Lung transplantation research: impact of a new surgical model

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Received 7 November 2011; accepted 8 November 2011

Keywords: Lung transplantation · Ischemia reperfusion injury · CXCR4 · CD26/DPP4 · SDF-1

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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 wide variety of substrates, interfering with many biological pathways including, for example, glucose metabolism and suppression of cancer development. Stromal cell-derived factor 1 (SDF-1, also called CXCL12) is a substrate of CD26/DPP4. The study by Jungraithmayr et al. [4] in this issue is a good example of this recent development.

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The main findings of the study are: 2 days after transplantation, lung isografts from mice undergoing CD26/DPP4 inhibition by vil dagliptin 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 leucocytes 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