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17

Immune Gene Polymorphisms Associate with Outcome in Kidney Transplantation

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1. Introduction

A short cold ischemic time, an optimal HLA match and other pre-transplant factors are in a key role in the success of kidney transplantation. Over the past decades, the acute rejection rate of kidney transplants has fallen dramatically and the 1-year graft survival rate has increased to 90% in transplantations with deceased donors and 95% with living related donors. This increase in graft survival is largely due to advances in immunosuppressant medication (Yates & Nicholson, 2006). But, due to undesired side effects usually associated with immunosuppressive regimens, reduced immunosuppression is warranted whenever possible.

Acute rejection has been the most common end point of genetic association studies. This is natural as acute rejection predicts decreased long-term allograft survival. Despite progress in immunosuppression, the long-term graft survival has not increased in patients suffering acute rejection episodes (Meier-Kriesche et al., 2004). In many genetic studies, chronic allograft nephropathy and subsequent graft loss have been the endpoints with which genetic variation has been compared.

1.1 Genetic polymorphisms affect on outcome of kidney transplantation

Although *human leukocyte antigen* (*HLA*) genes are the major genetic factors in the immunological acceptance of the graft, also other, non-*HLA* gene variants may predict outcome of kidney transplantation. Identification of genetic factors determining, for example, the strength of immunological response against the graft, or metabolism or side effects of drugs, could lead to more accurate risk assessments or more tailored immunosupressive regimens for patients.

1.1.1 Immune genes are interesting candidates

Immune genes, i.e. the genes encoding for molecules regulating or affecting immune responses, are involved in the etiopathology of autoimmune diseases and probably also in the outcome of organ transplantation. Polymorphisms in immune genes may induce functional or quantitative differences in immune responsiveness between patients, resulting in for example high and low cytokine producers. Single nucleotide polymorphisms (SNPs) can have an effect on gene expression, not only the SNPs located in exons, possibly changing amino acids, or in promoter regions, possibly changing the crucial regulatory sequences, but also polymorphisms in introns have been shown to be of importance in genetic susceptibility studies. Thus,

although functional variants are the most relevant to study, all polymorphisms are potentially interesting. Immune genes encode, for example, cytokines, chemokines, growth factors and T cell co-activation molecules.

1.1.2 Cytokines are major regulators of the immune response

Most genetic association studies in kidney transplantation have focussed on the genes encoding cytokines. Variations in the cytokine genes may lead to differences in the levels of their production or signalling, which in turn may modulate the strength of the immune response. Thus, they are potential candidate genes related to organ transplantation as they may predict the overall immunological responsiveness of the patient toward the graft.
Cytokines can be classified on the basis of their function to the pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)1β, interferon (IFN) γ, IL6, IL12, IL17 and IL18, and to the anti-inflammatory cytokines, including IL4, IL10, IL13, IFNα and transforming growth factor (TGF) β. However, it is of note that the effect of any single cytokine may depend on the exact environment it is acting in. The balance between pro- and anti-inflammatory cytokines partially determines the level or strength of the immune response (Dinarello, 1997). Below, we present a few examples from the wide variety of cytokines.

1.1.2.1 Tumor necrosis factor

Perhaps the most actively studied cytokine in genetic studies is the tumor necrosis factor (TNF), which has multiple roles in innate immunity, apoptosis and metabolism. TNF stimulates neutrophil and macrophage function and is a key mediator of inflammation. Production of TNF leads to massive inflammatory reactions in response to several immunological challenges (Hehlgans & Pfeffer, 2005). TNF and its receptors could be useful biomarkers for organ rejection, as TNF is not detectable in healthy individuals, but elevated serum levels are found in kidney transplant recipients (Maury & Teppo, 1987).
The *TNF* gene is located on chromosome 6 in the *HLA* class III region and is in linkage disequilibrium with classical *HLA* genes (Low et al., 2002). The -308G>A promoter variant of the *TNF* gene influences the expression of the TNF protein (Abraham & Kroeger, 1999).

1.1.2.2 Transforming growth factor β 1

Mammals have three isoforms of transforming growth factor β (TGFβ-1, TGFβ-2 and TGFβ-3) (Derynck et al., 1985). TGFβ-1 is the most abundant and most studied of the isoforms. It is a strong anti-inflammatory cytokine that regulates proliferation, apoptosis and differentiation of many cell types. TGFβ-1 affects T cell survival and Th differentiation for example regulating the development of effector cells and induction of Treg cells (Rubtsov & Rudensky, 2007). TGFβ-1 activates a profibrotic process and its increased expression has been associated with chronic rejection (Campistol et al., 2001).
The *TGFB1* gene lies on the chromosome region 19q13.2 and encodes a protein of 390 amino acids. A few polymorphisms have been identified in the gene and three of them (Leu10Pro, Arg25Pro and Thr263Ile) change an amino acid.

1.1.2.3 Interleukin 10

Interleukin 10 (IL10) promotes the Th2-type immune response and B-cell mediated functions leading to antibody production. Besides, it inhibits the Th1-type immune response by suppressing the expression of proinflammatory cytokines, hence being anti-inflammatory. IL10 also inhibits antigen presenting cells by downregulating the expression of HLA class II molecules (Ding et al., 1993).

The *IL10* gene, located in 1q32.2, is 4892 bases long and encodes a protein of 178 amino acids. There are several polymorphisms in the promoter region of *IL10*; they are in strong linkage disequilibrium (Turner et al., 1997) and thus, form haplotypes (Lin et al., 2003).

