Antibodies: The housekeepers of the body

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Autoimmune diseases have proved enigmas ever since the notion of the body attacking itself was first expressed by Paul Ehrlich in his treatise on *horror autoxicus*. The pre-war studies by Peter Medawar on skin grafting in mice established the paradigm of self-tolerance and of autoimmunity as a state of immune dysregulation in which self-tolerance had been breached. The principle of absolute tolerance to self has remained a pillar of immunological theory since, but it has not resolved the cause of, nor provided a cure for, autoimmune diseases.

In 1988, I started the journal *Autoimmunity* and entered a world of theoretical immunology that I had not been a part of before. At that time I came across a paper by Pierre Grabar (Grabar, 1983), a French immunologist whose interpretation of autoimmunity changed my life and has shaped my thinking ever since. A paper, I believe, in which a reversal in the direction of established thinking produced a step-change in the evolution of scientific understanding.

Perhaps inspired by Ilya Metchnikoff's seminal observations on the disposal of unwanted material by marine protozoa, Grabar viewed the immune system, not in its modern context as a defence against infection, but in a phylogenetically more basic context as a mechanism for the removal of everyday detritus. He coined the term *immunoglobulines transporteurs* for antibodies, housekeepers that roamed the body in low titre, 'picked up' apoptotic remains of dying cells and disposed of them down the chute of the reticulo-endothelial system. The transporters were shape-specific, and their clones would expand according to the job in hand. Working for most of the time below the sensitivity threshold of antibody assays, these clones would nevertheless become detectable where cell turnover was accelerated, or antigenicity altered. Once whatever mess it was had been cleared, the clones involved would once again contract and become undetectable.

On reading that perspective, and digesting how fundamental its message was, I published a series of papers developing the theme for thyroid autoimmunity and, latterly, diabetes (Wilkin, 1989; 1992; 2001). I began to view endocrine autoimmunity as the physiological and protective response of a healthy organism to up-regulation, not as the pathological and destructive ravages of a dysregulated immune system. Damage, rather than merely refuse collection, was confined to the small proportion of the population with particularly reactive immune response genes, but functional up-regulation would always be the driver of clonal expansion.

A new perspective

Autoimmunity that caused damage was analogous to anaphylaxis – not a disease as such, but an excessive response. Given this perspective, it was consistent that thyroid autoimmunity should be more common in areas of iodine deficiency, that most endocrine autoimmunity be directed towards either cell products or the enzymes associated with up-regulation and, given the variability of genetic background, that some cases of endocrine autoimmune disease, whether stimulatory as in the case of Graves' hyperthyroidism, or destructive as in the case of diabetes, should be antibody negative. I would even go as far as to muse that autostimulation by conformationally abnormal thyroid stimulating hormone (TSH) receptors is the cause of Graves' disease, and that the TSH receptor antibodies conventionally viewed as the cause may turn out to be a secondary response which is nevertheless capable in transfer experiments of transferring the shape specificity needed to reproduce the effect.

The Accelerator Hypothesis, which argues that type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds, owes its origins to Pierre Grabar, an out-of-the-box thinker who saw perspectives that others did not. Insulin resistance, the result of obesity and the basis for up-regulation of the β-cell, results in a house-keeping response (islet-related autoantibodies are now seen in up to 40% of individuals with type 2 diabetes) which further damages the β-cell in the minority whose immune response genes are particularly reactive (type 1 diabetes). If the planned Accelerator Prevention Trial (a randomised controlled trial to test the Accelerator Hypothesis based on reducing β-cell up-regulation) proves successful in preventing type 1 diabetes, Grabar's inspiration will have touched the lives of many.

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