A 50th anniversary is an auspicious date. In 50 volumes, *Rheumatology* has published many important papers in all the major areas of rheumatology. In this editorial, I shall review what I consider to be the important landmarks in the development of our understanding of the immunology, and hence the immunotherapy of RA over this time. My account should be read with caution. Apart from personal prejudice, which I shall try to avoid, there is the inevitable prejudice that we interpret the past with the preoccupations of the present.

My interest in the immunology of RA arose as a consequence of working with Professor Dudley Dumonde at the Kennedy Institute of Rheumatology on lymphokines, non-antibody mediators of T-cell activity [1]. This led me to dedicate my research work to investigating the function of T cells in the pathogenesis of RA in the firm belief that manipulating T-cell responses would lead to more effective and specific therapies.

One of the earliest and most significant technical advances in our understanding of the pathogenesis of RA was the introduction of mAbs by Kohler and Milstein [2], for which they were awarded the Nobel Prize in 1984. The mAbs were the perfect tools for investigating the cellular structure and mediator environment of the rheumatoid SM. The immunohistology of the RA SM was characterized by a predominant CD4+ memory-activated T-cell infiltrate, macrophages, which secrete many inflammatory cytokines and small molecular weight inflammatory mediators, and antigen-presenting dendritic cells that are highly positive for Class II HLA antigens [3, 4].

In parallel, genetic studies were showing that the disease was strongly linked to a particular HLA antigen namely HLA-DR4 [5, 6]. The nomenclature since then has changed to HLA-DRB1*04 with further refinements as molecular techniques were introduced that subdivided the complex *04 antigen into RA-susceptible and even RA-protective subtypes. Further developments in molecular genetic techniques now allow for rapid throughput analyses of genome-wide scans in order to uncover genes linked to the development of RA [7]. This will undoubtedly lead to diagnostic subdivisions of RA, thus proving the splitters to have been right all along. Pharmacogenetics may allow us to predict which patients have a greater likelihood to respond to a particular therapy and whether they will or will not tolerate the therapy.

Since HLA molecules are used to present antigenic peptides to CD4+ T cells thereby activating them so that they produce a large number of mediators including lymphokines and cytokines and since the RA SM is full of CD4+ memory T cells, we postulated the T-cell hypothesis which states that the CD4+ T cells within the SM initiate the inflammatory cascades within the rheumatoid joint [8]. At the time, it was believed that T-cell-dependent immune responses could be subdivided into TH1, the classical cell-mediated immune response and the TH2 response. The hallmark cytokine of the former was IFNγ. There was much argument as to whether IFNγ could or could not be found within the rheumatoid synovium. This problem has been resolved with the description of TH17 T cells that secrete a new pro-inflammatory cytokine, IL-17. Both TH17 and IL-17 are found in the RA SM [9] and are now therapeutic targets for the treatment of RA.

This episode illustrates a not uncommon problem in the history of science: heated arguments about a particular process that are resolved by the discovery of new facts.

The immunohistology of the RA SM also revealed infiltration with B cells, some of them aggregating in highly organized lymph node-like structures. This was a very major observation as ectopic lymph node formation is a very rare phenomenon in inflammation. The synovium is also characterized by the presence of plasma cells producing RFs. This reinforced Jo Edwards’ belief that B cells and RFs were the essential drivers of rheumatoid synovitis with T cells playing a subsidiary or ancillary role. This is not strictly true as B cells are very potent antigen-presenting cells as they are strongly Class II MHC positive, can take up specific antigen via the immunoglobulin on their cell surface, process the antigen and present the resulting antigenic peptides to CD4+ T cells that are thereby activated. Activated T cells can then activate B cells. This strong interaction between B and T cells needs to be borne in mind when considering the prolonged therapeutic effects of B-cell ablation in RA.