1.1.2.4 Interferon γ

IFNγ is a proinflammatory cytokine produced by activated T cells. IFNγ has several roles in the immune response: it activates macrophages, mediates the lytic effect, potentiates the actions of other interferons and it also inhibits intracellular microorganisms other than viruses (Dianzani & Baron, 1996). IFNγ acts both as an anti-rejection and pro-rejection cytokine, e.g. by inducing microvascularisation in the grafted organ and up-regulating the expression of HLA molecules. The predominant effect mainly depends on the secretion time after transplantation, being protective early on and then later becoming antagonistic (Hidalgo & Halloran, 2002).
The *IFNG* gene lies in 12q15 and encodes a protein of 166 amino acids. The most studied *IFNG* polymorphisms are the SNP +874T>A in the intron 1 and the short tandem repeat CA (rs3138557). These have been associated with acute rejection and chronic allograft nephropathy.

1.1.3 Co-stimulatory receptors mediate T cell activation

Besides cytokine genes, another interesting gene group is those coding for T cell co-stimulatory receptors. Co-stimulatory signals are essential for the activation of naïve T cells and productive immune response. For activation, naïve T cells must receive an antigen-specific signal through the T cell receptor and additionally a signal by co-stimulatory receptors. Without the co-stimulatory signal the T cell turns anergic. In addition, the co-stimulatory signal can be negative, that is, inhibitory after the initial activation. The fine balance between the positive and negative signals determines the outcome of an immune response.

1.1.3.1 CD28 is an essential co-stimulator

The CD28 pathway is crucial for T cell activation; signalling through CD28 increases cytokine production in T cells, by enhancing transcriptional activity and stabilizing messenger RNA (Thompson et al., 1989). CD28 ligation also reduces the number of engaged TCRs that are needed for proliferation or effective cytokine production, thereby lowering the threshold for T cell activation (Viola & Lanzavecchia, 1996). CD28 is expressed constitutively on T cells and it binds to ligands B7-1 (CD80) and B7-2 (CD86) found primarily on antigen presenting cells. These ligands have distinct but overlapping functions; B7-2 may mediate initial T cell activation, while B7-1 may be more important for maintaining the immune response (Vincenti & Luggen, 2007). Antigen specific signal without CD28 mediated signal turns T cells anergic.
Located on chromosome 2q33, the *CD28* gene was identified in the late 1980s (Aruffo & Seed, 1987). The gene contains one microsatellite and at least 50 SNPs, which, however but they are not associated with organ transplantation.

1.1.3.2 CTLA4 has an inhibitory function

Cytotoxic T lymphocyte associated antigen 4 (CTLA4) mediates a critical inhibitory signal for T cell activation. CTLA4 binds with higher affinity, to the same B7 ligands as CD28. It is induced on T cells after their activation, and functions in the downregulation of T cell

activation; CTLA4 ligation raises the activation threshold for T cells. CTLA4 decreases interleukin 2 (IL2) and IL2 receptor expression and arrests T cells at the G1 phase of the cell cycle (Vincenti & Luggen, 2007). The CTLA4 pathway may have an important role in peripheral T cell tolerance (Yamada et al., 2002). Principal evidence for an inhibitory function of CTLA4 was obtained from CTLA4 knockout mice. These CTLA4 deficient (CTLA4-/-) mice develop a fatal lymphoproliferative disorder with multiorgan autoimmune disease (Tivol et al., 1995; Waterhouse et al., 1995).

CTLA4 is located adjacent to *CD28*. *CTLA4* includes one microsatellite and four SNPs, of which +49A/G is in a coding region and leads to a change of amino acid (Ala-Thr). Genetic variation in *CTLA4* is associated with several autoimmune diseases including coeliac disease, type 1 diabetes, autoimmune hypothyroidism and Grave's disease (Duffy, 2007).

1.1.3.3 ICOS induces cytokine expression

Inducible co-stimulator (ICOS) plays a critical, independent role in T cell activation, in a manner that is synergistic with CD28 signalling. ICOS augments effector T cell cytokine responses; in particular, it appears to superinduce production of the anti-inflammatory cytokine IL10 (Hutloff et al., 1999). ICOS expression is enhanced on activated T cells by CD28 co-stimulation (Beier et al., 2000). ICOS binds B7 related protein 1, (B7RP-1) which is expressed constitutively by B cells and macrophages (Yoshinaga et al., 1999) but can also be induced on non-lymphoid cells by inflammatory stimuli (Swallow et al., 1999). ICOS knockout mice have reduced CD4+ T cell responses (Dong et al., 2001) as well as defects in immunoglobulin (Ig) class switching (McAdam et al., 2001).

ICOS is located in very close proximity to *CD28* and *CTLA4* on the 2q33 region (Hutloff et al., 1999). The remarkable homology (over 20 %) between the costimulatory receptor genes (Harper et al., 1991; Ling et al., 1999) strongly suggests that the genes belong to the same gene family, which is the result of gene duplications. *ICOS* contains two microsatellites in intron 4 and over 30 SNPs, but so far it has been included in only one genetic association study on solid organ transplantation.

