Reprogramming the Immune System

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The only treatments currently available for patients with autoimmune diseases or after organ transplantation basically only provide symptomatic relief, by non-specifically suppressing the whole immune system. The side effects of such immunosuppressive drugs include increased risk of infection and cancer, and even then they are not always effective, leading to disease relapses and graft rejection. Back in 1986 we published that foreign proteins could be accepted by the immune system of an adult mouse, as if they were "self", by giving them under the cover of a brief treatment of a monoclonal antibody (mAb) against the CD4 molecule found on the surface of thymus derived lymphocytes (T cells). We later showed that similar, short treatments with non-depleting, but functionally blocking, mAbs against various T cell surface molecules could induce life-long acceptance of tissue or organ grafts. It was these series of experiments that first clearly demonstrated that "reprogramming" of the adult immune system was a therapeutically obtainable goal.

Short-term treatment for long-term benefit

Over the next 20 or so years, the Therapeutic Immunology Group (TIG), and the Therapeutic Antibody Centre (TAC), under the leadership of Prof. Herman Waldmann, worked together to develop and test, with the help of many clinicians around the world, appropriate monoclonal antibodies aimed at achieving Immune System Reprogramming in human, clinical situations. The first generation of such mAbs was called CAMPATH, which depletes lymphocytes, allowing the immune system to regenerate and, in some cases, reset itself. CAMPATH was also found to be useful for treating certain types of chemotherapy resistant leukaemia, and this is what it is now licensed and marketed for, by a major pharmaceutical company. It is still being tested for its ability to reprogram the immune system in multiple sclerosis and in recipients of transplants. Second generation mAbs, such as a non-activating anti-CD3, are currently being tested for immune reprogramming in autoimmune diseases, such as type 1 diabetes.

From bench to bedside and back again

Our direct involvement with the clinical application of mAbs has now waned, as the costs to run larger, and more regulated, clinical trials have increased to the point where only large pharmaceutical companies can continue. The TAC has now relinquished all the clinical development to industry, and has pursued other areas, such as vaccine development, that are currently more appropriate for an academic centre. What has become clear, however, is that to successfully extend immune reprogramming therapies from animal models to human clinical situations, depends on a much broader understanding of how the immune system is regulated in both health and disease. In particular, we now recognise that clinical situations are complicated by other factors, such as the infectious history of the patient and the concurrent use of other medications, which may interact or block attempts to achieve immune reprogramming. This all means that our main focus has shifted back to the basic mechanisms of immune regulation, which can only be fully investigated in animals where we can safely model the various factors that we have learned are a barrier to immune reprogramming in the clinic.

Current research: it's all about regulation

Immune tolerance, until the early 1990's, was considered to depend entirely on the clonal deletion of potentially reactive T cells during development in the thymus. Only in the past 10 years or so has it become clear that tolerance induced through immune reprogramming in the adult is dependent on regulatory T cells (Tregs). Our current focus is therefore to determine the mechanisms by which Tregs are induced by mAb treatment, and how they work to reprogram the immune system, particularly in the acceptance of foreign tissue grafts. We have recently demonstrated that transforming growth factor beta (TGFβ) is always essential for the generation of new graft specific Tregs, even if the therapeutic manipulations used to generate tolerance were quite different. Whether we use therapeutic mAbs as above, or specialised, tolerogenic donor-derived cells (modulated dendritic cells), we generally find Tregs are generated and concentrated

within the tolerated graft tissue. This is leading us to investigate how Tregs interact with, and influence the properties of, both the grafted tissue itself and the dendritic cells that infiltrate it.

