Molecular mechanisms behind the liver-induced acceptance of renal grafts in highly sensitized patients

Akademisk avhandling

Som för avläggande av medicine doktorsexamen vid Sahlgrenska akademin vid Göteborgs universitet kommer att offentligen försvaras i hörsal Arvid Carlsson, Medicinaregatan 3, Göteborg
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av Madeleine Ingelsten

Fakultetsopponent: Dr Gunnar Tufveson, Adj. Prof. Uppsala Universitet, Uppsala

Avhandlingen baseras på följande delarbeten:

I. Post-ischemic inflammatory response in an auxiliary liver graft protects against renal graft rejection in highly sensitized patients
Ingelsten M, Karlsson-Parra A, Björnson Granqvist A, Olausson M, Haraldsson B and Nyström J.
Submitted

II. Is indoleamine 2,3-dioxygenase important for graft acceptance in highly sensitized patients after combined auxiliary liver-kidney transplantation?
Ingelsten M, Gustafsson K, Oltean M, Karlsson-Parra A, Olausson M, Haraldsson B and Nyström J.
Transplantation, 2009. 88:911-919.

III. Recruitment and activation of natural killer cells in vitro by a human dendritic cell vaccine
Gustafsson K, Ingelsten M, Bergqvist L, Nyström J, Andersson A and Karlsson-Parra A.
Cancer Research, 2008. 68(14):5965-71.

IV. Rapid increase of IL-10 plasma levels after combined auxiliary liver-kidney transplantation
Ingelsten M, Gustafsson K, Olausson M, Haraldsson B, Nyström J and Karlsson-Parra A.
Manuscript

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Molecular mechanisms behind the liver-induced acceptance of renal grafts in highly sensitized patients

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Abstract

Preformed antibodies directed at donor HLA are considered an absolute contraindication for kidney transplantation, because of the high risk of rejection. Thus, patients with high levels of HLA antibodies have little chance of receiving a kidney transplant. Recently it was demonstrated that an auxiliary liver graft from the same donor may protect a subsequently grafted kidney from these harmful antibodies. The aim of this thesis was to elucidate the mechanisms behind the kidney protection afforded by the auxiliary liver graft in highly sensitized patients. We focused on the activation of dendritic cells, because these cells, which reside in all peripheral tissues, play a key role in the initiation of an immune response.

This thesis demonstrates that gene expression in the liver graft correlates with clinical outcome: In patients without an acute rejection episode, 14 out of 45 investigated immunological genes were significantly higher expressed in the liver graft 4h after reperfusion, compared with patients that experienced an acute rejection episode within the first month. This indicates that high- and low-risk patients can be identified within hours after transplantation.

One gene of particular interest was indoleamine 2,3-dioxygenase (IDO), which is a tolerance-inducing enzyme previously found to play a key role in maintenance of semi-allogeneic pregnancy in mice. In our study, mRNA levels of IDO were strongly upregulated in patients after combined auxiliary liver-kidney transplantation and IDO expression in the liver graft correlated with clinical outcome. Furthermore, IDO activity was higher in patients after combined auxiliary liver-kidney transplantation and liver transplantation compared with patients undergoing kidney transplantation. Strongly increased serum levels of the anti-inflammatory cytokine interleukin (IL) 10 were also found after liver but not kidney transplantation. IL-10 has several immune inhibitory effects on dendritic cells. We found that IL-10 inhibited the production of chemokines MIG, IP-10 and I-TAC in monocyte-derived dendritic cells in vitro. When comparing different cytokine cocktails for dendritic cell maturation, we showed that MIG, IP-10 and I-TAC were essential for dendritic cell-mediated recruitment of natural killer (NK) cells. This is considered important for the initiation of a type 1 T helper cell response. We also showed that IL-10 treated dendritic cells, which expressed less of these chemokines, had reduced potential to activate NK cells.

Thus, the liver provides IDO and IL-10, both of which have the ability to reduce the immunostimulatory ability of dendritic cells, giving them a tolerance-promoting profile. We therefore suggest that the protective effect of an auxiliary liver in presensitized patients may, at least in part, be mediated by the liver-specific expression of IDO and IL-10.

Keywords: kidney transplantation, liver tolerance, HLA antibodies, dendritic cells, indoleamine 2,3-dioxygenase, IL-10, natural killer cells

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