1.1.3.4 Therapeutic potential of co-stimulatory receptors

Blockade of the CD28 co-stimulatory pathway provides a promising therapeutic strategy for transplantation. CTLA4-Ig is a fusion protein which consists of the extracellular binding domain of CTLA4 linked to a modified Fc domain of human antibody IgG. The Fc domain mediates complement activation and interacts with Fc cell surface receptors. The CTLA4 fragment defines the specific targets of the fusion antibody, which are the B7 ligands. It was developed to selectively interrupt full T cell activation by blocking the interaction of CD28 and B7 ligands (Vincenti & Luggen, 2007). The use of CTLA4-Ig is effective in inducing long-term allograft survival in solid organ transplantation in mouse, rat and primate models (Snanoudj et al., 2006). The first clinical trial with CTLA4-Ig in human renal transplantation showed promise although immunosuppressive drug cyclosporine was still more effective in preventing acute rejection (Vincenti, 2005).

The impact of the ICOS co-stimulation pathway on emerging rejection episodes has been demonstrated by anti-ICOS therapy (Özkaynak et al., 2001). Anti-ICOS antibody treatment has also been studied together with anti-CD40L and CTLA4-Ig in animal models of transplantation; the animals displayed fewer signs of chronic rejection (Snanoudj et al., 2006).

2. Accumulated literature of immune gene studies

In this review, we aim to examine all the published association studies of potential candidate genes of cytokines and co-stimulatory receptors. We did a systematic search for literature in the PubMed database (National Library of Medicine, Bethesda, MD, US; www.ncbi.nlm.nih.gov/pubmed). We used search terms renal transplant, renal transplantation, kidney transplant or kidney transplantation and gene*, polymorphism or SNP. Literature addressing genetic association studies related to cytokines and co-stimulatory receptors was selected. Articles not reported in English were excluded; otherwise no limitations were set on the publishing manner.

3. Results

We found 85 original articles which are listed in Tables 1 and 2. Most genetic association studies in kidney transplantation focus on cytokine genes. Despite the number of reported positive associations with cytokine genes, the results are confusing because different studies report differing variants as demonstrating the strongest association. All the genetic associations are listed in the Tables 1 and 2 as they have been published although most of them are just nominally significant, and only in a few studies, the correction for multiple testing is performed appropriately.

3.1 Cytokine genes associate with poor outcome of kidney transplantation

The *TNF* gene is one of the most frequently studied cytokine genes and variation in this gene has been shown to have functional effects (Wilson et al., 1997). The most interesting -308 variant of the gene has a potential functional effect, being associated with elevated TNF levels (Elahi et al., 2009). One of the first large genetic association studies containing cytokine gene polymorphisms was done by Mytilineos et al (2004). A total of 2,298 first and 1,901 repeat kidney recipients were included in the study involving 73 transplant centres. An association was found between the high TNF producer genotype -308A and lower graft survival (P=0.0116 after Bonferroni correction) in retransplant patients (Mytilineos et al., 2004). Other parameters than graft survival were not analysed due to difficulties in getting standardized clinical variables from different centres in the retrospective study. The *TNF* gene, albeit in organ donors, is also associated with acute rejection (Alakulppi et al., 2004; Lee et al., 2004) and delayed graft function (Israni et al., 2008). In a relatively large study by Israni et al (2008), in addition to 965 kidney recipients, also 512 deceased donors were genotyped. The G allele of TNF +851 in donors was found to be associated with delayed graft function (Israni et al., 2008).

The variants of the *IL10* gene have been reported to be associated with acute rejection either by increasing risk or by being protective, depending on the polymorphism and related genotype. The haplotypes containing the promoter region SNPs -1082A>G, -819C>T and -592C>A have been reported to correlate with IL10 production, leading to high (GCC/GCC), intermediate (GCC/ACC or GCC/ATA) and low producers (ATA/ATA) (Koss et al., 2000). In a meta-analysis, combining the data of 1,087 patients from eight studies, a suggestive association was found between a poor outcome (meaning graft failure, acute or chronic rejection and chronic allograft nephropathy) and the *IL10* haplotype -1082A, -819C, -592C (Thakkinstian et al., 2008). The number of cases was high (approximately 300 depending on genetic variant analysed) but the authors had to accept

compromises while pooling the data, which may be the reason for the insufficient power in statistical tests.

A total of 237 kidney transplantation patients were included in a multicentre study by Grinyo et al (2008), in which associations were found between the *IL10* and *TNF* gene polymorphisms (P=0.024 and 0.03) and acute rejection (Grinyo et al., 2008). The results were not corrected for multiple testing and would not have been statistically significant after correction. A sufficient number of infrequent genotypes and acute rejection episodes could not be found among 237 patients and thus, some of the groups compared were too small to give adequate power for analysis. The same cytokine genes, *IL10* and *TNF*, were reported to associate with cardiovascular disease after renal transplantation in a cohort of 798 of Italian patients (La Manna et al., 2010). On the other hand, a Czech single centre study did not confirm the association with *TNF*, *TGFB1* or *IFNG* although the authors had collected samples of 436 kidney recipients, of whom 122 had chronic allograft nephropathy and 190 had acute rejection (Brabcova et al., 2007).

In a recent study by Israni et al (2010), altogether 2,724 SNPs were genotyped in a total of 990 kidney recipients. They found several SNPs to be associated with acute rejection and its severity, among them a polymorphism in the gene of the cytokine IL15 receptor. An interesting finding to arise from this multicentre study was the significant difference (P<0.0001) in rates of acute rejection (0-30%) between different transplantation centres. The data was stratified by centres, thus associations were not masked by the centre to centre variation. This stratification could also be recommended for other multicentre studies. The authors speculated that the variation between transplantation centres can explain why associations are so difficult to repeat in other patient cohorts from different transplantation centres (Israni et al., 2010).

