Lung transplantation research: impact of a new surgical model

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Experimental lung transplantation in mice has been deemed ‘infeasible’ for many years and has been cracked technically only a few years ago by some extraordinarily dedicated researchers. Okazaki and colleagues published the first experimental report based on a series of successful murine left lung transplants in 2007 [1, 2]. While other animal models may more closely resemble the human setting, mouse models have huge advantages when it comes to the study of mechanistic questions on the molecular level. Gene knockout mice have revolutionized whole areas of medical and basic science research and are of no lesser value in transplantation research. Above that, reagents needed for in vivo treatment, such as depleting antibodies, proteins or peptides, are easily available is sufficient quantities for mice, but not necessarily for larger animals. The murine heterotopic (non-vascularized) trachea transplantation model was used as an approximation to experimental lung transplantation in mice resembling bronchiolitis obliterans [3], but remains a contraption with severe methodological shortcomings. With the advent of orthotopic mouse lung transplantation, this field of transplantation surgery is now accessible to the modern tools of mechanistic life sciences, and the study by Jungraithmayr et al. [4] in this issue is a good example of this recent development.

CD26, also called dipeptidyl peptidase-4 (DPP4) is a protein expressed on many cell types including lymphocytes and lung parenchyma. It is a membrane glycoprotein with a cell surface epitope acting as an antigen detectable by the respective monoclonal antibodies. Its function is the enzymatic cleavage of certain dipeptides from polypeptides such as growth factors, chemokines and neuropeptides. This degradation inactivates the respective polypeptides. Apparently, CD26/DPP4 cleaves a number of cytokines and other chemokines, such as SDF-1, together with its receptor CXCR4, important in the modulation of stem cell homing in response to ischaemic injury of the lung. In their experimental setting, they make use of CD26/DPP4 knockout mice, of in vivo inhibition of CD26/dipeptidyl peptidase IV activity in vivo prolongs cardiac allograft survival in rat recipients. Transplantation 1997;63: 1495-500.


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The main findings of the study are: 2 days after transplantation, lung isografts from mice undergoing CD26/DPP4 inhibition by vildagliptin showed lesser signs of ischaemia-reperfusion injury in histological samples when compared with untreated control grafts. CD26/DPP4 inhibition in experimental animals abrogated SDF-1 degradation, leading to elevated SDF-1 concentrations in plasma and lung grafts. This was adjoined by a concomitant increase in expression of the SDF-1 receptor CXCR4 on leukocytes in peripheral blood and in lung grafts. Together with CXCR4, important for homing of haematopoietic stem cells, T cells and other CD45+ leukocytes, CD34, the regenerative progenitor marker Flt-3 or the regenerative stem cell marker c-kit (CD117) were coexpressed in transplanted lung tissue harvested 2 days following surgery from CD26/DPP4-inhibited mice. The authors conclude that targeting the SDF-1/CXCR4 axis by CD26/DPP4 inhibition improves recovery from ischaemia reperfusion injury. Further, they state that this intervention ‘may be a promising strategy to intensify sequestration of regenerative stem cells and thus emerges as a novel therapeutic concept’.

There are two obvious criticisms. SDF-1 is only one among many, known and unknown, substrates of CD26/DPP4 and improved recovery from ischaemia-reperfusion injury through enhanced regenerative stem cell engrafting in lung transplants is only one among many biological effects of SDF-1. There could be many other, potentially detrimental, effects of SDF-1 overexpression. To name only one example, increased homing of effector leukocytes including T cells to the graft through SDF-1/CXCR4 interaction could have the result of aggravated rejection. Additional transplant experiments with longer follow-up, including isogeneic but also allogeneic strain combinations, are necessary in the future to further validate this approach in the setting of lung ischaemia-reperfusion injury after transplantation.

Taken together, this study showcases the exciting possibilities resulting from merging a new surgical animal model, i.e. murine orthotopic lung transplantation, with the established field of mechanistic molecular science in mice. It would be my prediction that we have yet only seen a very small fraction of the exiting experimental results to come from murine orthotopic lung transplantation models in future. Entire fields of lung transplantation research await thorough application of this new model, not only ischaemia-reperfusion injury, but also chronic rejection (bronchiolitis obliterans syndrome) or the induction of donor-specific tolerance.

REFERENCES