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Humoral Theory of Transplantation: Mechanism, Prevention, and Treatment

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ABSTRACT: We discuss the potential mechanisms of antibody-induced primary endothelium injury, which includes complement-dependent pathway (membrane attack complex formation, recruitment of inflammatory cells, and complement-complement receptor-mediated phagocytosis) and complement independent pathway antibody-dependent cell cytotoxicity. Secondary to endothelium injury, the following pathological reactions are found to be responsible for progressive tissue injury and final graft function loss: platelet activation and thrombosis, pathological smooth muscle and endothelial cell proliferation, and humoral and/or cellular infiltrate-mediated parenchyma damage after endothelium injury. We also introduce three categories of therapeutic strategy in the prevention and treatment of antibody-mediated rejection: (1) inhibition and depletion of antibody producing cells (immunosuppressants, antilymphocyte antibodies, splenectomy); (2) removal or blockage of preexisting or newly developed antibodies (immunoadsorption, plasmapheresis/plasma exchange, intravenous immunoglobulin); and (3) impediment or postponement of antibody-mediated primary and secondary tissue injury (anticoagulation, glucosteroids). In conclusion, because alloantibodies have destructive effect on allografts, alloantibody monitoring becomes extremely important. It will help clinicians to determine a patient's humoral responses against allograft and will therefore direct clinicians to optimize and/or minimize immunosuppressive drug therapy. *Human Immunology 66, 334–342 (2005).* © American Society for Histocompatibility and Immunogenetics, 2005. Published by Elsevier Inc.

KEYWORDS: HLA antibody; antibody monitoring; allograft; antibody-mediated rejection; chronic rejection

ABBREVIATIONS

HLA human leukocyte antigen
MIC major histocompatibility complex class I–related chain
PE plasma exchange
PPH plasmapheresis

INTRODUCTION

We have reviewed accumulated evidence regarding the role of antibody in graft injury [1]. Antibodies are associated with hyperacute, acute, and chronic rejection [2]. In a prospective trial, it has already been found that by using antibody screening tests with flow cytometry or enzyme-linked immunosorbent assay, about 14%–23% of transplant recipients with functioning grafts have detectable human leukocyte antigen (HLA) antibodies [3]. Within a 1-year follow-up period, 21 (8.6%) of 244 antibody-positive patients experienced graft rejection, which is significantly higher than that found in the HLA antibody–negative patient group ($43/1421 \times 100\% = 3\%$, $p = 0.00003$). These data suggest that some transplants may still function well in the presence of alloantibodies, which might be because of the compensational reactions of the transplanted organ to tissue injury. However, the graft may finally be rejected when the tissue repair system can not fully compensate for the antibody-mediated injury. This damage-repair-damage process could take years to result in irreversible graft loss. This hypothesis has been supported by the study of Lee *et al.,* who found that in some patients, it took many years for antibody-positive transplants to finally be rejected [4].

Why are some transplants rejected sooner and other transplants rejected later, after the presence of alloantibodies is found in the periphery blood? In this review, we discuss how antibody causes graft rejection after it binds to its target and how to prevent and treat antibody-mediated rejection.

MECHANISM OF HUMORAL REJECTION

Endothelial Cell—The Primary Target of Antibody

Among cellular and humoral immunologists, there is limited debate that the endothelium of transplanted

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organs serve as the primary target of patient immune responses. In the humoral theory of organ transplantation, the endothelium of a donor organ is primarily targeted by alloantibody, either preexisting or developed *de novo* after transplant [5–15].

Primary Effects of Antibody-Antigen Interaction

As proposed here and shown in Figure 1.1–4, binding of antibodies to antigens on endothelial cells can finally cause endothelium damage via four distinct pathways. Damage of endothelium can be mediated directly by complement via forming membrane attack complex [16] (Figure 1.2) or inflammatory cells recruited by soluble complement fragments [17, 18] (Figure 1.1), or by phagocytes that recognize complement fragments deposited on endothelial cells via a complement receptor [19] (Figure 1.3). These three pathways are complement dependent. The finding of complement C4d in graft capillaries provided strong evidence to support this complement-dependent hypothesis [20]. However, it is also possible that after antibody binds to its target antigen on the surface of the endothelial cell, antibody-dependent cell cytotoxicity may play a role in mediating endothelium damage without the involvement of complement [21–24] (Figure 1.4).