3.2 Co-stimulator receptor genes may predispose to the poor outcome of transplantation

Two of the genetic variants of *CD28* were included in three different association studies but no association was found (Haimila et al., 2009b; Krichen et al., 2009; Kusztal et al., 2010).

CTLA4 gene polymorphisms have been examined in relation to kidney transplantation in a few studies (Table2). An association with outcome of kidney transplantation was reported in seven genetic studies (Slavcheva et al., 2001; Gendzekhadze et al., 2006; Wisniewski et al., 2006; Gorgi et al., 2006; Kusztal et al., 2007, 2010; Kim et al., 2010). On the other hand, four studies did not succeed in replicating the association with *CTLA4* (Dmitrienko et al., 2005; Haimila et al., 2009b; Krichen et al., 2009, 2010). The SNP CTLA4+49 A/G (rs231775) is the most frequently studied variant and most often found to be associated. For example Kim et al studied 325 Korean renal patients for a haplotype of three *CTLA4* markers and reported an association (P=0.039 after Bonferroni correction) with late acute rejection (Kim et al., 2010). The microsatellite CTLA4(AT)n was included in two studies, both reporting an association (Slavcheva et al., 2001; Kusztal et al., 2010). A high number of AT repeats predisposed to acute rejection (Slavcheva et al., 2001) and decreased long-term allograft function (Kusztal et al., 2010).

Variants of the *ICOS* gene are found to predispose to the delayed graft function and the decreased graft survival in kidney transplantation patients (Haimila et al., 2009b). A total of 678 kidney transplantation patients, all from a single transplantation centre, were genotyped for 13 markers across the whole *CD28-CTLA4-ICOS* gene region. A statistically significant association between the *ICOS* marker rs10932037 and graft survival (P= 0.026) was found, in

addition to an association with delayed functioning or non-functioning, of the graft with the *ICOS* markers rs10183087 and rs4404254 (P=0.020, OR=5.8 and P=0.019, OR=5.8). This is to date the only study to examine the association of the *ICOS* gene in relation to kidney transplantation.

The distance between the genetic markers used and the actual risk factor may be long due to the strong LD in the region (Holopainen & Partanen, 2001). A thorough examination of polymorphisms within the 2q33 region is necessary for the reliable identification of the primary variant. The association analyses of the published co-stimulator gene studies are solely limited to a few markers in the *CTLA4* gene, unfortunately leaving out the neighbouring *ICOS* and *CD28* genes. In our previous study, we examined genetic markers through the entire chromosome region and the results suggested that *ICOS*, rather than *CTLA4*, is the genetic factor affecting the outcome of kidney transplantation (Haimila et al., 2009b).

Gene polymorphism	**dbSNP rs number**	**Citation Association**	**Citation No association**
TNF -308G>A	rs1800629	Sankaran et al., 1999; Pelletier et al., 2000; Poli et al., 2000; Hahn et al., 2001; Reviron et al., 2001; Wramner et al., 2004; Park et al., 2004; Alakulppi et al., 2004; Grinyo et al., 2008; Pawlik et al., 2005; Tinckam et al., 2005; Lacha et al., 2005; Canossi et al., 2007; Coppo et al., 2007; Manchanda et al., 2008; Manchanda & Mittal, 2008; Mendoza-Carrera et al., 2008; Nikolova et al., 2008; Pawlik et al., 2008; Grenda et al., 2009; La Manna et al., 2010; donor: Nikolova et al., 2008	Hutchings et al., 2002; Marshall et al., 2000; Cartwright et al., 2001; George et al., 2001; Muller-Steinhardt et al., 2002; Weimer et al., 2003; McDaniel et al., 2003; Uboldi de Capei et al., 2004; Ligeiro et al., 2004; Dmitrienko et al., 2005; Gendzekhadze et al., 2006; Azarpira et al., 2006; Brabcova et al., 2007; Breulmann et al., 2007; Satoh et al., 2007; Rodrigo et al., 2007; Alakulppi et al., 2008; Azarpira et al., 2009; Kao et al., 2010; Jacobson et al., 2010; Khan et al., 2010; Omrani et al., 2010; Israni et al., 2010; Kocierz et al., 2011; donor: Sankaran et al., 1999; Poole et al., 2001; Marshall et al., 2001; Hoffmann et al., 2004; Alakulppi et al., 2004; Ligeiro et al., 2004; Israni et al., 2008; Manchanda & Mittal; 2008; Mendoza-Carrera et al., 2008; ; Azarpira et al., 2009; Lobashevsky et al., 2009
TNF -238G>A	rs361525		Rodrigo et al., 2007; Satoh et al., 2007; Lobashevsky et al., 2009; Kao et al., 2010; Khan et al., 2010
TNF +123G>A	rs1800610		Israni et al., 2010; Jacobson et al., 2010

