Genetics of hemolytic uremic syndrome

STELLINGEN

behorende bij het proefschrift

Genetics of the Hemolytic Uremic Syndrome

Marina Noris

Chronic activation of the alternative pathway of complement occurs in most patients with familial HUS, as documented by lower than normal complement C3 serum levels and normal levels of C4. Low C3 levels are associated with high risk of developing HUS within affected families and in the overall study population. In familial HUS, reduction of complement C3 correlates with abnormalities in complement factor H (CFH).

(This thesis)

One third of patients with non-Stx-HUS carry mutations in *CFH*. The C-terminus part of CFH is a hot spot for mutations in this disease. Common polymorphisms of *CFH* contribute to non-Stx-HUS manifestation in subjects with and without *CFH* mutations. Mutations in the gene encoding membrane cofactor protein (MCP) are found in around 10% of patients with non-Stx-HUS.

(This thesis)

CFH gene mutations have a role in determining renal complications in patients with thrombotic microangiopathy caused by deficiency of the von-Willebrand factor-cleaving protease ADAMTS13.

(This thesis)

Impaired restriction of complement deposition on glomerular endothelial cells in response to complement-activating stimuli, as a consequence of CFH and MCP defects, is a critical step leading to microvascular cell damage and tissue injury in the kidney.

(This thesis)

In patients with end stage renal failure caused by non-Stx-HUS who receive a kidney transplant the outcome of the graft is influenced by the specific genetic defect. *CFH* mutations are associated with a very high frequency of relapses on the graft. Patients with MCP mutation have a favorable graft outcome.

(This thesis)

The activity of ADAMTS13, a specific plasma metalloprotease that degrades large von Willebrand factor multimers to smaller sizes, is decreased in patients with TTP. ADAMTS13 deficiency may be constitutive, due to homozygous or

compound heterozygous mutations in the encoding gene located on chromosome 9q34, or acquired, due to the presence of circulating inhibitory antibodies.

(G.G. Levy et al, 2001)

In patients with TTP and ADAMTS13 deficiency platelet microthrombi cause the activation of complement. This phenomenon initiates a cascade of events, including complement deposition on microvascular endothelium and neutrophil recruitment and activation, that culminates in microvascular endothelial damage and loss of thromboresistance, so that microvascular thrombi continue to grow, causing tissue ischemia and infarction.

(M.P.. Ruiz-Torres et al, 2005)

Suppression by regulatory T cells has emerged as an essential tool by which the immune system can actively silence self-reactive T cells and turn off activated T cells, thus controlling immune responses to self-antigens and maintaining immune homeostasis. Regulatory T cells can also be induced by tolerance protocols and play a key role in preventing allograft rejection, as demonstrated in many animal models.

A single pre-transplant intravenous infusion of donor peripheral blood mononuclear cells into recipient rats promotes donor-specific tolerance of a subsequent kidney allograft from MHC-incompatible rats. $CD4^{+}CD25^{+}$ T regulatory cells are found in lymph nodes and in the grafts from long-term surviving rats tolerized by this procedure.

(R.A. Cavinato et al, 2005)

"Scienza è che la vita media dell'uomo è passata da 35 anni (nel medioevo) a quasi 80 (oggi), che certe malattie infettive (il vaiolo per esempio) sono scomparse, che malattie terribili come la tubercolosi oggi non fanno più paura. Scienza è l'anestesia e gli psicofarmaci. Scienza è essere stati capaci di trapiantare organi e consentire che la morte di qualcuno significhi per altri, gravemente ammalati, continuare a vivere. Scienza è che presto costruiremo organi in laboratorio (si fa già con le arterie e le vene o con al pelle). Scienza è tutto questo ed altro ancora. Cose che hanno cambiato profondamente la vita dell'uomo."

(Giuseppe Remuzzi, 2005)

"The success of science requires individual talent, but it is driven by personal values. Prominent among these values is honesty. Scientists depend on the truthfulness of their colleagues. Each of us builds our discoveries on the work of others. If that work is false, our constructions fall like a house of cards and we must start all over again"

(J. Michael Bishop, 2003)

Maastricht, 16 march 2006