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Regulatory T Cells for More Targeted Immunosuppressive Therapies	1
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<p>There has been a prolific amount of research dedicated to the T-regulatory cells (Tregs) and their role in achieving immune homeostasis. Here, the authors briefly discuss the known biology, utilization, and potential of Tregs, for current trials and future immunotherapy. Most current trials of Treg therapies include either ex vivo expanded Tregs transferred into the peripheral blood of patients with diseases of immunologic origin or interleukin 2 injected to stimulate Tregs directly. Ongoing trials designed to measure the clinical efficacy and safety profile of these novel therapeutic approaches have resulted in largely favorable outcomes in a variety of autoimmune and alloimmune diseases.</p>	
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<p>B cells shape the alloimmune response through polarized subsets. These cells inhibit or promote immune responses by expressing suppressive or proinflammatory cytokines. Their summed activity dictates the influence of B cells on the alloimmune response. We review the evidence for regulatory B cells and effector B cells in mice and humans, discuss current limitations in their phenotypic identification, and discuss regulatory B cells as a signature for clinical renal allograft tolerance and predictive markers for allograft outcomes. We discuss the effects of therapeutic agents on regulatory B cells and potential approaches to augment their numbers as a therapeutic tool.</p>	
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<p>The complement system, traditionally considered a component of innate immunity, is now recognized as a crucial mediator of the adaptive immune response in solid organ transplantation. Preclinical and early human trials have demonstrated the importance of complement effector mechanisms in driving allograft injury during specific antigraft immune responses, including ischemia-reperfusion injury, T-cell-mediated rejection, and antibody-mediated rejection, as well as a potential role for complement-derived risk stratification biomarkers. These data support the need for further testing of complement inhibitors in solid organ transplant recipients.</p>	

- Donor-Specific HLA Antibodies as Biomarkers of Transplant Rejection** 45
Olga A. Timofeeva
- This article reviews the current evidence to classify donor-specific antibodies (DSAs) using Food and Drug Administration–National Institutes of Health Biomarkers, EndpointS, and other Tools (BEST) resource terms as diagnostic, prognostic, predictive, monitoring, and risk biomarkers for graft rejection. The emphasis is on DSA characteristics, including the DSA levels determined by mean fluorescence intensity and/or titers, the ability to activate a complement cascade (C1q, C3d, and C4d binding), and specific IgG subclasses to define distinct roles of DSAs as biomarkers in clinical practice. In addition, technical limitation of DSA testing is discussed.
- Biomarkers for Early Complications After Hematopoietic Stem Cell Transplantation** 61
Courtney M. Rowan and Sophie Paczesny
- Advances in the field of omics have led to a significant expansion in biomarkers identified for complications after hematopoietic stem cell transplantation (HSCT). Biomarkers can offer an effective method for early identification of a specific disease and can be used to guide therapies. Ongoing investigations to discover biomarkers for acute graft-versus-host disease as well as other post-HSCT complications may improve early diagnosis, prognosis, and the development of new therapeutic targets. The authors review the most recent and validated diagnostic, prognostic, predictive, and response to treatment biomarkers for early complications following HSCT consistent with 2014 NIH consensus on biomarker criteria.
- Biomarkers in Solid Organ Transplantation** 73
John Choi, Albana Bano, and Jamil Azzi
- After more than 6 decades of clinical practice, the transplant community continues to research noninvasive biomarkers of solid organ injury to help improve patient care. In this review, we discuss the clinical usefulness of selective biomarkers and how they are processed at the laboratory. In addition, we organize these biomarkers based on specific aims and introduce innovative markers currently under investigation.
- The Role of Costimulatory Pathways in Transplant Tolerance** 87
Mayuko Uehara and Martina M. McGrath
- Costimulation is a critical step in T-cell activation, and costimulatory blockade at the time of T cell activation leads to T-cell anergy and allograft tolerance in animal models of transplantation. CD28:B7 is the most important costimulatory pathway and the balance of signals between CD28 and cytotoxic T-lymphocyte associated protein 4 (CTLA-4) is a central determinant of transplant outcome. From a clinical standpoint, CTLA-4 Ig is the only approved agent for costimulation blockade in transplantation. Advantages and disadvantages of its use are discussed. Progress in developing novel agents to target other pathways, including the promising CD40:CD154 pathway, is also discussed.