Gene polymorphism	dbSNP rs number	Citation Association	Citation No association
TNF +851G>A	rs3093662		Israni et al., 2010; Jacobson et al., 2010; donor: Israni et al., 2008
TNF +3512G>A	rs1800628		donor: Israni et al., 2008
TGFB1 +869T>C and +915C>G	rs1800470, (rs1982073), rs1800471	McDaniel et al., 2003; Alakulppi et al., 2004; Park et al., 2004; Dmitrienko et al., 2005; Tinckam et al., 2005; Lacha et al., 2005; Hueso et al., 2006; Amirzargar et al., 2007; Manchanda et al., 2008; Nikolova et al., 2008; Kocierz et al., 2011; donor: Park et al., 2004; Ligeiro et al., 2004; Hoffmann et al., 2004; Lacha et al., 2005; Canossi et al., 2007; Nikolova et al., 2008	Pelletier et al., 2000; Marshall et al., 2000; Hutchings et al., 2002; Muller-Steinhardt et al., 2002; Ligeiro et al., 2004; Uboldi de Capei et al., 2004; Mytilineos et al., 2004; Gendzekhadze et al., 2006; Brabcova et al., 2007; Coppo et al., 2007; Satoh et al., 2007; Rodrigo et al., 2007; Manchanda & Mittal, 2008; Grinyo et al., 2008; Mendoza-Carrera et al., 2008; Cho et al., 2008; Khan et al., 2010; Jacobson et al., 2010; Israni et al., 2010; Omrani et al., 2010; Lobashevsky et al., 2009; La Manna et al., 2010; Kozak et al., 2011; donor: Poole et al., 2001; Marshall et al., 2001; Alakulppi et al., 2004; Israni et al., 2008; Manchanda & Mittal, 2008; Mendoza-Carrera et al., 2008
TGFB1 exon 5 (713-8delC)	rs8179182	Manchanda et al., 2008	Manchanda & Mittal, 2008; donor: Manchanda & Mittal, 2008
TGFB1 -509C>T	rs1800469		Satoh et al., 2007; Cho et al., 2008; Grenda et al., 2009; Kozak et al., 2011
TGFB1 +11929C>T	rs1800472		donor: Israni et al., 2008
TGFB1 -800G>A	rs1800468		Kozak et al., 2011
IL10 -1082G>A	rs1800896	Sankaran et al., 1999; George et al., 2001; Hutchings et al., 2002; McDaniel et al., 2003; Uboldi de Capei et al., 2004; Alakulppi et al., 2004; Tinckam et al., 2005; Lacha et al., 2005; Canossi et al., 2007; Coppo et al., 2007;	Pelletier et al., 2000; Cartwright et al., 2000; Marshall et al., 2000; Hahn et al., 2001; Poole et al., 2001; Cartwright et al., 2001; Asderakis et al., 2001; Muller-Steinhardt et al., 2002; Weimer et al., 2003; Plothow et al., 2003; Mytilineos et al., 2004;

Gene polymorphism	dbSNP rs number	Citation Association	Citation No association
		Nikolova et al., 2008; Khan et al., 2010; Amirzargar et al., 2007; La Manna et al., 2010; donor: Nikolova et al., 2008	Ligeiro et al., 2004; Dmitrienko et al., 2005; Loucaidou et al., 2005; Azarpira et al., 2006; Rodrigo et al., 2007; Breulmann et al., 2007; Grinyo et al., 2008; Gendzekhadze et al., 2006; Manchanda & Mittal, 2008; Mendoza-Carrera et al., 2008; Alakulppi et al., 2008; Grenda et al., 2009; Lobashevsky et al., 2009; Azarpira et al., 2009; Jacobson et al., 2010; Omrani et al., 2010; Kocierz et al., 2011; Israni et al., 2010; donor: Sankaran et al., 1999; Poole et al., 2001; Marshall et al., 2001; Alakulppi et al., 2004; Hoffmann et al., 2004; Ligeiro et al., 2004; Lacha et al., 2005; Loucaidou et al., 2005; Manchanda & Mittal, 2008; Mendoza-Carrera et al., 2008; Azarpira et al., 2009
IL10 -819C>T and -592C>A	rs1800871 rs1800872	McDaniel et al., 2003; Alakulppi et al., 2004; Ligeiro et al., 2004; Tinckam et al., 2005; Lacha et al., 2005; Coppo et al., 2007; Amirzargar et al., 2007; Nikolova et al., 2008; Grinyó 2008; Khan et al., 2010; La Manna et al., 2010; donor: Alakulppi et al., 2004; Nikolova et al., 2008	Cartwright et al., 2000; Marshall et al., 2000; Cartwright et al., 2001; Muller-Steinhardt et al., 2002; Weimer et al., 2003; Plothow et al., 2003; Mytilineos et al., 2004; Uboldi de Capei et al., 2004; Loucaidou et al., 2005; Gendzekhadze et al., 2006; Rodrigo et al., 2007; Satoh et al., 2007; Manchanda & Mittal, 2008; Alakulppi et al., 2008; Mendoza-Carrera et al., 2008; Lobashevsky et al., 2009; Jacobson et al., 2010; Israni et al., 2010; Kocierz et al., 2011; donor: Marshall et al., 2001; Ligeiro et al., 2004; Hoffmann et al., 2004; Loucaidou et al., 2005; Lacha et al., 2005; Manchanda & Mittal, 2008; Mendoza-Carrera et al., 2008

