Transplantation, ABO incompatibility and immunology

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Learning objectives

After reading this article, you should:

- understand the mechanisms of graft recognition
- be able to list the three main different types of rejection
- appreciate the different techniques used to limit the rejection process.

Abstract

An allograft is tissue transplanted from another individual within the same species. Mechanical trauma to a graft and recipient transplant site along with graft-derived proinflammatory mediators stimulate a non-specific innate immune response. Dendritic cells and macrophages present foreign antigen to the adaptive immune system cells and thus initiate a specific and directed response. In order to respond to a specific pathogen, an individual must be able to recognize foreign cells as non-self. Major and minor histocompatibility antigens (MHCs) and the ABO blood group antigens are central to distinguishing one human from another and therefore in recognizing self from non-self. Genetic polymorphism describes genes encoded by varying alleles resulting in varied phenotypes within a species. The blood group and MHC are polymorphic, with many different possible allelic combinations leading to differences between individuals and allowing an individual to recognize self from non-self. Rejection describes the graft injury and loss of function due to the recipient's non-acceptance of the graft as 'self' and the response which aims to remove it from the body. Rejection can be classified into hyperacute, acute and chronic states. Both cell-mediated and antibody-mediated mechanisms lead to allograft tissue destruction. By minimizing MHC mismatch and using immunosuppression therapy, the immune response to a graft can be reduced. This involves familial grafting when possible, matching donors and recipients for similar human leucocyte antigen and identification of preformed recipient antibodies.

Keywords acute rejection; allograft; chronic rejection; hyperacute rejection; isohaemagglutinins; major histocompatibility; polymorphism

Introduction

Autograft describes tissue transplanted from one part of the body to another, such as skin and bone marrow; allograft describes tissue transplanted from another individual within the same species, including blood, kidney and heart. A xenograft is tissue transplanted from another species. An isograft describes tissue transplanted between genetically identical individuals.

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The immune system recognizes an allograft as foreign and therefore mounts a response, as it would to any foreign pathogen. After transplant of a graft, damage to both graft and recipient tissues leads to activation of the non-specific innate immune system as well as the specific adaptive immune system. These responses must be prevented or depressed if the graft is to survive and function.

Innate immune system

Mechanical trauma to the graft and transplant site as well as graft-derived proinflammatory mediators (following peritransplant ischaemia then reperfusion) stimulate a non-specific innate immune response. This consists of inflammatory changes around and within the graft. There is local vasodilatation and increased vascular permeability with infiltration of neutrophils and macrophages and activation of clotting and complement systems. These cells are activated by inflammatory mediators and do not recognize donor cells as foreign. They respond in a non-specific way to kill the supposed pathogen or to minimize any invasion while a more specific immune response is mounted. These cells secrete cytotoxic substances and phagocytose foreign material. Dendritic cells are innate immune cells which, along with activated macrophages, present foreign antigen to the adaptive immune system cells and thus initiate a specific and directed response.

Adaptive immunity

In order to respond to a specific pathogen, an individual must be able to recognize foreign cells as non-self. Major histocompatibility complex (MHC) and minor histocompatibility antigens and the ABO blood group antigens are central to distinguishing individuals and therefore to recognizing self from non-self. Although the innate immune system can be effective in eliminating a potential pathogen, the specific adaptive immune system allows a targeted approach. The adaptive system is also able to remember potential pathogens in order to respond more quickly and efficiently if re-exposed. Adaptive immune responses are led by lymphocytes with cellular and antibody-mediated components.

Recognition of the allograft

Genetic polymorphism describes genes encoded by various alleles resulting in varied phenotypes within a species. It was thought that most proteins, for example albumin, were genetically coded by non-polymorphic genes with uniformity within a species. Polymorphic proteins, including the blood group and MHC, have many different possible allelic combinations leading

to massive phenotypic variation within a population, and, importantly, to differences between individuals. The elucidation of the human genome has made this picture more complex. It seems that all proteins are produced by genes with more or fewer alleles with greater consequent degrees of variation of the end product.

Polymorphism allows an individual to recognize self from non-self. In an isograft the donor MHC is identical to the recipient's and the graft is accepted as self. The likelihood of two non-identical individuals having an identical MHC allelic make-up is very small and therefore allografts are inevitably recognized as foreign.

Blood group antigens

The ABO and rhesus systems are two of many blood group systems describing antigenic differences between individuals. In the ABO system, there are four blood groups (A, B, AB, O) depending on an individual's allelic make-up. Alleles A and B code for enzymes producing specific erythrocyte cell membrane carbohydrate antigens A and B. The blood group allele O is a null allele. These alleles are inherited in a simple Mendelian pattern with A and B alleles as dominant. Both inherited alleles are expressed antigenically on the erythrocyte.

