



Figure 2. Pathogenesis of transplant arteriosclerosis and possible targets of therapeutic intervention (see next page for legend) (fig002jhg).

Figure 2. Pathogenesis of transplant arteriosclerosis and possible targets of therapeutic intervention.

The scheme shows the proposed sequential events before and after solid-organ transplantation that lead to the development of transplant arteriosclerosis (TA) and chronic transplant dysfunction (CTD). Possible targets of therapeutic intervention to prevent transplant arteriosclerosis are indicated (a–e), and are discussed in more detail in the section entitled ‘Possible targets for TA prevention and treatment’. Before transplantation and during the transplant procedure, graft endothelial cells (ECs) become activated and damaged as a result of alloantigen-independent factors such as donor brain death, ischaemia and reperfusion of the graft. Most of the damage, however, is inflicted after transplantation and the most important contributor in this process is the alloreactive response, which might be enhanced by cytomegalovirus (CMV) infections. Abolishing the alloreactive response by either use of improved immunosuppressive agents or the induction of transplant tolerance (a) are feasible strategies to reduce vascular damage in the graft, thereby preventing or slowing down the process of TA development. Additional treatment of acute CMV infections (b) might further reduce vascular damage. Damage of the graft EC lining might result in replacement of graft ECs with host-derived ECs, which most probably originate from a pool of non-bone-marrow (non-BM)-derived circulating endothelial cells (CECs). Whether or not graft endothelium will be replaced depends on the severity of vascular rejection (i.e. EC damage). EC replacement with host-derived ECs is an indicator for severe vascular damage but is not a prerequisite for the subsequent development of TA per se. In addition to EC damage, the medial vascular smooth muscle (VSM) cells are also damaged as a result of the alloreactive inflammatory response. Inflammatory cytokines and growth factors induce medial VSM cell apoptosis, resulting in disappearance of the medial VSM cells. Recruitment of host-derived VSM cells (primarily non-BM origin) occurs in an attempt to restore vascular wall function. However, neointimal VSM cells proliferate in an uncontrolled fashion, resulting in the development of TA and eventually CTD. Since medial VSM cell apoptosis appears to be an important event in initiating the recruitment of neointimal VSM cells, prevention of medial VSM cell apoptosis might be a possible target for therapeutic intervention (c). Uncontrolled proliferation of neointimal VSM cells is the main cause of luminal occlusion. Inhibition of the proliferative capacity of VSM cells by intervention strategies might result in decreasing the rate of TA development (d). The recruitment and proliferative capacity of neointimal VSM cells seems to be controlled by genetic factors, suggesting the existence of genetic predisposition for the development of TA and CTD. Identification of the gene products involved will be essential both in tracing patients who are at risk (genetically predisposed) to develop TA rapidly, as well as in developing new strategies to prevent or treat TA (e) (**fig002jhg**).