So what is the antigen driving RA? To date no viable candidate has survived close scrutiny. However, we may have stumbled on one possible aetiological agent. Post-translationally modified proteins may act as autoantigens because the modification may not have been presented to the developing immune system. Consequently, tolerance to the modified protein may not develop. Individuals who develop RA produce ACPAs, such as fibrinogen and α-enolase, years before they develop overt disease. The production of these antibodies is strongly
linked to HLA-DR4. There is evidence of T-cell autoreactivity to citrullinated proteins. What is particularly interesting is that Porphyromonas gingivalis, a bacterium responsible for periodontal disease, expresses an enzyme that is able to citrullinate proteins. An extensive search by Patrick Venables and his colleagues has failed to uncover any other bacterium that has such an enzymatic potential. What is fascinating is that there is increasing and compelling evidence linking RA to periodontitis: there is a high prevalence of periodontitis in patients with RA and treatment of periodontitis may improve joint inflammation in RA. Perhaps the development of an anti-periodontitis vaccine incorporating P. gingivalis will also prevent the RA.

Hence, after considerable research four crucial cellular players were defined as being involved in one way or another in the pathogenesis of rheumatoid synovitis, namely, T cells, B cells, antigen-presenting cells and macrophages. Other cells are undoubtedly important, such as synovial fibroblasts and endothelial cells, but these are worthy of a historical overview in their own right. mAbs are so exquisitely specific, it is not surprising that from very early on in investigators and start-up biotechnology companies decided to develop these reagents for therapy. Indeed, George Janossy and I discussed the use of anti-CD3 for the treatment of RA with Ortho in 1980. We were amongst the first to carry out a randomized double-blind control study of an mAb directed against CD7, a molecule on T cells [10]. Unfortunately, it proved to have no effect. Other targeted therapies included an anti-CD5 mAb conjugated to ricin and anti-CD4 antibodies. For a variety of reasons these biologics did not enter the clinic. Subsequently, two TNF-α-neutralizing biologics were trialled. Infliximab and etanercept have proved highly effective in a significant proportion of patients with RA. They, and newer formulations of anti-TNF biologics such as adalimumab and certolizumab, have now entered standard routine clinical practice. The rest is history. Other biologic therapies have been introduced including tocilizumab, an inhibitor of the soluble IL-6 receptor, and abatacept, an inhibitor of co-stimulation between antigen-presenting cells and T cells. Abatacept is the first clinically applicable therapy based on the T-cell hypothesis.

Meanwhile, Jo Edwards was working away at University College Hospital. He published his short series of patients with RA treated with rituximab, a B-cell ablating antibody, with startling results in some of them; in particular the fact that patients can go into very prolonged drug-free remission. This observation is highly significant because it shifts the goal for the treatment of RA to prolonged drug-free remission. The longest remission that is possible is life-long. Could this be considered a cure? It is my belief that consistent attainment of this goal will only be possible by manipulating T cells so as to induce a Treg environment. So why does B-cell ablation lead to drug-free remission? We do not know but two possibilities exist: rituximab may induce a regulatory cell or T cells involved in the pathogenesis of RA are very dependent on antigen presentation by B cells.

When infliximab was shown to be an effective anti-inflammatory agent for the treatment of RA, it seemed to provide incontrovertible evidence of a cytokine hierarchy in RA with TNF-α at its peak. However, the success of IL-6 inhibition casts doubt on this hypothesis. Furthermore, other biologic therapies are successful. However, all of them are successful only in the short term apart from rituximab, which may give prolonged drug-free remission. A more likely hypothesis is that there is an inflammatory network within the RA SM such that inhibiting one part leads to suppression of the whole network. The true regulator for RA awaits discovery: is it a B cell, a Treg or the T cell that responds to P. gingivalis?

Thus, over the past 50 years there has been a seemingly endless increase in our understanding of the cells and molecules involved in the pathogenesis of RA. The goal of research is to gain greater understanding that will lead to more effective and safer medication. There is still a long way to go before we can be truly satisfied with the way that we treat patients with RA.

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References