Gene polymorphism	dbSNP rs number	Citation Association	Citation No association
IL10 -851C>T	rs1800894		Grinyo et al., 2008
IL10 +4259A>G	rs3024498		donor: Israni et al., 2008
IL10 +434C>T	rs2222202		donor: Israni et al., 2008
IL10 IVS3-112A>G	rs3024494		donor: Israni et al., 2008
IL10 IVS3-474C>G	rs1878672		donor: Israni et al., 2008
IL10 gIVS3+284G>T	rs3024493		donor: Israni et al., 2008
IL10 IVS3+19T>C	rs1554286		donor: Israni et al., 2008
IL10 IVS1-192A>C	rs3021094		donor: Israni et al., 2008
IL6 -174G>C	rs1800795	Hahn et al., 2001; Reviron et al., 2001; Muller-Steinhardt et al., 2002; Lacha et al., 2005; Nikolova et al., 2008; Pawlik et al., 2008; Kocierz et al., 2011; donor: Marshall et al., 2001; Ligeiro et al., 2004; Canossi et al., 2007; Nikolova et al., 2008	Cartwright et al., 2000; Cartwright et al., 2001; Marshall et al., 2001; Hutchings et al., 2002; McDaniel et al., 2003; Ligeiro et al., 2004; Uboldi de Capei et al., 2004;Alakulppi et al., 2004; Hoffmann et al., 2004; Loucaidou et al., 2005; Tinckam et al., 2005; Gendzekhadze et al., 2006; ; Coppo et al., 2007; Breulmann et al., 2007; Satoh et al., 2007; Rodrigo et al., 2007; Alakulppi et al., 2008; Manchanda et al., 2008; Manchanda & Mittal; 2008; Grenda et al., 2009; Martin et al., 2009; Kruger et al., 2009; Lobashevsky et al., 2009; Khan et al., 2010; Jacobson et al., 2010; Sanchez-Velasco et al., 2010; La Manna et al., 2010; Israni et al., 2010; donor: Alakulppi et al., 2004; Loucaidou et al., 2005; Lacha et al., 2005; Manchanda & Mittal, 2008; Martin et al., 2009; Krajewska et al., 2009
IL6 +565>A	rs1800797		Rodrigo et al., 2007; Lobashevsky et al., 2009

Gene polymorphism	dbSNP rs number	Citation Association	Citation No association
IL6 +1888G>T	rs1554606		Kruger et al., 2009
IL6 Pro32Ser	rs2069830		Kruger et al., 2009
IL6 Asp162Val	rs2069860		Kruger et al., 2009
IFNG +874T>A	rs2430561	McDaniel et al., 2003; Tinckam et al., 2005; Mendoza-Carrera et al., 2008; Nikolova et al., 2008; Lobashevsky et al., 2009; Zibar et al., 2011; donor: Hoffmann et al., 2004; Canossi et al., 2007; Nikolova et al., 2008	Hahn et al., 2001; Hutchings et al., 2002; Muller-Steinhardt et al., 2002; Ligeiro et al., 2004; Alakulppi et al., 2004; Uboldi de Capei et al., 2004; Azarpira et al., 2006; Gendzekhadze et al., 2006; Brabcova et al., 2007; Coppo et al., 2007; Rodrigo et al., 2007; Satoh et al., 2007; Azarpira et al., 2009; Singh et al., 2009; Khan et al., 2010; Omrani et al., 2010; Crispim et al., 2010; La Manna et al., 2010; Kocierz et al., 2011; donor: Alakulppi et al., 2004; Ligeiro et al., 2004; Mendoza-Carrera et al., 2008; Azarpira et al., 2009
IFNG (CA)n	rs2234688	Mendoza-Carrera et al., 2008	donor: Mendoza-Carrera et al., 2008
IL1A -889T>C	rs1800587	Jin & Ruiz, 2008; donor: Jin & Ruiz, 2008	Rodrigo et al., 2007; Lobashevsky et al., 2009; Khan et al., 2010
IL1B -31C>T	rs1143627		Grenda et al., 2009
IL1B -511C>T	rs16944	Rodrigo et al., 2007, Jin & Ruiz, 2008; donor: Jin & Ruiz, 2008	Manchanda & Mittal, 2008; Khan et al., 2010; donor: Manchanda & Mittal, 2008
IL1B +3962C>T	rs1143634	Manchanda & Mittal, 2008; Jin & Ruiz, 2008; donor: Jin & Ruiz, 2008	Rodrigo et al., 2007; Manchanda & Mittal, 2008; Lobashevsky et al., 2009; Khan et al., 2010; donor: Manchanda & Mittal, 2008; Krajewska et al., 2009; Khan et al., 2010
IL1R +1970C>T	rs2234650		Rodrigo et al., 2007; Lobashevsky et al., 2009
IL1RA +11100 T>C	rs315952		Rodrigo et al., 2007; Lobashevsky et al., 2009; Khan et al., 2010,
IL1RN VNTR	rs2234663	Jin & Ruiz, 2008; donor: Jin & Ruiz, 2008	Manchanda & Mittal, 2008; Grenda et al., 2009; donor: Manchanda & Mittal, 2008

