Immunology 2017: Lecture 17 handout

Transplant rejection

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INTRODUCTION

we learned about GVHD, where the donor's T lymphocytes attack the recepient. In this handout we'll give a breif idea about graft rejection: when the recepient's immune system attacks and destroys the foreign graft.

Rejection is a complex phenomenon involving cell and antibody mediated reactions.

IMMUNE RECOGNITION OF THE GRAFT

The major antigenic differences between a donor and recipient that result in rejection of transplants are differences in HLA alleles. Grafts exchanged between individuals of the same species (the usual clinical situation) are called allografts, and grafts from one species to another (still an experimental procedure) are called xenografts.

Because HLA genes are highly polymorphic, there are always some differences between individuals (except, of course, identical twins). Following transplantation, the recipient's T cells recognize donor antigens from the graft (the allogeneic)

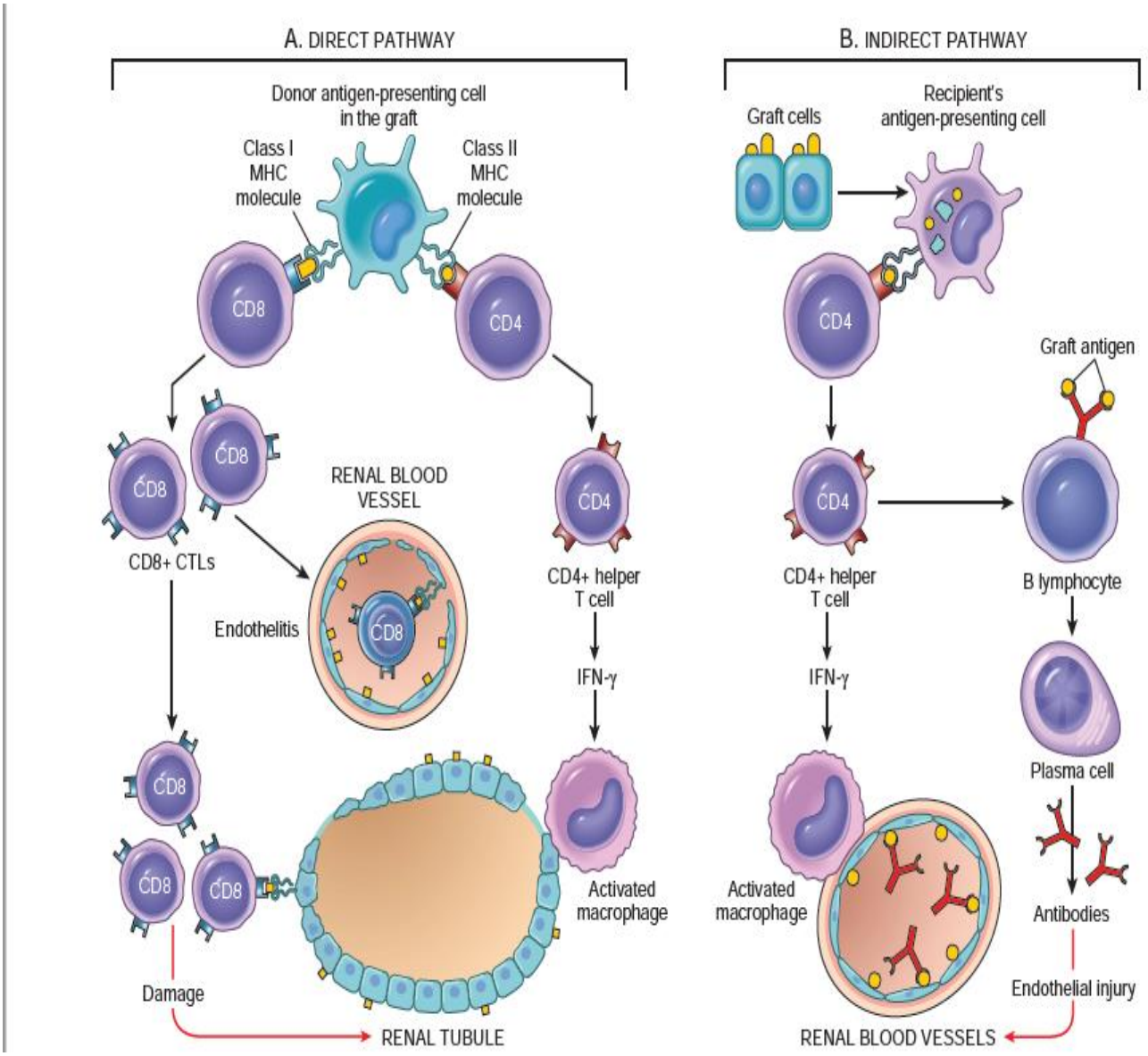
The host immune system recognizes graft MHC molecules by two mechanisms:

1. **Direct recognition**: host T directly recognize the graft MHC expressed on the graft APC cells. This direct recognition of allogeneic MHC molecules seems paradoxical to the rules of self MHC restriction: If **T cells normally are restricted to recognizing foreign peptides displayed by self MHC** molecules, why should these T cells recognize foreign MHC? The probable explanation is that allogeneic MHC molecules, with their bound peptides, resemble, or mimic, the self MHC–foreign peptide complexes that are recognized by self MHC–restricted T cells. In other words, recognition of allogeneic MHC molecules is a **cross-reaction** of T cells selected to recognize self MHC plus foreign peptides.

2. **Indirect pathway of recognition** :recipient T lymphocytes recognize MHC antigens of the graft donor after they are presented by the recipient's own APCs. This process involves the uptake and processing of MHC molecules from the grafted organ by host APCs. The peptides derived from the donor tissue are presented by the host's own MHC molecules, like any other foreign peptide.

NOTE: **B lymphocytes also recognize antigens** in the graft, including HLA and other antigens that differ between donor and recipient.

RECOGNITION OF THE GRAFT AS NONSELF



EFFECTOR MECHANISMS OF GRAFT REJECTION

Both B ant T cells play a role in graft rejection.

1. **T cell mediated rejection :** CTLs kill cells in the graft tissue. T helper cells also secrete cytokines and trigger an inflammatory reaction that destroys the graft.

2. antibody mediated rejection: Ab against graft MHC cause complement activation and inflammatory reaction.

CLINICAL FORMS OF REJECTION

Graft rejection can be hyperacute, acute or chronic.

1. Hyperacute rejection occurs within minutes to a few hours after transplantation in a pre-sensitized host . Preformed antidonor antibodies are present in the circulation of the recipient. Such antibodies may be present in a recipient who has **previously rejected a transplant**. **Multiparous women** who develop antibodies against paternal HLA antigens shed from the fetus may have preformed antibodies that will react with grafts taken from their husbands or children, or even from unrelated individuals who share HLA alleles with the husbands. **Prior blood transfusions** can also lead to presensitization, because platelets and white blood cells are rich in HLA antigens and donors and recipients are usually not HLA-identical.

Hyperacute rejection was a concern in the early days of kidney transplantation, but with the current practice of cross-matching, that is, testing recipient's serum for antibodies against donor's cells, it is no longer a significant clinical problem.

2. **Acute**, occurs within days to weeks of the transplantation

It can be Ab mediated or cell mediated.

I. Ab mediated acute rejection is caused by antidonor antibodies produced after transplantation. In recipients not previously sensitized to transplantation antigens, exposure to the class I and class II HLA antigens of the donor graft, as well as other antigens that differ between donor and recipient, may evoke antibodies.

The antibodies formed by the recipient may cause injury by several mechanisms, including complement dependent cytotoxicity, inflammation, and antibody dependent cell-mediated cytotoxicity. The initial target of these antibodies in rejection seems to be the graft vasculature.

II. Cellular mediated acute rejection: Acute cellular rejection, also called acute T cell–mediated rejection, is most commonly seen within the initial months after transplantation and is heralded by clinical and biochemical signs of organ failure. It was thought that direct killing of graft cells by CD8+ CTLs is a major component of the reaction. However, more recent studies have established that an important component of this process is an inflammatory reaction in the graft triggered by cytokines secreted by activated CD4+ T cells. The inflammation results in increased vascular permeability and local accumulation of mononuclear cells (lymphocytes and macrophages), and graft injury is caused by the activated macrophages.

3. **Chronic rejection :** this occurs months to years after transplantation and again could be antibody mediated or cellular mediated**.**

I. **antibody-mediated** chronic rejection usually develops insidiously, without preceding acute rejection, and primarily affects vascular components. Antibodies are detected in the circulation but are not readily identified within the graft. The mechanisms of the vascular lesions are not well understood.

II. **Cellular chronic rejection**: T cells also contribute to chronic rejection, in which lymphocytes reacting against alloantigens in the vessel wall secrete cytokines that induce local inflammation and may stimulate the proliferation of vascular endothelial and smooth muscle cells.

METHODS OF IMPROVING GRAFT SURVIVAL

1. better HLA matching of donor and recipient

2. immunosuppression.

THANK YOU