Genetic Polymorphism in Cytokines and Costimulatory Molecules in Stem Cell and Solid Organ Transplantation 107

Peter T. Jindra and Matthew F. Cusick

There is growing evidence supporting the genetic variability outside of HLA system that is contributing to the variation in transplant outcomes. Determining novel predictors could help to identify patients at risk and tailor their immunosuppressive regimens. This article discusses the various single nucleotide polymorphisms in costimulatory molecules and cytokines that have been evaluated for their effect on transplantation. An overview of how gene polymorphism studies are conducted and factors to consider in the experimental design to ensure meaningful data can be concluded are discussed.

MicroRNAs and Transplantation 125

Zahraa Khan, Manikkam Suthanthiran, and Thangamani Muthukumar

miRNAs, ~20 to 22 nucleotide single-stranded RNA species that play a pivotal role in the regulation of protein-coding genes, are emerging as robust biomarkers for assessing allograft status. Herein, the authors briefly review the biogenesis and function of the miRNAs and provide an overview of the tools to quantify miRNAs in tissues and body fluids. They then review their studies of discovery and validation of alterations in miRNA expression within kidney allografts with or without acute rejection, as well as with or without fibrosis, and summarize published data on miRNA expression patterns in kidney transplant recipients.

Biomarkers in Fetomaternal Tolerance 145

Sudipta Tripathi and Indira Guleria

Multiple mechanisms of tolerance operate in the immune cross-talk at the fetomaternal interface, contributing to successful pregnancy outcome. The cross-talk includes interaction between various cell subsets and between cytokines and molecules of the endocrine system. A depiction of how all these components interact with each other and contribute to tolerance of the fetus is not clearly understood. Dysregulation in one or more of these mechanisms leads to fetal loss. Few effective biomarkers are available that can safely predict fetal loss. This review discusses some potential biomarkers that can predict failure of tolerance at the fetomaternal interface.

Novel Targets of Immunosuppression in Transplantation 157

Ho Sik Shin, Ivica Grgic, and Anil Chandraker

It is increasingly recognized that calcineurin inhibitors (CNI) such as cyclosporine and tacrolimus are not ideal immunosuppressive agents. Side effects, including increased rates of infection, hypertension, and malignancy, can be severe. Thus, in the past decade, there has been much focus on the development of novel therapeutic agents and strategies designed to replace or minimize CNI exposure in transplant patients. This article reviews potential novel targets in T cells, alloantibody-producing B cells, plasma cells, and complement in transplantation.

Signaling Molecules in Posttransplantation Cancer**171**

Murugabaskar Balan, Samik Chakraborty, and Soumitro Pal

Immunosuppression is essential to prevent graft rejection. However, immunosuppression impairs the ability of the host immune system to control viral infection and decreases tumor immunosurveillance. Therefore, immunosuppression after organ transplantation is a major risk factor for posttransplantation cancer. Notably, recent reports suggest that immunosuppressive agents can activate tumorigenic pathways independent of the involvement of the host immune system. In this review, we focus on cell-intrinsic tumorigenic pathways directly activated by immunosuppressive agents and discuss the much-described infection- and immune-mediated mechanisms of cancer development in organ transplant recipients.

Immunologic Effects of the Microbiota in Organ Transplantation**185**

Kevin Rey and Jonathan C. Choy

The microbiota is a community of microbes that colonizes body surfaces. It has many effects that influence immune activation and regulation. The success of organ transplantation is limited by rejection of grafts by the immune system so it is important to understand how immunologic responses are controlled in this setting. This review discusses the immunologic effects of the microbiota and how this microbial community may affect organ transplant rejection.