Selective Immunosuppression: Basic Concepts and Clinical Applications

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Selective immunosuppression is at the frontier of immunological research, and enough is known about the immune system to permit new ideas on immunoregulation to be tested in patients. Several concepts validated in experimental systems are currently being applied in clinical situations: a few pass, some fail, and most are encouraging enough to be submitted for further testing. This is a very interesting time to survey what is happening along the frontier, as sufficient information is now available on basic mechanisms and their clinical applicability to suggest the most promising pathways for future development.

Selective immunosuppression can be induced by a variety of approaches, which could be grouped into two broad categories: approaches directed specifically at autoreactive T cells by targeting the MHC/antigenic peptide/TCR complex, and less-selective approaches targeting a substantial fraction of T cells, including the pathogenic ones.

The first category includes very effective modes of immunosuppression, at least in experimental models. The holy grail is induction of tolerance to the autoantigens as a treatment for human autoimmune diseases. This requires, in principle, knowledge of the autoantigens, still poorly defined in most autoimmune situations, although progress is expected in their identification and characterization. Once the inciting autoantigen has been identified, specific immunosuppression of T cells recognizing it could be induced by exploiting one or more of the mechanisms controlling the peripheral tolerance described in this volume. In this respect, basic research has made considerable advances, but induction of tolerance to the relevant antigen in clinical situations still remains a long-term goal. This category also includes approaches targeting MHC molecules or the TCR. Unfortunately, MHC blockade can only prevent, not treat, autoimmune diseases. In addition, peptides, due to their unfavorable pharmacokinetics, cannot be developed as MHC antagonists. Approaches targeting the TCR itself are also very problematic; the TCR used by human pathogenic T cells is probably too heterogeneous to represent a useful target for immunosuppression.

The problems surfacing in the clinical applicability of these approaches definitely represent major challenges for pharmacological development.

In the second category of approaches, very heterogeneous indeed, some strategies have been clinically tested more thoroughly. Among them, some look extremely promising, e.g. TNFα antagonists in rheumatoid arthritis. It is likely that the next generation of immunosuppressive drugs will include several cytokine antagonists, and in particular those able to inhibit, directly or indirectly, the development and function of Th1 or Th2 CD4+ T cells. This underscores the impact on immunotherapy of the current paradigm in Immunology: the Th1/Th2 dichotomy. The subdivision of T cells into Th1 and Th2 subsets can be oversimplified to suggest that most organ-specific autoimmune diseases are Th1 mediated, whereas immediate-type hypersensitivities are Th2
mediated. Although clinical situations are certainly more complex, this paradigm offers the possibility to design straightforward experiments to probe the role of Th1 and Th2 cells in immunoregulation and in the pathogenesis of immunological diseases. It is hoped that tipping the Th1/Th2 balance may offer novel approaches for immunointervention in autoimmune diseases and allergies. In this volume, we are accompanied on the road from basic concepts to clinical applications of selective immunosuppression by leading immunologists, each with a distinct interest in applying the progress of immunological research to the treatment of human diseases. I think their contributions have assembled a very interesting volume, covering many facets and portraying the state of the art in selective immunosuppression. I would like to thank them for sharing their views and their thoughts with us. I also wish to acknowledge the editorial skills of Marianne Fratangelo, and her help in bringing this volume from an idea to a reality.

Luciano Adorini

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