Preface **xi**
Adriana Zeevi and Steven A. Webber

Novel Noninvasive Assays to Predict Transplantation Rejection and Tolerance: Enumeration of Cytokine-Producing Alloreactive T Cells **365**
Fanny Benítez and Nader Najafian

Treatment and prevention of allograft loss in organ transplant recipients relies chiefly on non–antigen-specific immunosuppression. Current approaches to the management of these immunosuppressive drugs are largely empiric and reactive because of lack of immune monitoring assays. Alloreactive T cells play a key role in acute rejection and in development of chronic allograft nephropathy, the leading cause of late allograft failure. There is thus an increasing interest in development of simple, reliable, noninvasive assays measuring allogeneic anti-donor responsiveness or donor-specific nonresponsiveness to predict ransplantation rejection and tolerance. Because the frequency and cytokine profile of alloreactive T cells play an important role in these processes, this article mainly focuses on assays that enumerate cytokine-producing alloreactive T cells.

Dendritic Cells and Chemokine-Directed Migration in Transplantation: Where Are We Headed? **375**
Bridget L. Colvin, Benjamin M. Matta, and Angus W. Thomson

The role of dendritic cells (DC) in transplantation is often overshadowed by the more prominent roles of T and B cells, which interact directly with and, in the absence of immunosuppressive therapy, destroy the allograft. It has become increasingly recognized, however, that these potent antigen-presenting cells exert control over the immune response and regulate the balance between tolerance and immunity to transplanted organs and tissues. The role that chemokines play in influencing DC function with impact on regulation of immune responses against the graft is only beginning to be understood. This article considers how the manipulation of DC trafficking during an alloimmune response can affect graft outcome.

Microarrays: Monitoring for Transplant Tolerance and Mechanistic Insights **385**
Valeriya Zarkhin and Minnie M. Sarwal

With recent advances in immunology and a growing understanding of transplantation biology, the development of reliable assays that may be used for identification and prediction of the current state of an immune response (rejection and tolerance) are urgently needed to allow us to predict the development of immunologic graft injury, individualize immunosuppression, rationally minimize immunosuppressive drug toxicity, promote a better understanding of the mechanisms underlying stable graft acceptance, and aid in the design of tolerance-inducing clinical transplantation trials. Microarrays can provide nonbiased, simultaneous global expression patterns for more than 40,000 human genes across different experiments. High throughput microarray technology offers a means to study disease-specific transcriptional changes in tissue biopsy, peripheral blood, and biofluids.

Pharmacogenomics: The Key to Improved Drug Therapy in Transplant Patients **411**
Gilbert J. Burckart

The current success in organ transplantation has been brought about by immunosuppressive therapy. Improvements in transplant outcome using these drugs have stalled, and an understanding of the pharmacogenomics of immunosuppressive dosing and response holds the greatest promise for advancing the use of these agents.

Clinical Impact of Cytokine and Growth Factor Genetic Polymorphisms in Thoracic Organ Transplantation **423**
Diana M. Girnita, Steven A. Webber, and Adriana Zeevi

Demographic and clinical risk factors may only partially predict short- and long-term outcomes after thoracic transplantation. The interindividual variability seen in rejection profiles could be related to the recipient's or donor's genetic background. Rejection, either acute or chronic, elicits an alloimmune response that involves a complex network of cytokines, growth factors, adhesion molecules, and other molecules, which may modulate the immune response toward rejection or, conversely, mediate graft acceptance. Herein, the authors discuss the current evidence regarding the importance of genetic polymorphisms as independent predictors of allograft outcome. They believe that pretransplant genotype profiling of patients, in combination with other relevant clinical information, might be useful to predict the risk for posttransplant adverse events and also to facilitate the implementation of individualized immunosuppression.

Chemokine-Directed Strategies to Attenuate Allograft Rejection **441**
Austin D. Schenk, Joshua M. Rosenblum, and Robert L. Fairchild

A key event during T cell–mediated rejection of allografts is the trafficking of donor antigen-primed effector T cells from the lymphoid tissue to the graft. This trafficking is mediated in part by chemokine produced in the graftengaging receptors on the T cells and other graftinfiltrating leukocytes. The presence of specific sets of chemokines and chemokine receptors is detectable in rejecting allografts. In animal models, allograft rejection is delayed when chemokine–chemokine receptor function is absent or antagonized but cellular infiltration and graft survival eventually occur, suggesting that T cells and other leukocytes use several trafficking mechanisms during rejection. The use of chemokines as footprints of rejection may be of considerable value as noninvasive biomarkers in transplantation.

The Impact of Immune Gene Polymorphisms in Kidney and Liver Transplantation **455**
Peter Nickerson

Since the completion of the Human Genome Project, it has become clear that genetic variation exists among individuals that can affect functional gene expression. This finding raises the possibility that differences in genetic phenotypes may account for the interindividual responses seen in the context of the alloimmune response. This review highlights studies examining the relative role of immunologic gene polymorphism in the context of renal and liver transplant outcomes (eg, acute rejection and graft survival). Furthermore, it examines the limitations and pitfalls in the study designs and concludes with the potential of single nucleotide polymorphism analysis in the future care of transplant recipients.

Yin and Yan of Cytokine Regulation in Solid Organ Graft Rejection and Tolerance **469**
Persis P. Wadia and Anat R. Tambur

Solid organ transplantation is the therapy of choice for end stage diseases. The alloimmune response generated after transplantation induces the production of a "cytokine storm" that can lead to either the rejection of the organ or graft acceptance. These key decisions, which determine the transplant fate, depend on the type of cytokine response (Th1/Th2). An inflammatory response will lead to graft loss; a tolerogenic response assists in graft acceptance. A balance between different factors often determines outcome. The same cytokine may assist in either allograft rejection or graft survival depending on: (1) the cell types in the vicinity, (2) the

amount of each cytokine produced, (3) different sites, and (4) if it acts in a synergistic or antagonistic manner with other cytokines. This review focuses on cytokines that manipulate the alloimmune response after organ transplantation and that play a role either in graft rejection (yin) or tolerance (yang).

Index **481**