age. Standardized methods of determining lymphocyte memory populations would facilitate comparisons of the reports in the literature, but the general consensus does seem to favour the increase of memory B cell subsets with age.

Studies of lymphocyte repertoires using high-throughput DNA sequencing (HTS) of antigen receptor genes

Of particular interest in studies of human ageing is the diversity of the B cell and T cell populations, most often considered to be the number of distinct species present in the repertoire, a quantity known as 'richness' in the ecology literature [30]. Decreases in repertoire diversity would be expected to leave 'holes in the repertoire' that could prevent recognition of novel antigens and would therefore contribute to decreased vaccine responses and increased vulnerability to pathogens. Before the advent of high throughput DNA sequencing (HTS) methods, the quantitative analysis of B and T cell repertoires was severely limited by experimental constraints. PCR-based spectratyping analyses of the lengths of CDR3 regions have been employed to assess repertoire diversity, and have shown age-related changes in the relative proportions of large clonal populations and rarer populations for both T cells and B cells [7,31•,32], but provide no information on gene usage. Heroic efforts at Sanger sequencing could produce on the order of 200 sequences, but with an average human blood volume containing approximately 1–2 billion B cells, and several-fold more T cells, only overt differences between samples can be detected using such small numbers. The true number of distinct rarer sequences in a population cannot be determined in this way, and only very conservative estimates of the lower limit of diversity are feasible, not the upper limit or the most likely value. Even in high-throughput DNA sequencing experiments, where thousands to millions of sequences are determined and the B cells

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