Review

Ageing, autoimmunity and arthritis
An introduction

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As populations grow, greater effort is made to understand the political and economic impact of ageing. Understanding the pathophysiology of this degenerative process has engendered no less effort or interest. At the subcellular and molecular level, ageing heralds changes in the balance between DNA damage and repair, changes in the frequency of somatic mutations, as well as deterioration in the functional integrity of mitochondria and its own DNA [1]. At a cellular level, these changes can manifest as clonal expansions driven by a strong survival advantage, and in some cases as malignant transformation. Recent events in the cloning arena have forced scientists and physicians to reflect upon the potential impact of somatic cell nuclear transfer. What is the impact of genetic chimaerism? Does it accelerate ageing? What are the mechanisms, and at what level do they work? Readers of *Arthritis Research & Therapy* must be particularly curious to know why Dolly the sheep, the first mammal to be cloned from an established adult somatic cell, subsequently developed arthritis [2]. We have yet to find the answer to these important questions.

It has long been recognised that there exists a relationship between ageing and susceptibility to infection. It follows from this that defects in the ageing immune system must somehow be to blame. Quite how the immune system ages, and how immune senescence predisposes individuals to disease is still a mystery. Nevertheless, advances in basic cell biology and a better appreciation of how cells integrate and respond to signals acquired from their environment has made it possible to piece together aberrations of the ageing immune system, largely at the cellular level. New laboratory techniques are at our disposal, and these have most certainly facilitated progress. For example, we can now study thymic function, or perhaps more accurately newly generated T cells [3], and we can also utilise biomarkers to define specific cell subsets and correlate genotype and phenotype with function. Particularly important for studying ageing is an appreciation of replicative history and proliferative senescence made possible by the capacity to directly measure it, through analysis of telomere length [4]. And of course a list of experimental approaches wouldn't be complete without mentioning gene expression profiling.

Data suggest that while antigen presenting function is relatively well preserved during the ageing process [5], lymphocyte function is perturbed, characterised by depression of both cellular and humoral immunity. Accordingly, to begin to address how ageing influences immunity, a focus on lymphocyte biology seems a good starting point. For example, over the decades numerous studies have reported altered production of T cell progenitors, reductions in the generation of naïve T cells, ageing of resting and clonally expanding cells, and in particular disrupted intracellular signalling leading to perturbations in cytoskeleton reorganisation and cell migration [reviewed in 6]. In this issue, Goronzy and Weyand begin by exploring how the dynamics of T cell repertoire diversity promote the expansion of effector cells [7]. Through an analysis of the expression of T cell receptor excision circles as surrogate markers of recent thymic emigrants, together with assays of telomerase activity, they have established models that provide compelling evidence for premature immunosenescence in patients with rheumatoid arthritis. Particularly striking are the contractions of the T cell repertoire and, through mechanisms likely to involve homeostatic proliferation, clonal expansions of potent effector T cells carrying an unusual phenotype. The T cell theme continues in the next issue, where Fülöp and Pawelec summarise a series of remarkable defects in T cell antigen receptor signalling, comparing and contrasting these anomalies with those signalling defects reported in chronic inflammatory diseases such as rheumatoid arthritis and systemic lupus erythematosus [8]. They raise the intriguing possibility that while T cell hyporesponsiveness to T cell antigen receptor engagement is likely to impair host defense and tumour immunity, such defects may also provoke autoimmunity. In

the third review of the series, Johnson and Cambier discuss age-related changes during B cell development, emphasising the skewing in immunoglobulin variable region usage as one possible mechanism for the susceptibility of the ageing population to infection [9]. During ageing there is also an associated decline in B cell development in the bone marrow, the most significant being at the transition of pro-B cells to pre-B cells, while in the periphery, homeostatic proliferation drives the expansion and accumulation of autoantibody secreting cells in the follicular compartment. One cannot help but remark upon the similarities between T cell and B cell developmental defects, in this regard. Of particular interest, Johnson and Cambier discuss prospects for reconstituting ageing organisms with stem cells from younger individuals.

Despite the use of sophisticated laboratory tools to uncover the perturbations of immune senescence, a major challenge remaining will be to determine quite how such aberrations translate to autoimmune disease in general, but arthritis in particular. While giving due consideration to each hypothesis, we must also consider the potential evolutionary advantages of immunosenescence. Do these perturbations reflect an adaptive response, generated over decades, to suppress inappropriate lymphocyte reactions to immunogenic, post-translationally modified host tissue proteins subjected to decades of environmental stress? If this is the case, one can envisage why the process of attenuation of T and B cell reactivity might develop in accelerated form in younger patients with inflammatory joint disease. As Goronzy and Weyand state from the outset, exploring the immunobiology of ageing could help us to understand the pathogenesis of chronic inflammatory syndromes, and more importantly, to develop therapies that target these crippling degenerative processes.

Competing interests

None declared.

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