Secondary Effects After Endothelium Injury

Secondary pathological changes after endothelium damage include platelet activation and thrombosis, endothelial and smooth muscle cell proliferation, and humoral and/or cellular infiltrates mediated direct organ/tissue damage (Figure 1A–D). Hyperacute rejection, the best documented example of antibody-mediated rejection, is mediated by preexisting antibodies (*e.g.,* anti–blood group antigen A or B antibodies, or anti-HLA antibodies) that bind to endothelium and activate complement. Antibody binding and complement activation induce a series of pathological changes in the graft endothelium that promote intravascular thrombosis. Endothelial cells are stimulated to secrete von Willebrand factor that mediates platelet adhesion and aggregation. Complement activation leads to endothelial cell injury and exposure of subendothelial basement membrane proteins that activate platelets. These series processes contribute to thrombosis and vascular occlusion; therefore, the organ suffers irreversible ischemic damage (Figure 1A).

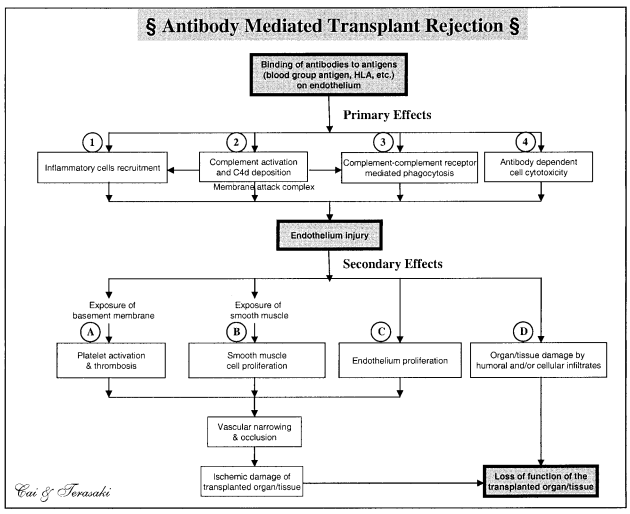

FIGURE 1 Mechanisms of antibody-mediated transplant rejection.

We know that the rapid progress of antibody-mediated hyperacute rejection is related to a large amount of preexisting alloantibodies and it usually happens in ABO-incompatible or presensitized patients. However, in current transplant clinics, transplantation is performed primarily in ABO-compatible, low-sensitized patients; moreover, highly effective immunosuppressive drug therapies are widely used in transplant recipients. Therefore, unlike hyperacute rejection, acute or chronic graft function loss might not result mainly from thrombosis-related rapid vascular occlusion. Instead, they are most likely due to a progressive damage-repair-damage pathological process. As found in chronic rejection, which is manifested as atherosclerosis of the vessels of the transplanted organ, the intimal thickening is the result of the proliferative effects of anti-HLA antibodies (Figure 1B,C) [25]. It is also a possibility that after endothelium injury, humoral and/or cellular infiltrates can directly cause organ parenchyma damage (Figure 1D). This direct parenchyma injury also follows the law of "quantitative change to qualitative change." The process speed of any potential pathological changes after endothelium injury depends on the following three major factors: the level of alloantibodies; the capability of transplanted organ tissue repair; and immunosuppressive and other supportive therapy.

The first factor is the level of alloantibodies. In ABO-compatible transplantation, there was considerable variation in antibody titers against blood group antigens [26]. Recipients with higher antibody titers against blood group antigens had a much higher incidence of early graft failure [27, 28]. In ABO-compatible transplantation, there was a significant stepwise decrease in graft outcome with increasing levels of sensitization. Patients with less than 10% panel-reactive antibodies had a significantly longer half-life than patients with higher levels of sensitization [29]. These data suggested that graft outcome is strongly associated with the alloantibody level. High levels of antibodies result in more irreversible rejection. These data also implied that in lower sensitized patients, because of the lower levels of preexisting antibodies, the rejection process is slower, but the transplanted graft may finally be rejected when