

Transplant rejection: T-helper cell paradigm

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Transplants that are from a genetically unrelated donor of the same species are termed **allografts**. **Allogeneic transplantation** is deemed the last resort for the treatment of chronic organ failure. Even with the aid of organ preservation and the advances in immunosuppression, the major complication post-transplantation is rejection. Rejection occurs despite pre-transplant tissue typing/blood analysis and is seen in almost all transplant recipients, to varying degrees. Outside **hyperacute rejection**, which occurs due to the presence of pre-existing antibodies (resulting from pregnancy, blood transfusions and/or previous transplants), transplant rejection (**Figure 1; see following page**) can be split broadly into two types; acute and chronic. **Acute rejection** is thought to be solely an immunological response, whereas **chronic rejection** involves both immunologic and non-immunologic mechanisms.

Allorecognition (Figure 2) is the processing and presentation of graft antigen (**alloantigen**) and is divided into two main subtypes: direct and indirect. Dendritic cells migrating from the graft initiate **direct allorecognition**, where recipient T cells recognise allogeneic MHC plus associated peptides directly. Later, recipient APCs pick up fragments of donor MHC and present allogeneic peptides to recipient T cells in association with self-HLA (**indirect allorecognition**). A third subtype, **semidirect allorecognition**, involving transfer of donor MHC to host cells, has also been proposed. Naïve CD4⁺ T helper cells (**nTh**) are one of the first immune cells to be activated post-transplant, playing a key role in rejection. Activated nTh develop into either **Th1** (pro-inflammatory) or **Th2** (anti-inflammatory) subtypes. Each subtype orchestrates a characteristic, immune response profile (each being mutually suppressive). In the presence of TGF- β and IL-6, nTh differentiate into Th17 cells, a novel subset of Th cells that secrete IL-17 whose role in transplant immunology is still unclear.

A Th1 response is correlated with **acute rejection** episodes with the production of pro-inflammatory cytokines – IFN γ , IL-2, IL-12, TNF α and GM-CSF. This cytokine profile activates macrophages, **natural killer (NK) cells** and **cytotoxic T cells (Tc)** which are drawn to the graft. **Tc** attack by releasing **perforin**, which creates pores in the graft endothelium; **granzymes** released from the Tc then enter the cell, and activate **caspases** which induce cell apoptosis (**cytolytic granule exocytosis pathway**).

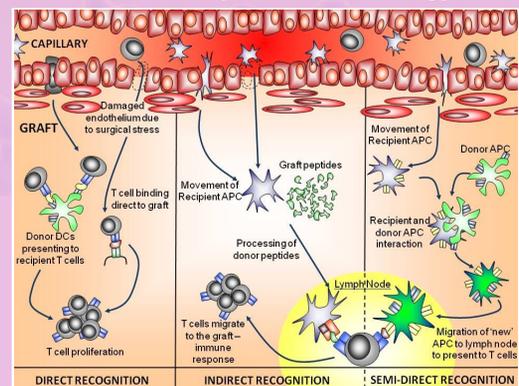


Figure 2. Types of allorecognition

Activated **NK cells** have a number of effector functions at their disposal: cytolytic granule exocytosis, death receptor expression (FASL + TRAIL), antibody dependent cell-mediated cytotoxicity (ADCC) and cytokine secretion. Activated **macrophages** can orchestrate and maintain a localised pro-inflammatory response against the graft via cytokine release (IFN γ and IL-12).

An anti-inflammatory allogeneic response predominantly sees a Th2 phenotype, which has a strong correlation with **chronic rejection**. Th2 cells result in the activation of **B cells**. Cell-to-cell contact and cytokine exchange between both Th2 and B cell is required for antibody production towards the graft. B cells express **MHC class II**, which present to Th2 cells (indirect), resulting in Th2 activation/proliferation. The resultant Th2 cells are specific for the alloantigen presented initially by the B cell and secrete IL-2 for B-cell proliferation and IL-4 and -5 for antibody class switching. The bulk of activated B cells differentiate into antibody secreting plasma cells (mainly **IgG** and **IgM**) with specificity towards the graft. Attachment of Ab to the graft endothelium eventually leads to the activation of **complement**, resulting in cell lysis. Alternatively, B cells develop into **memory cells** and return to the bone marrow, developing an immunological memory towards the graft.