All humans have antibodies, called isohaemagglutinins, to those ABO blood group antigens that they do not express. In the absence of prior exposure this is thought to occur because of cross-reactivity between blood group and microbial and food antigens. These antibodies result in severe transfusion reactions if unmatched blood is transplanted, typifying a type-2 hypersensitivity reaction (see Hyperacute Rejection).

Major histocompatibility complex

The MHC is a gene complex encoding three classes of molecule. In humans these molecules are also called human leucocyte antigens (HLAs). MHC class III molecules include complement and various cytokines. The primary function of MHC class I and class II molecules is to present self and foreign peptides to T cells. T cells recognize foreign peptides only when they are associated with a MHC molecule; therefore, MHC molecules are critical in the recognition of and consequent response to foreign material. MHC class I molecules, expressed by all cells, indicate what is occurring intracellularly by presenting peptides from the internal cell environment. Conversely, MHC class II molecules present peptides from the extracellular compartment and are expressed only by 'antigen-presenting' cells.

For antigen peptides to be presented, the antigens must be processed intracellularly, with antigenic breakdown, association with MHC molecules and transportation to the cell membrane. Extracellular antigens must also first be endocytosed into the cell.

The two main types of T cells are CD4 and CD8 T cells, which recognize MHC class II- and I-associated antigen respectively. Like antibody, T cells are antigen specific and recognize only one antigen. Recognition of a foreign antigen occurs when the innate immune antigen-presenting cells present antigen to CD4 T cells in the lymphoid tissue of the lymph nodes. T cells specific to that antigen bind to the MHC–antigen peptide complex via the T-cell receptor. This stimulates the cells to differentiate into T-helper cells. These further activate B cells and CD8 T cells, which have also recognized antigen. These cells differentiate into plasma cells and cytotoxic T cells respectively, which then eliminate the recognized foreign tissue (Figure 1).

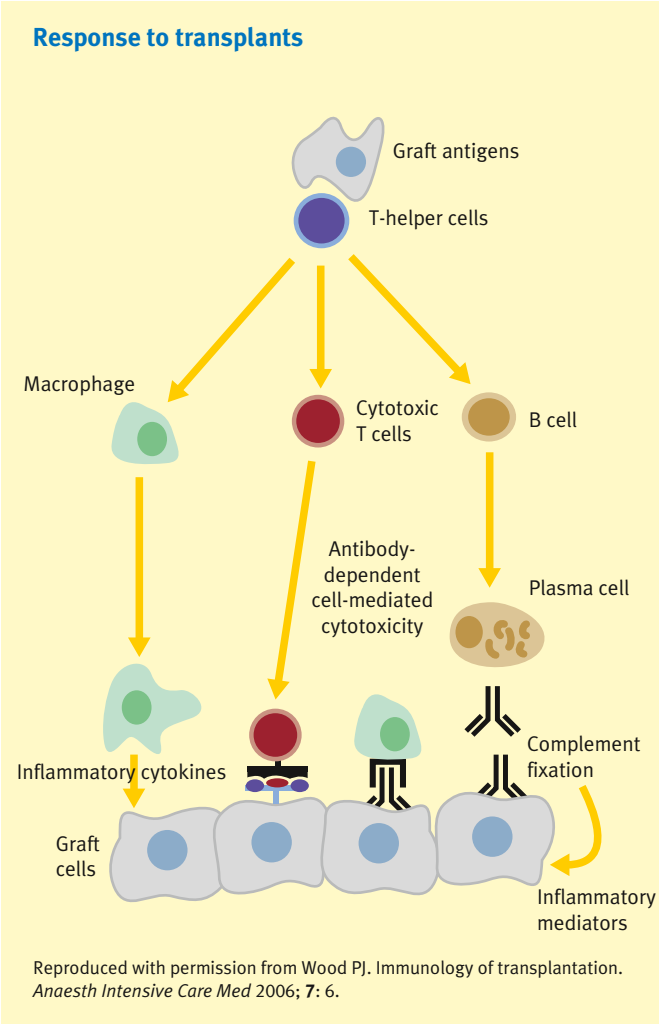

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Figure 1

Minor histocompatibility complex

Minor transplantation antigens are probably involved in late-onset rejection because they are less effective stimuli to the immune system. Over 80 have been identified, although there are potentially thousands including non-ABO blood group antigens and those associated with the sex chromosomes.

Rejection: response to the allograft

Rejection describes the graft injury and loss of function due to the recipient's non-acceptance of the graft as 'self' and the response which aims to remove it from the body.

The recognition of an allograft as foreign is almost inevitable. In addition, the response to an allograft is highly exaggerated. There is a 50-fold increase in the number of T cells that respond to an allograft in comparison with the number in a response to environmental antigens. This is due to the complexities of recognizing self and non-self. Direct recognition when donor MHC is recognized as foreign; this is thought to cause the exaggerated