



GÖTEBORGS UNIVERSITET

The Clinical Importance Of Anti-Endothelial Cell Antibodies In Chronic Kidney Dysfunction And Organ Transplantation

Akademisk avhandling

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av

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Avhandlingen baseras på följande delarbeten:

I. Hernandez NM, Casselbrant A, Joshi M, Johansson BR, Sumitran-Holgersson S. Antibodies to kidney endothelial cells contribute to a "leaky" glomerular barrier in patients with chronic kidney diseases. *Am J Physiol Renal Physiol*, 2011 Dec; 302(7):F884-894.

II. Sigurdardottir V, Kolsrud O, **Hernandez N**, Dellgren G. Endothelial cell antibody-mediated rejection and successful retransplantation in a heart transplanted patient. *Eur J Cardiothorac Surg*, May 2012; 42(6):1044-1046.

III. Hernandez NM, Niiniskorpi T, Torén B, Sumitran-Holgersson S, Sigurdardottir V. A significant role for non-HLA donor-specific anti-endothelial cell antibodies in heart allograft rejections. 2013 (Manuscript).

IV. Olausson M, Patil PB, Kuna VK, Chougule P, **Hernandez N**, Methe K, Kullberg-Lindh C, Borg H, Ejnell H and Holgersson-Sumitran S. Transplantation of an allogeneic vein bioengineered with autologous stem cells: a proof-of-concept study. *Lancet*, Jun 2012; 380(9838):230-237.

The clinical importance of anti-endothelial cell antibodies in chronic kidney dysfunction and organ transplantation

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ABSTRACT

The endothelium is the thin layer of cells that lines the interior surface of blood vessels and is the first site of contact between immune cells and tissues. Therefore, alterations at the level of the endothelium are crucial to understand the nature of vascular diseases and organ damage. The presence of anti-endothelial cell antibodies (AECAs) has been associated with such conditions. However, their immunomodulatory and clinical relevance is unclear.

This work focused on two clinical groups, patients with chronic kidney disease and heart- and vein-transplanted patients. In chronic kidney disease patients, some biological mechanisms by which AECAs may affect the kidney microvascular permeability were explored. In transplanted patients, special emphasis on the clinical contribution of these antibodies to monitor graft outcome pre- and post-transplantation was analyzed. Detection of AECAs using different tissue endothelial cells as targets and experimental *in vitro* assays were utilized to evaluate immune interactions of AECAs.

In patients with end-stage renal disease, AECAs were specifically reactive with kidney endothelial cells. *In vitro*, these antibodies decreased the expression of intercellular junction assembly proteins altering endothelial permeability. In heart-transplanted patients, the presence of autologous AECAs post-transplantation was associated with the presence of donor-specific AECAs and early rejection episodes. In the context of a first case report of a bioengineered transplanted vein, AECAs appeared after nearly a year post-transplantation.

In summary, AECAs in patients with chronic kidney diseases may be novel biomarkers of kidney endothelial dysfunction, and may be used as indicators of renal diseases. Additionally, AECAs have important implications in organ transplantation regarding the development of techniques for improved donor organ selection and monitoring of recipients. Results may also be extended to new approaches in tissue engineering.

Keywords: endothelial cells, AECAs, CKD, organ rejection, tissue engineering