Thyroid disease comprises a wide spectrum ranging from focal thyroiditis associated with a positive thyroid antibodies, but only subclinical effects on thyroid function, to Graves’ disease and autoimmune hypothyroidism. These two are frequently seen as being B and T cell mediated, respectively, although undoubtedly the situation is more complex in reality. In addition there are well recognised variants, such as silent thyroiditis seen most frequently in the post partum period, and the enigma of thyroid association ophthalmopathy is still unresolved. Genetic susceptibility is dealt with elsewhere in this meeting, although it is worth mentioning here that such genetic factors operate in a complex way, interacting not only with each other but with a host of environmental factors, including stress, smoking, iodide intake, and other less well defined factors. Any hypothesis to explain the pathogenesis of thyroid disease must take into account these various susceptibility factors to provide an adequate explanation for the pathology [1].

Characterisation of the major thyroid antigens has been a big step forward in understanding the pathogenesis of thyroid autoimmunity. The availability of recombinant antigens together with improvements in immunological assays, has allowed partial characterisation of the major epitopes for B and T cells, on each of the major thyroid antigens: thyroglobulin, thyroid peroxidase and TSH receptor. The area, which is least well understood, is the epitope recognition of autoantibodies against the TSH receptor. The area, which is least well understood, is the epitope recognition of autoantibodies against the TSH receptor, and characterisation of the pathogenic effects of these antibodies will depend on the availability of human monoclonal antibodies, which in turn might allow crystallisation studies of the antibody interacting with the receptor. In turn such information might provide better assays for the analysis of antibodies whose activity can only be determined in bioassays currently.

A variety of animal models have been established which have yielded valuable insights into the pathogenesis of thyroid autoimmunity. As well as contributing to our understanding of the genetics and environmental factors, these experiments have clearly shown that in good responder strain animals, autoreactive T cells exist, and these must therefore be kept under control either through the actions of regulatory cells, or through the mechanism of clonal ignorance. T cells but not antibodies from animals with immunisation induced thyroiditis can transfer disease to recipients, and the critical effector cells appear to be CD8+ although dependent on CD4+ T cells. There is increased interest in the concept of regulatory T cells, with the characterisation of a subset of CD4+ T cells which express high levels of the IL2 receptor (CD25). The antigen specificity of these regulatory T cells is unclear, but it is unlikely to be identical to the epitopes recognised by the effector T cell. Similarly we do not yet know the exact mechanism whereby suppression is mediated, although this appears to involve self contact as well as the risk of inhibitory cytokines, including IL-10, IL-13 and transforming growth factor beta. Whilst other regulatory T cell subsets may exist, it is this population which is the focus of current attention, and these studies will be undoubtedly extended to man in the near future.

Another mechanism whereby T cell mediator regulation might occur is reciprocal inhibition of T helper cell subsets. When a TH2 response is mounted, TH1 responses are suppressed, and vice versa, and animal models have clearly demonstrated that there can be deviation away from TH1 mediated injury by enhancing TH2 responses. It is possible that such mechanisms might be behind the emergence of autoimmune thyroid disease during treatment with cytokines, or with monoclonal antibodies directed against T cell subsets, these agents being given for other diseases such as chronic active hepatitis and multiple sclerosis. Animal models have also been important in demonstrating the potential role for cytotoxic T cells in causing injury.

In man, autoimmune hypothyroidism is clearly T cell dependent, but the exact measurement of thyroid cell damage remains to be fully understood. Perforin containing T cells exist in the thyroid infiltrate in human autoimmune thyroid disease, but recent attention has focused on apoptosis as the major mechanisms for thyroid cell loss. Thyroid cells in autoimmune hypothyroidism overexpress Fas, possibly in response to locally...
released cytokines. Such Fas expression could increase the chance of thyroid cell destruction by CD8+ T cells that can bind Fas, although controversially thyroid cells themselves may express Fas ligand which could lead to suicide or fratricide by the thyroid cells themselves [2]. A number of anti-apoptotic intracellular proteins exist and these seem to be upregulated particularly in Graves’ disease, which may limit thyroid cell death in this situation.

Another protective mechanism within the thyroid is the upregulation of a variety of membrane attack complex inhibitory proteins, which reduce the proinflammatory effects of membrane attack complex formation following complement activation. The most important of these is CD59, which is upregulated also in response to cytokines released by the inflammatory T cell infiltrate. As a result thyroid cells are not necessarily killed unless complement activation is extreme. Instead, complement activation seems to cause a number of sublethal effects, including metabolic down regulation and release of cytokines.

The release of cytokines by thyroid cells is one example of many in which the thyroid cells express immunologically active molecules. For instance, MHC class 1 and class 2 molecules are upregulated by cytokines, which could have a number of proinflammatory effects, and adhesion cell molecule expression is also upregulated which could increase the susceptibility of thyroid cells to cytotoxic T cell attack. Thyroid cells make a number of pro-inflammatory cytokines, and also express the molecule CD40, whose ligation by T cells induces cytokine expression by thyroid cells. Interference with these intrathyroidal events may explain the remission of Graves’ disease after antithyroid drug treatment [3].

The pathogenesis of ophthalmopathy is becoming clearer, based on a better understanding of the target of the autoimmune process. It now seems highly likely that the extra ocular muscles are the main focus of the autoimmune process, and it is the orbital fibroblasts which are the cell within the muscles to which the autoimmune response is directed [4]. Stimulation by locally released cytokines leads to glycosaminoglycan production, water trapping and oedema, with fibrosis occurring later. There is little if any evidence of cytotoxicity until late in the disease process, and even then only in the most extreme examples. The real question is the nature of the autoantigen to which the T cells are responding. The current best candidate appears to be the TSH receptor, which is expressed on a subpopulation of so called preadipocyte fibroblasts, but it still remains possible that other autoantigens exist within the orbit, which accounts for the close association with Graves’ disease and to a lesser extent autoimmune hypothyroidism.

REFERENCES