Gene polymorphism	dbSNP rs number	Citation Association	Citation No association
IL2 -330T>G	rs2069762	Satoh et al., 2007	Rodrigo et al., 2007; Grinyo et al., 2008; Manchanda et al., 2008; Manchanda & Mittal, 2008; Pawlik et al., 2008; Lobashevsky et al., 2009; donor: Manchanda & Mittal, 2008
IL2 +166G>T	rs2069763		Rodrigo et al., 2007; Grinyo et al., 2008; Lobashevsky et al., 2009
IL3 +132C>T	rs40401	Lee et al., 2010	
IL3 -1107G>A	rs181781	Lee et al., 2010	
IL3 -1484G>A	rs2073506	Lee et al., 2010	
IL4 VNTR intron 3	rs8179190	Manchanda et al., 2008	Manchanda & Mittal, 2008; donor: Manchanda & Mittal, 2008
IL4 -1098T>G	rs2243248		Rodrigo et al., 2007; Lobashevsky et al., 2009
IL4 -590T>C	rs2243250		Rodrigo et al., 2007, Satoh et al., 2007; Pawlik et al., 2008; Lobashevsky et al., 2009
IL4 -33T>C	rs2070874		Rodrigo et al., 2007; Lobashevsky et al., 2009
IL4R +1902G>A	rs1801275	Lobashevsky et al., 2009	Rodrigo et al., 2007
IL8 -251A>T	rs4073	Singh et al., 2009	La Manna et al., 2010; Ro et al., 2010; donor: Ro et al., 2010
IL12 -1188C>A	rs3212227	Rodrigo et al., 2007; Hoffmann et al., 2008; Lobashevsky et al., 2009	
IL12A +8685G>A	rs568408	Jacobson et al., 2010	Israni et al., 2010
IL12B -1188C>A	rs3212227		Kolesar et al., 2007; Satoh et al., 2007; Chin et al., 2008; Khan et al., 2010
IL18 -137G>C	rs187238	Kim et al., 2008; Mittal et al., 2011	donor: Mittal et al., 2011
IL18 –607A>C	rs1946518	Kolesar et al., 2007	Mittal et al., 2011; donor: Mittal et al., 2011
IL23R +2199A>C	rs10889677	Tsai et al., 2011	

Table 1. All the published genetic association studies related to cytokines listed according to the polymorphisms examined.

3.3 Kidney transplantation is a challenging study subject

During the last decade, a number of genetic association studies focusing on the outcome in kidney transplantation have been published. The results as a whole are contradictory and the effect of genetic variation on the outcome of transplantation still requires confirmation. It might be that the results of genetic studies are not reproduced due to a high level of genetic and environmental heterogeneity, both certainly relevant in kidney transplantation. There is growing evidence that certain genes or gene loci, such as *CTLA4–CD28–ICOS* cluster, regulate the immune response as their variation is associated with both susceptibility to autoimmunity and the outcome of transplantation. However, the same genes may also indirectly predispose to the underlying disease and its progression, or to the need for transplantation. Non-genetic, confounding factors are numerous: the original disease causing the need for kidney replacement, donor matching, surgical aspects, condition of the donor organ prior to transplantation etc. Besides, immunosuppressive drugs are highly effective and their administration can mask the genetic effect on the variance in immune response. Furthermore, it is essential to consider the effects of immunosuppressive drugs: gene variants regulating e.g. T cell response may not be detectable in patients receiving immunosuppressants affecting the T cell response.

As the current immunosuppressive regimens are very effective, the patients who still develop rejection, or some other complication, can be assumed to belong to the extreme high-responder end of patients. In genetic analysis this can be regarded as strength -we know we are studying the patients with a very strong tendency to develop immunological problems in kidney transplantation.

The problems related to the environmental factors can be reduced by a careful study design, such as attention to the precise definition of outcome phenotypes. Recruitment of sufficient numbers of patients would naturally improve the quality of studies. Prospective studies, if possible in a single centre single-centre would also be preferable, as many environmental factors could then be controllable but the number of cases available may remain relatively modest. Most studies have focused on allograft recipients, but evaluating also donors or even donor-recipient pairs, would give a new point of view.

Genetic variants should be carefully chosen instead of settling for a few most studied single nucleotide polymorphisms. Strong linkage disequilibrium (LD) influences association studies. It is currently assumed that our chromosomes are composed of haplotypic blocks that are relatively well conserved, in other words the genetic markers are said to be in linkage disequilibrium with each other. LD may help genetic studies as certain informative markers can be used as tags for a preliminary screening of haplotype blocks. On the other hand, the conserved structure of the blocks may be a hurdle in pinpointing the actual causative polymorphism. Exceptionally strong LD throughout the *HLA* region is well known. This fact also affects the interpretation of the role of *TNF* as it is located within the *HLA* block and hence *HLA* compatibility or matching leads to *TNF* matching as well. There is also strong LD on the 2q33 region (Holopainen & Partanen, 2001); not only within co-stimulatory receptor genes but also between them. *CD28* and the 5'end of *ICOS* exist in their own LD blocks, and between them, *CTLA4* and the 3' part of *ICOS* are within the same LD block (Ueda et al., 2003). Conservative haplotypes containing variants of both *CTLA4* and *ICOS* genes are found (Haimila et al., 2009a) and thus, the haplotypes must be taken in consideration when making conclusions from association results. Once good candidate polymorphisms with detectable and confirmed genetic effects are found, it is essential to start looking for functional differences. This has turned out to be problematic but not

impossible. For example certain genetic variations in the *CTLA4–CD28-ICOS* cluster appear to affect the gene expression level or change the alternative splicing preferences of the genes (Ueda et al., 2003; Kaartinen et al., 2007).

More complex statistical analyses of many genetic and environmental variants simultaneously are required to test joint contributions to the risk and adjustment for potential confounders. Multivariate analyses have more power to detect minor impacts of single variables. Besides, correction of multiple comparisons is required due to a high probability of false positives (type 1 error) when several polymorphisms related to several outcomes are tested. A particular statistical challenge in the transplantation settings, which has not been tackled so far, is the fact that we are studying donor – recipient pairs instead of merely patients versus non-affected.