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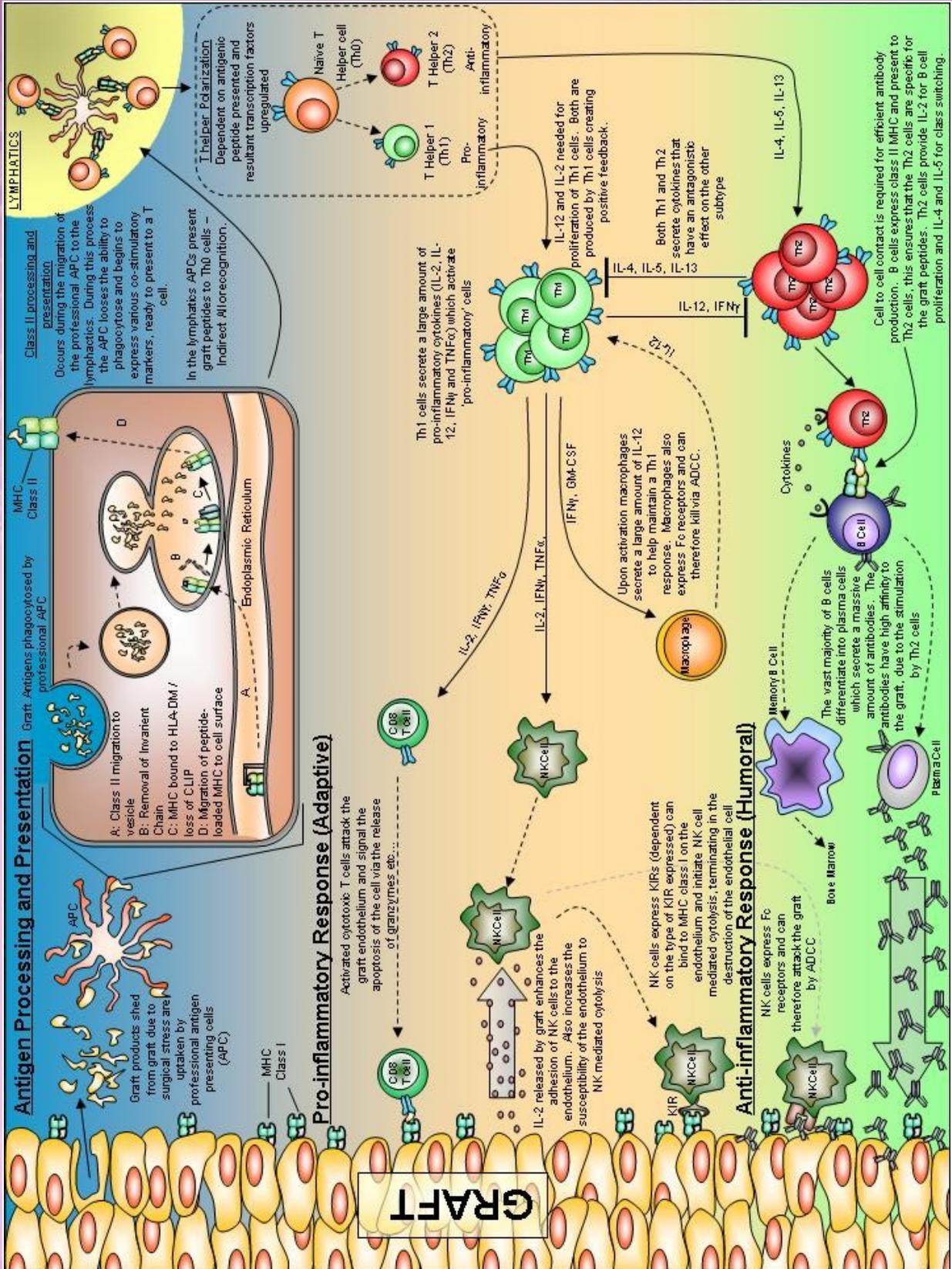


Figure 1. Summary of transplant rejection mechanisms