Abdominal Solid Organ Transplantation

Immunology, Indications, Techniques, and Early Complications

Antonio Daniele Pinna
Giorgio Ercolani *Editors*

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Preface

Since 1963, when Thomas E. Strarzl performed the first human liver transplantation in a baby, a long way has been passed in the field of solid organ transplantation. Improvements in the surgical techniques and in immunosuppression in the early years not always achieved the expected results, and outcome was more often measured in months rather than years. In the late 1980s, a dramatic improvement in the patient's management and the discoveries of new immunosuppressive drugs led the shifting of organ transplantation from an experimental procedure to a real treatment that could have been offered to a larger proportion of patients affected by end-stage acute or chronic organ failures.

From those years, the clinical and scientific interest in organ transplantation has broadened, involving ethical issues, transplant infectious disease, critical care management, and new strategies to increase the donor pool. Furthermore, because post-transplant outcome is now measured in terms of years and decades, new clinical issues have been raised, like management of metabolic disease or viral reinfection or neoplastic disease, either recurrence or de novo.

Under the incentive of my active associate Giorgio Ercolani, we decided to try to summarize in a single book the new immunological strategies, the surgical innovative techniques, risks of infections after transplantation with a look to potential transmission from donors and innovative transplant procedures. We have asked my friend Dr. Alessandro Nanni Costa, President of the Italian Transplant Network, to report the Italian Guidelines in the evaluation and management of potential donors. We have then tried to focus on peculiar aspects of transplantation of liver, kidney, and small bowel underlining the indications, the technical aspects with special attention to living donor transplantation and the diagnosis and the management of the complications. Finally, two separate chapters are dedicated to the most frequently combined abdominal solid organ transplants (liver-kidney and kidney-pancreas).

I would like to thank all the contributors for the excellent work they have done, and I believe that this book might be useful for all physicians and surgeons involved in this field.

Bologna, Italy — Antonio D. Pinna, MD

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Donor Evaluation, Immunosuppression and Early Complications in S.O.T.

Transplantation Immunology

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Mihir M. Shah*, Naftali Presser*, and John J. Fung

1.1 Introduction

The twentieth century began with uniformly unsuccessful endeavors at investigational allotransplantation, and the next half-century was marked by repeated failure. The recognition of histocompatibility antigens [1] and the primary role of lymphocytes [2] in allorecognition were the two innovations that laid the foundation of transplant immunology that was to eventually form the basis for strategies leading to successful solid organ transplantation.

In the era preceding the development of dialysis, where end-stage renal disease meant imminent death, numerous attempts at renal transplantation failed to yield long-term survivors. The first successful renal transplant, performed between identical twins at the Peter Bent Brigham Hospital in Boston on December 23, 1954, by Moore, Murray, Merrill, and Harrison, energized the transplant community with passion – the barrier of histoincompatibility overcome by virtue of transplantation of a kidney between identical twins, nevertheless demonstrating the utility of organ replacement. Subsequently, Starzl performed the first successful kidney transplant between histoincompatible individuals, under azathioprine-based immunosuppression, 6 years following the twin transplant [3].

"The Relation of Immunology to Tissue Homotransplantation" was the title for the first international transplant conference sponsored by the New York Academy of

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Sciences in 1954 [4]. Current strategies in solid organ transplantation are based upon a comprehensive understanding of immunology and the use of potent immunosuppressive agents, which have led to high rates of success. Investigations in transplantation immunology have led to paradigm shifts in immunology and have greatly contributed to novel approaches to enhance allograft survival while minimizing morbidity.

In this chapter, we will provide an overview of transplant immunology including the principles of allorecognition, the immunological basis of organ rejection (including the immunology of xenotransplantation), and the rationale for historical and current immunosuppressive therapy. Focus will be placed on clinical solid organ transplantation with emphasis on fundamental concepts related to the up-to-date practice of transplant medicine.

1.2 Allorecognition

1.2.1 Major Histocompatibility Complex

The major histocompatibility complex (MHC) refers to a collection of genes, or genetic region, whose fundamental function is the production of proteins that present self and foreign antigens (peptide fragments) to immunocytes as part of normal immunologic surveillance. These complexes of peptide fragments in conjunction with MHC molecules are recognized by specific receptors on immunocytes and under specific circumstances initiate an immunologic cascade with the intent of creating a regulated and targeted response.

Human leukocyte antigen (HLA) is the term used for human MHC molecules. Two distinct classes of MHC antigens, Class I (HLA-A, HLA-B, HLA-C) and Class II (HLA-DR, HLA-DP, HLA-DQ), are located on chromosome 6. HLA Class I molecules are expressed on all nucleated cells as well as platelets, while HLA Class II are associated with antigen-presenting cells (APCs), including lymphocytes, monocytes, macrophages, and dendritic cells. A limiting factor in the exchange of organs between nonidentical individuals is the high degree of polymorphisms within the HLA loci, with resultant large numbers of allelic combinations resulting in low probabilities of complete matching in a random setting. The difference in MHC molecules between the donor and recipient is a primary cause of graft rejection.

1.2.2 Mechanisms of Allorecognition

In the thymus, T lymphocytes are selected for their ability to differentiate self from nonself, i.e., those T lymphocytes with excessive affinity for self-MHC are deleted (negative selection), whereas those with appropriate affinity are designated for maturation and export to the peripheral immune system (positive selection). This process is designed to deal with altered self (both viral- and tumor-related changes) as well as foreign antigens from bacterial and parasitic infections. Physiologic antigen processing involves peptide fragment generation via proteasome degradation of

cytosolic proteins and presentation on Class I MHC and via proteolytic degradation of proteins within phagosomes and subsequent presentation with Class II MHC antigens. This process entails indirect antigen presentation, meaning that the immunocyte receptor recognizes the peptide fragments in context within the MHC binding groove.