Privileged to be off drugs

Historically, a state of immune privilege was used to explain why certain organs, such as the eye, testes, brain, and the foetus, were generally "less rejectable" by the immune system. Very recently, there has been a convergence of data and ideas that suggest that the tolerance induced to transplants and the mechanisms of immune privilege are both the consequences of a localised interaction between the tissue with infiltrating dendritic cells and Tregs. We are starting to find that Tregs are able to turn on a protective gene profile when recognising donor-derived dendritic cells and in tolerated tissue grafts, which further amplifies the tolerogenic microenvironment such that any new, non-tolerant T cells that enter the graft are suppressed from rejecting, and may even be converted to Tregs themselves (a process we call "infectious tolerance"). Our aim now is to understand this tolerogenic microenvironment, and eventually how it may be influenced by the various factors we found to be a limitation to clinical application of immune reprogramming, such as memory T cells (acquired via infections or after immune depletion) and immunosuppressive drugs. In the process of defining and understanding the tolerogenic microenvironment we should also be able to develop clinical tests (biomarkers) that would indicate whether treated patients can develop sufficient immune tolerance to allow selective reductions, or even cessation, of immunosuppressive drugs.

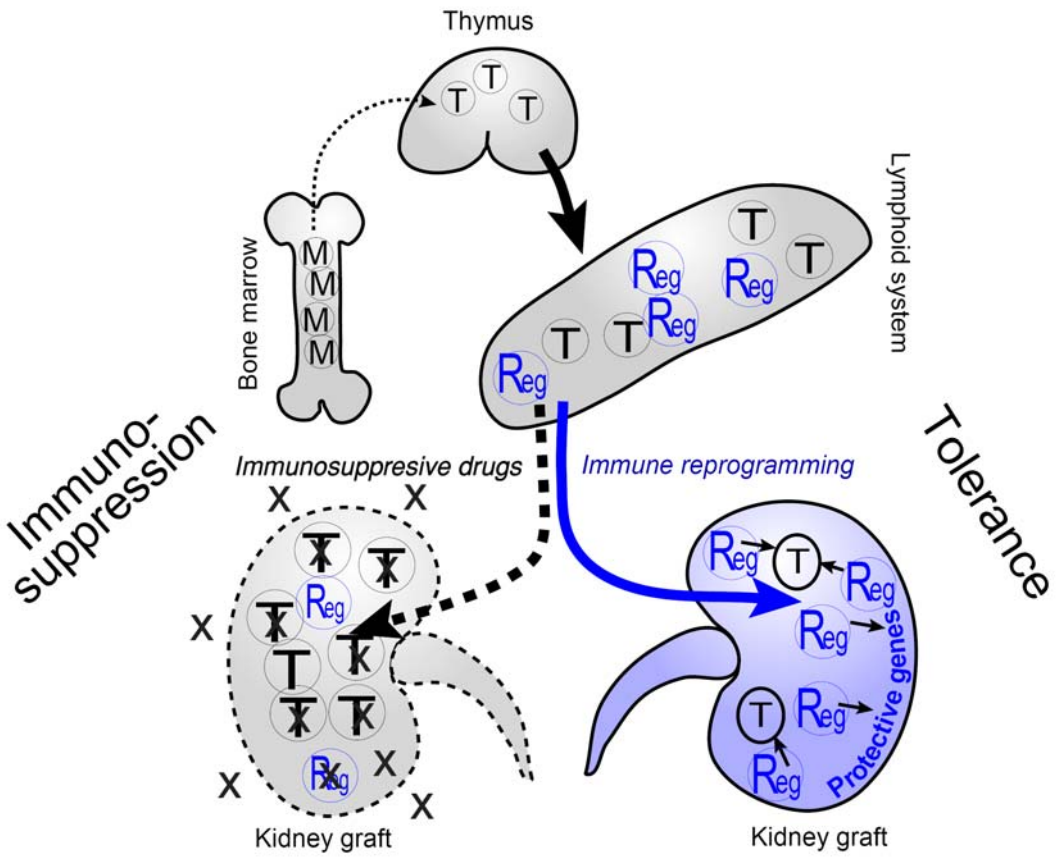

Figure legend

T cells (T) develop in the thymus from bone marrow stem cells (M). The normal lymphoid system contains a balance of potentially aggressive T cells (T) and regulatory T cells (Reg). In patients given a kidney graft, conventional immunosuppressive drugs are used to control the aggressive T cells, but these same drugs may also compromise regulatory T cell activity. After immune reprogramming, however, regulatory T cells specific for the kidney graft predominate and naturally control any locally aggressive T cells. The regulatory T cells also induce protective genes within the graft that help to maintain the tolerant state.