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Review

The mechanisms of rejection in solid organ transplantation

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ABSTRACT

Organ transplantation represents the preferred treatment option for many patients in terminal organ failure. The half-life of transplanted organs, however, is still far from being satisfactory with the vast majority of the organs failing within the first two decades following transplantation. At this stage, it has become apparent that rejection (prevalently mediated by humoral events) remains the primary cause of graft loss after the first year. In this light, studies are underway to better comprehend the immune events underlying graft rejection and novel immunosuppressive strategies are being explored. In this context, therapeutic apheresis techniques, that include therapeutic plasma exchange (TPE), immunoadsorption (IA) and extracorporeal photochemotherapy (ECP), represent an important adjunct in the current immunosuppressive armamentarium. This article briefly reviews our current understanding of the immune process underlying rejection of a solid organ transplant and describes the principal areas of application of therapeutic apheresis techniques in transplantation.

Contents

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1. Introduction

Organ transplantation represents the ideal treatment option for patients in terminal organ failure. Indeed, whilst in the case of heart or lung failure, transplantation may in many cases represent the only available approach, in the case of renal failure transplantation offers several advantages over dialysis. In particular, it has been clearly demonstrated that kidney transplantation is associated with a better quality of life, lower mortality and reduced social costs to healthcare systems compared to patients on dialysis [1]. To date, however, the potential benefit of organ transplantation has been dramatically restricted by the scarce availability of human organs but also by the limited survival compared to the expected life of non-transplanted organs. Actually, the current estimated half-life of transplanted organs is generally less than 15 years and it is as low as 6 years in the case of single lung transplantation [2]. Several contributing factors have been put forward to explain the reduced half-life of transplanted organs. These include both non-immune causes (such as ischemia/reperfusion injury, IRI) and immunological events [3]. In this context, cell-mediated rejection was originally believed to be the only immunological event responsible for graft damage. Progress in the understanding of the fine immunological mechanisms underlying graft rejection, however, has challenged the cell-only theory of organ rejection. As a consequence, immune cells are no longer viewed as the only mediator of the anti-graft immune response. On the contrary, it is now well accepted that the contributing role of humoral events are probably as important to the extent where they are perceived by some as the key factors determining the ultimate fate of the graft [4]. In this review the key immunological players involved and the crucial mechanisms underlying graft rejection will be briefly illustrated. The objective is to point out to the reader the key steps of this complex cascade of immune events where therapeutic apheresis (TA) may constitute a crucial therapeutic adjunct and rescue otherwise untreatable rejection episodes.

2. Natural versus adaptive immunity

Conventionally, the immune response can be broadly divided into two main components. The first component is comprised of the more primitive defense mechanisms that are collectively grouped under innate (or natural) immunity. Innate immunity represents the first line of defense against microbes; it will act rapidly and in a nonspecific manner to timely eliminate pathogens [5]. It is essentially made of physical and chemical barriers, proteins of the complement system and immune cells which include macrophages, neutrophils, natural killer cells and innate lymphoid cells. Innate immunity is furthermore characterized by a limited, germline encoded receptor diversity [5,6]. In particular, cells of the innate immune response express a limited number of receptors referred to as pattern-recognition receptors (PRR) that, in the case of infection, enable them to recognize pathogen-associated molecular patterns (PAMPS) [7,8]. PRR belong to different classes of receptors which include the toll-like receptors, NOD-like receptors, C-type lectin-like receptors and scavenger receptors. PRR binding results in activation of the immune cells of the innate immune response with production of pro-inflammatory molecules resulting in inflammation and elimination of pathogens. Interestingly, PRR may also recognize molecules released by cells undergoing tissue injury, such as heat-shock or nuclear proteins. Such molecules are collectively named damage-associated molecular patterns (DAMPS) and are also released in the case of tissue damage occurring as a consequence of graft rejection [7–9]. On the other hand, the second component of the immune system, globally named as adaptive (or acquired) immunity, is a more refined defense barrier that nicely integrates and reinforces the basic defense provided by the innate immunity [9,10]. The acquired immunity is characterized by secretion of antibodies and relies on a cellular compartment essentially comprised of lymphocytes. Interestingly, adaptive immunity stands out for its very large diversity at the level of both T- and B-cell receptors. Such a broad repertoire of receptors derives from somatic recombination of gene segments and enables the immune system to react very specifically against a broad array of antigens. Importantly, the effector cells of the acquired immune response are characterized by the capacity to retain the memory of previous encounters with antigens. Such a peculiarity renders the response to the repeated exposure to a same antigen much more rapid and vigorous. This situation will be very helpful in the case of an infectious agent but will be highly harmful in the case of a transplant rejection. It is noteworthy that, as for other immune responses, it has now been clearly demonstrated that allograft rejection is a complex process that requires the interplay of both the innate and acquired components of the immune response [10,11]. In particular, following transplantation, DAMPS released as a consequence of tissue injury (for instance as a result of IRI) will bind PRR and trigger activation of innate immune cells. These, in return, will stimulate the adaptive immunity that is the primary effector of the rejection process but also the immune compartment whose effector functions may be more amenable to treatment with TA.

3. The adaptive response in transplant rejection

The adaptive response to a foreign, non-self body such as a graft will involve the activation of both recipient's T and B lymphocytes.

3.1. The T-cell compartment

3.1.1. Antigen recognition and activation

Following transplantation, cells of the innate immune system activated by DAMPS trigger activation of dendritic cells that will act as the source of antigen presenting cells (APC) in the transplanted organ. These donor APC undergo functional maturation and migrate into the recipient lymph nodes where the actual alloreactive T-cell priming will take place. Two basic requirements need to be satisfied in order to enable antigen-specific T-cell activation by donor activated dendritic cells [9,10,12]. First, it is indispensable that the complex constituted by the foreign MHC molecule – peptide presented by the donor APC is directly recognized by the T-cell receptor (direct presentation). In this regard, $CD4^+$-T cells, more often equipped with helper functions, are only able to recognize the foreign peptide in the context of MHC Class II molecules; in contrast, $CD8^+$-T cells, usually associated with a cytotoxic role, will exercise their effector function only if they are primed by the recognition of the foreign peptide presented in the context of MHC Class I molecules. Second, the donor APC must provide efficient co-stimulatory signals and actively contribute to the full T-cell activation. In this context, it is worth remembering the important co-stimulatory role played by the B7 molecules (namely CD80 [B7-1] or CD86 [B7-2]) on APC once they bind the CD28 counterpart on T-cells. In contrast, binding of B7 molecules to CTLA-4 on T-cells will provide inhibitory signals. Furthermore, the CD40-CD154 co-stimulatory pathway represents an additional and very important source of co-stimulatory signals to T-cells. Whilst in the early phase of the anti-graft immune response donor-derived dendritic cells will act as the APC, at a later stage $CD4^+$-T stimulation will depend on antigen presentation by recipient APC (indirect presentation).

3.1.2. Effector functions mediated by T-cells

T cell-mediated graft damage is ultimately provided by the contribution of both $CD4^+$ T and $CD8^+$ T cells. Activated $CD4^+$ T cells