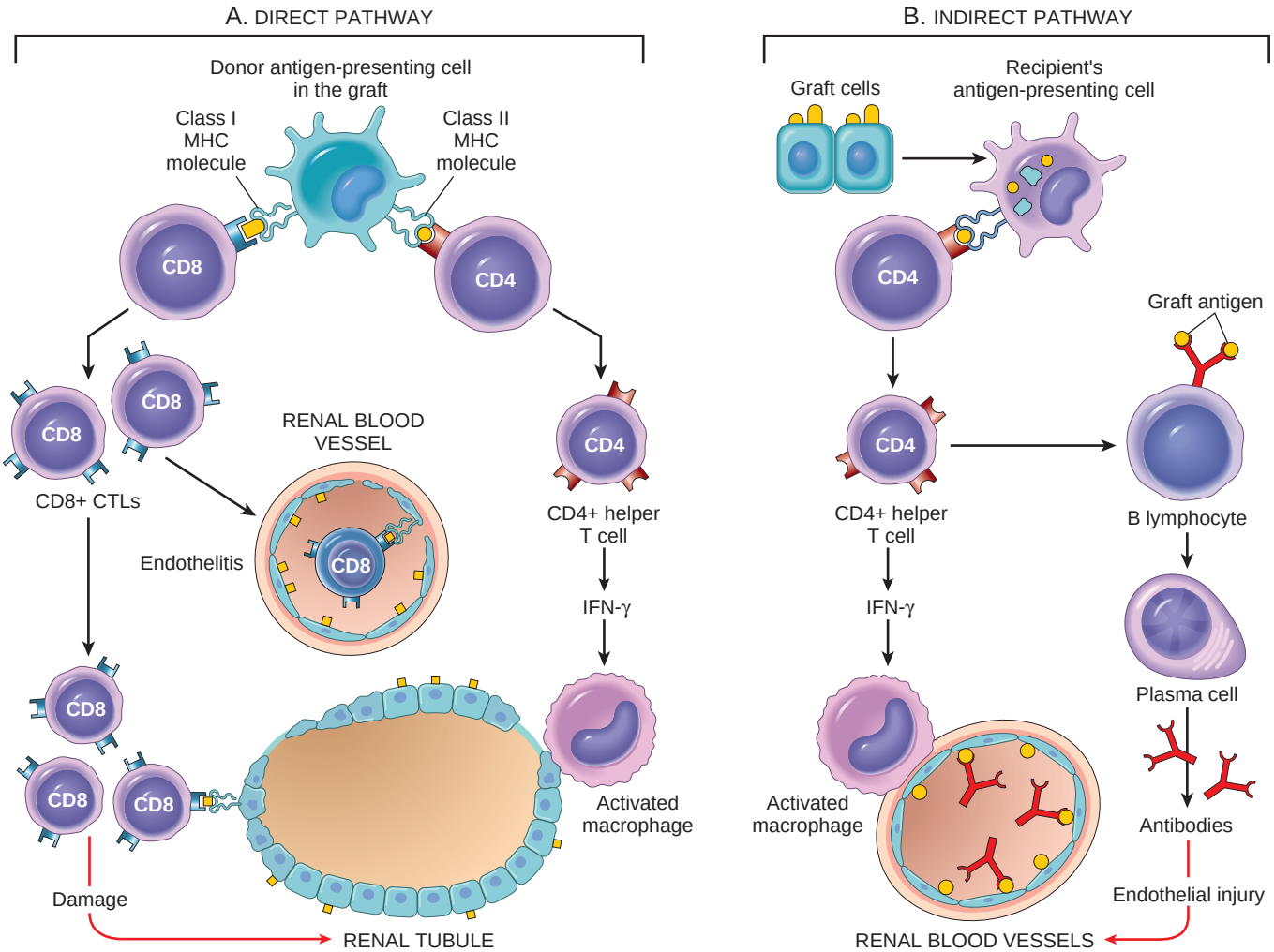

Figure 6-32 Recognition of alloantigens in organ grafts. **A,** In the direct pathway, donor class I and class II MHC antigens on antigen-presenting cells in the graft (along with costimulators, not shown) are recognized by host CD8+ cytotoxic T cells and CD4+ helper T cells, respectively. CD4+ cells proliferate and produce cytokines (e.g., IFN-γ), which induce tissue damage by a local inflammatory reaction. CD8+ T cells responding to graft antigens differentiate into CTLs that kill graft cells. **B,** In the indirect pathway graft antigens are picked up, processed, and displayed by host APCs and activate CD4+ T cells, which damage the graft by an inflammatory reaction and stimulate B lymphocytes to produce antibodies. An example of the reaction to kidney allografts is shown, but the same principles are applicable to all solid organ grafts.

antigens, or alloantigens) by two pathways, called *direct* and *indirect* (Fig. 6-32).

- **Direct pathway of allorecognition.** In the direct pathway, T cells of the transplant recipient recognize allogeneic (donor) MHC molecules on the surface of APCs in the graft. It is believed that dendritic cells carried in the donor organs are the most important APCs for initiating the antigraft response, because they not only express high levels of class I and II MHC molecules but also are endowed with costimulatory molecules (e.g., B7-1 and B7-2). The T cells of the host encounter the donor dendritic cells either within the grafted organ or after the dendritic cells migrate to the draining lymph nodes. CD8+ T cells recognize class I MHC molecules and differentiate into active CTLs. CD4+ helper T cells recognize allogeneic class II molecules and proliferate and differentiate into T_H1 (and possibly T_H17) effector cells. The 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.
- **Indirect pathway of allorecognition.** In the indirect pathway, 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. Thus, the indirect pathway is similar to the physiologic processing and presentation of other foreign (e.g., microbial) antigens. The indirect pathway generates CD4+ T cells that enter