Conceptually, the immune system would never naturally encounter alloantigens – the sole exception being in the context of pregnancy. Although the placenta provides a barrier between the mother and fetus during pregnancy, low levels of maternal and fetal cells can be found circulating in the fetus and the mother, respectively. Persistence of fetal cells in the mother has been associated with late autoimmune disorders [5], while the presence of maternal cells in the fetus is associated with tolerance to maternal antigens [6] and may also be associated with autoimmune disorders in offspring [7]. Since all pregnant women have detectable fetal cells in their blood by 36 weeks of gestation, elimination of these cells may be mediated by peripherally circulating T cells with high affinity for nonself HLA and would entail direct allorecognition rather than generating alloantibody responses through indirect antigen presentation, which may adversely affect subsequent pregnancies.

In allotransplantation, recognition of foreign MHC likely involves both indirect and direct allorecognition. Indirect allorecognition utilizes a mechanism similar to the one involved in recognition of foreign antigens – specifically, fragments of foreign MHC molecules are processed through the phagosome and presented as antigenic peptides bound in the groove of self-MHC Class II molecules on APC. In direct allorecognition, foreign MHC molecules on donor cells that migrate out of the allograft are directly recognized by T lymphocytes, perhaps secondary to the innate affinity of T-cell receptors (TCR) for MHC molecules [8]. The binding of these TCR in direct antigen presentation is not thought to be specifically to the MHC binding groove; in fact, the recognition of donor MHC does not require antigen processing through APC [9].

It is possible that the direct allorecognition pathway predominates in the early phases of alloimmune responses and accounts for the strength of the alloimmune response related to a high T-cell precursor frequency, estimated to be as high as one in ten circulating T cells. It has been speculated that indirect alloantigen presentation may be important in chronic transplant rejection, which is likely to be mediated through various cytokines and chemokines released by T helper cells, as well as the effects of alloantibody generated by B cells stimulated via an indirect antigen presentation pathway.

1.2.3 Transplant Rejection

1.2.3.1 Hyperacute Rejection

Patients, who have had prior exposure to MHC antigens via previous transplant procedures, blood transfusions, or pregnancies, are at risk for developing antibodies reactive with alloantigens. When preexisting antibodies to blood groups, HLA, or other polymorphic antigens expressed on the graft are present in the recipient, they

can immediately bind to the graft and activate complement or arm cytolytic cells via antibody-dependent cellular cytotoxicity (ADCC) pathways. When the B-cell surface immunoglobulin receptor binds specific noncarbohydrate antigens in the context of soluble T helper cytokines, B cells are activated. CD4+ helper T-cell cytokines are responsible for the activation of B cells and thus indirectly for the majority of antibody production. B cells undergo differentiation, divide, and become plasma cells, which secrete soluble forms of the antigen-specific antibodies displayed on their cell surface. Plasma cells are long-lived and migrate to the bone marrow, where low levels of antibodies are secreted throughout the life of the plasma cell. Both IgM and IgG alloantibodies can be detected in the serum as well as in the graft of animals and humans undergoing allograft rejection. Preformed anti-HLA Class I antibodies, and occasionally anti-endothelial antibodies, play an important role in hyperacute rejection and accelerated vascular rejection seen in previously sensitized transplant recipients [9].

Events culminating in hyperacute rejection include binding of complement components, which themselves can cause direct damage through the membrane attack complex (MAC), and indirectly through chemokine properties of complement breakdown products, C3a and C5a, as well as deposition of platelets and fibrin, infiltration by granulocytes and monocytes, and fibrinoid necrosis of the vessel wall. This form of rejection manifests within minutes to hours after transplant, leading to graft failure as well as systemic manifestations such as disseminated intravascular coagulopathy. Fortunately, the incidence of hyperacute rejection has decreased significantly by employing routine HLA cross-matching screening, as well as avoiding ABO incompatilbility, prior to transplantation [10].

1.2.3.2 Acute Rejection

HLA differences activate a variety of events that result in acute cellular rejection and also set the stage for the development of chronic rejection. Recent advances in molecular and cellular immunology have further unraveled interactions between APC and T and B cells. These include elucidation of pathways involved in T-cell activation and apoptosis; identification of novel regulatory cells, including T-regulatory cells, B-regulatory cells, and suppressive APCs; as well as greater appreciation of the complex interactions between innate and adaptive immunity. Furthermore, elucidation of triggers of B-cell activation and antibody synthesis have allowed for the development of B-cell-specific immunosuppression.

Since T cells serve as the central hub in the cascade of alloimmunity, a brief overview of the current understanding of T-cell activation and proliferation is warranted. Optimal activation of naïve T cells requires coordinated signal transduction through three pathways: (1) nuclear factor-κB (NF-κB) pathway, (2) mitogen-activated protein (MAP) kinase-induced activator protein-1 (AP-1) activation, and (3) calcium-dependent calcineurin dephosphorylation of nuclear factor of activated T cells (NFAT) [11, 13]. Antigen-specific T cells interact with APC through the T-cell receptor (TCR)/MHC Class II molecule (signal 1) and CD28 costimulatory molecule/B7 (CD80 and CD86) molecules (signal 2) within the contact area, also