Humanizing the Problem of Transplant Vasculopathy

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A frequent problem in transplantation is allograft survival, which can be exacerbated by nonimmune mechanisms in response to perioperative injury of the blood vessels. In addition to inflammatory responses, nonimmune mechanisms may also contribute to the development of graft arteriosclerosis (GA), found frequently in cardiac allografts. GA of the coronary arteries, or cardiac allograft vasculopathy, is characterized by expansion of the intima and inadequate outward remodeling of the arteries of the graft. Similar pathology is also observed in other solid organ graft types, such as renal allografts. It is unclear whether this type of GA is a direct response of the vasculature to injury, including rejection and perioperative injury, or whether it is an indirect response to injury that changes the way the immune system interacts with the graft.

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Immune-mediated chronic graft rejection requires a strong adaptive immune response to foreign antigens (termed alloantigens) expressed by the graft. Such immune responses can be mediated by memory T lymphocytes, which are frequently found in the circulation of human adults. Consistent with this, the frequency of circulating memory T lymphocytes correlates with the frequency and severity of rejection. Furthermore, T lymphocytes have been found surrounding the adventitia of the vessels in specimens of cardiac allograft with GA. This “circumstantial” evidence suggests that T lymphocytes are involved in the process of arterial narrowing observed in GA.

Current mouse models of graft rejection have shed some light on the role of perioperative injury in accelerating T-cell–mediated rejection. However, rodent models of graft rejection may not accurately reflect the pathogenesis of the human process, as several important immune differences have been reported. These differences include the timing and enzymes involved in the response to ischemic/reperfusion (IR) injury that occurs in vessels, immune composition of the artery wall, and ability of the endothelial cells to induce proliferation and cytokine secretion by resting memory T cells.

In this issue Yi et al demonstrate that nonimmune injury leads to alterations in the T-cell response to the graft using a humanized mouse system. In order to develop a model to study the effects of perioperative injury in human allograft rejection, the authors modified a transplant model they previously described, where a human artery segment is used to replace the infrarenal aorta of severe combined immuno-deficient mice (SCID). SCID mice have a loss-of-function mutation in the protein kinase, DNA activated, catalytic polypeptide gene and lack the ability to recombine the variable, diversity, and joining segments of the T-cell receptor and immunoglobulin genes. Because B and T lymphocytes are unable to mature in a SCID background, these mice have significantly reduced ability to reject allografts and xenografts and thus easily tolerate and support the transplant of human tissues.

In the current study, Yi et al exploit this feature of SCID mice by transplanting coronary vessels from the hearts of patients receiving a cardiac transplant or epigastric vessels from cadaver organ donors to immunodeficient mice (see Figure A). Following a 30-day equilibration period, vessels are then harvested along with a 1 to 2 mm cuff of mouse aorta at both ends. To induce IR injury, these grafts were then cultured ex vivo at room temperature for 3 hours prior to retransplantation either in room air or in a hypoxic chamber (to mimic conditions likely associated with organ handling during retransplantation). In contrast to grafts immediately retransplanted, exposure of the graft to hypoxic conditions prior to retransplantation resulted in neutrophil infiltration and elevated interleukin-6 transcripts, along with some focal disruption of the endothelium and mitochondrial swelling in graft endothelial and smooth muscle cells, consistent with IR injury as it is manifested in humans.

Having established a good model for human IR injury of the graft, the authors examined the effects of IR injury in graft rejection (Figure B). In the absence of functional lymphocytes, IR injury of human grafts followed by retransplantation into SCID mice for 21 days did not reveal significant signs of rejection. Thus, to assess the effect of nonimmune injury in the T-cell–mediated allogeneic response to the human graft, the investigators retransplanted the graft into SCID hosts that had previously received human peripheral blood mononuclear cells. Ex vivo exposure of the human graft to hypoxic conditions prior to retransplantation into mice with peripheral blood mononuclear cells, resulted in a significant increase in intimal expansion and vascular smooth muscle cells within the intima. However, hypoxia did not significantly affect T-cell infiltration or cytokine levels, indicating that perioperative injury caused allogeneic T-cell–mediated intimal expansion without affecting the nature or intensity of inflammation. Importantly, intimal expansion in response to perioperative injury was shown to be T-cell–mediated, as transfer of purified T-cell populations from peripheral blood mononuclear cells showed the same effect as whole periph-
Injury in different contexts. In summary, this model should provide insight into the mechanisms mediating vascular autoimmunity. Moreover, the humanized model allows for manipulation of the vascular environment using biochemical interventions, such as neutralizing antibodies, enzymatic inhibitors, or diet that should occur simultaneously.

The development of this innovative model provides a powerful system to study the in vivo dynamics of both innate and adaptive immune infiltration not only in the context of transplantation, but also in the context of other immune-mediated vasculopathies, such as atherosclerosis and autoimmune-mediated vascular injury. In addition to this, the humanized model allows for manipulation of the vascular environment using biochemical interventions, such as neutralizing antibodies, enzymatic inhibitors, or diet that should provide insight into the mechanisms mediating vascular injury in different contexts. In summary, this model should provide more precise and exciting information on the pathogenesis of human vascular disease, especially in those instances where mouse and human physiology differ significantly.

Disclosures

None.

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