Gene polymorphism	**dbSNP rs number**	**Citation Association**	**Citation No association**
CD28-594A>G	rs35593994		Haimila et al., 2009b
CD28ivs3+17C >T	rs3116496		Krichen et al., 2010; Kusztal et al., 2010
CTLA4-1722A>G	rs733618		Gendzekhadze et al., 2006
CTLA4-1661G>A	rs553808		Gendzekhadze et al., 2006; Haimila et al., 2009b
CTLA4-1147C>T	rs16840252		Wisniewski et al., 2006; Kim et al., 2010
CTLA4-318C>T	rs5742909	Wisniewski et al., 2006; Gorgi et al., 2006; Kusztal et al., 2007	Dmitrienko et al., 2005; Gendzekhadze et al., 2006; Haimila et al., 2009b; Kim et al., 2010; Kusztal et al., 2010
CTLA4+49A>G	rs231775	Gendzekhadze et al., 2006; Gorgi et al., 2006; Kusztal et al., 2007; Kim et al., 2010; Kusztal et al., 2010	Slavcheva et al., 2001; Dmitrienko et al., 2005; Wisniewski et al., 2006; Haimila et al., 2009b
CTLA4(AT)n		Slavcheva et al., 2001; Kusztal et al., 2010	Krichen et al., 2010
CT60G>A	rs3087243		Haimila et al., 2009b
ICOSivs+173T>C	rs10932029		Haimila et al., 2009b
ICOSc602A>C	rs10183087	Haimila et al., 2009b	
ICOSc1564C>T	rs4404254	Haimila et al., 2009b	
ICOSc1624C>T	rs10932037	Haimila et al., 2009b	
ICOSc2373G>C	rs4675379		Haimila et al., 2009b

Table 2. All the published genetic association studies related to T cell co-stimulatory receptors listed according to the polymorphisms examined.

Although genome-wide association studies are simple to conduct and commonly used in other complex trait studies, none have been carried out in organ transplantation. In a typical genome-wide association study, up to a million genetic markers covering a significant portion of the common variation are simultaneously tested. The two main characteristics of

genome wide studies are the large number of SNPs and the unbiased selection of these SNPs. Another approach, already demonstrated to be effective in bone marrow transplantation (McCarroll et al., 2009), is the systematic screening of gene deletions in the genome. Homozygous deletion of a gene in a recipient leads to immunological recognition of the encoded molecule if the graft can express the molecule. The results demonstrate that deletions are surprisingly common in our genome.

4. Conclusions

The identification of genetic factors that can modulate severity of acute rejection episodes may help to improve long-term graft survival. Functional variation in the gene regions of cytokines and/or T cell co-stimulatory receptors may affect the immune responsiveness of a graft recipient and thus, may predispose to the poor outcome of kidney transplantation. Technological advances in high-throughput genotyping methods would allow more intense genotyping of patients before transplantation. On the basis of genetic information, an amount of immunosuppressants could be set to a right level to avoid graft loss, on one hand, and undesired side effects of drugs, on the other hand.

The genes of cytokines and T cell co-stimulatory receptors are highly interesting but the final evidence for their role in renal transplantation still remains to be found. Genetic risk may not be due to a polymorphism in a single gene but rather a few haplotypes carrying a pattern of variations that act together. The combinatory effect may allow classification of patients into low- and high-responders. The involvement of several polymorphisms as well as confounding non-genetic factors, in particular differences in immunosuppression would explain the conflicting association reports from different populations. Larger studies are, however, still required. Even more importantly, true disease risk variants must be confirmed by functional assays. In addition, implementation of genome-wide association studies is necessary. Besides SNPs, the effect of structural variants, such as insertion/deletion and copy number variations should also be scrutinized in organ transplantation.

The major problem with genetic association studies is the small size of study populations (Hattersley & McCarthy, 2005). Although the sizes have increased in the more recent studies, the number of endpoint cases is still small and thus, the power of analysis is inadequate. The median rate of acute rejection was 18% in the recent multicentre study by Israni et al (2010). This means that thousands of patients need to be enrolled to the study before the number of acute rejection (or another endpoint) cases is sufficient for detecting the real underlying genetic variants, each of which may only have a weak individual effect.

Despite improved immunosuppressive medicaments, new organ preservation techniques, and decreased rejection rates, the improvement in long-term kidney allograft survival has been modest. There is growing interest in immunogenetics: if genetic factors determining the level of the immune response are combined with knowledge on effects of gene variation on drug metabolism, more personalized immunosuppression regimes for the patients can be developed.

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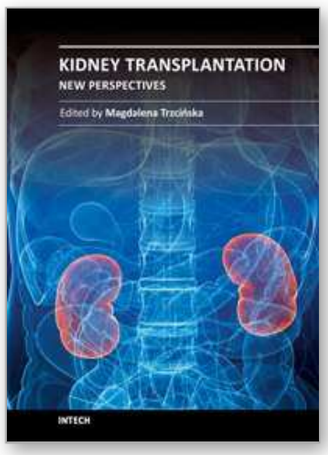

Kidney Transplantation - New Perspectives

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Although many years have passed since the first successful kidney transplantation, the method, although no longer considered a medical experiment, is still perceived as controversial and, as such, it triggers many emotions and thatâ€™s why conscious educational efforts are still needed for kidney transplantation, for many people being the only chance for an active lifestyle and improved quality of life, to win common social acceptance and stop triggering negative connotations. Apart from transplantation controversies piling up over years transplantologists also have to face many other medical difficulties. The chapters selected for this book are of high level of content, and the fact that their authors come from many different countries, and sometimes even cultures, has facilitated a comprehensive and interesting approach to the problem of kidney transplantation. The authors cover a wide spectrum of transplant-related topics.

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