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Genetic polymorphisms in the immune response: A focus on kidney transplantation

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ABSTRACT

The modulation of the immune system following solid organ transplantation has made considerable progress with new immunosuppressive regimens and has considerably improved rejections rates. The improvement in long-term allograft survival is, however, modest. A complex network of cytokines, chemokines, adhesion, activation and co-stimulatory molecules are the frontline contributors to allograft rejection, which in turn determines the evolution of graft function and its long-term survival. Polymorphisms in these genes influence protein levels and presumably their signaling effects. In this review, we present a relevant panel of candidate genes related to the immune system in the context of solid organ transplantation; we discuss the most convincing reports of genetic associations with outcomes in renal transplantation and highlight the most promising loci among the vast body of literature.

1. Introduction

The success of solid organ transplantation depends on many donor or recipient characteristics including HLA mismatch, pre-formed antibodies, age and ethnicity, as well as on specific events linked to the surgical procedure (e.g., cold ischemia time, reperfusion injury). Careful use of immunosuppressants likewise has an impact, and while experience has led to the titration of these drugs to blood levels within thresholds to improve outcomes and avoid adverse effects, there remains unexplained variability in outcomes.

A large body of literature provides evidence that the efficacy and toxicity of immunosuppressive therapy might be mitigated by polymorphisms in important pharmacogenes related to their pharmacokinetics and, to a minor extent, pharmacodynamics. Only a few of the reported associations have translated into validated pharmacogenetic applications. Pharmacogenetics is defined as "the study of variations in DNA as related to drug response". Variations of interest are non-pathogenic and usually relatively common. Most studies in transplantation have focused on genetic variations that may change the relationship between the dose of the drug administered and its blood levels. The aim in this context was to obtain additional tools to better achieve or maintain levels in effective and non-toxic concentration targets. Genotyping of cytochrome P450 3A5 (CYP3A5; a key enzyme in tacrolimus hepatic clearance) is an example of routine application that was demonstrated to be beneficial to the refinement of tacrolimus first dose through a randomized multicentre trial [1]. However, the benefit in terms of clinical outcomes for the CYP3A5 specific example, and others, remains to be proven.

Pharmacogenetics of solid organ transplantation is indeed a very particular area: clinical outcomes are influenced by immunosuppressive therapy but additionally by the milieu of immune system players, including cytokines and their receptors, chemokines and their receptors, adhesion molecules, co-stimulatory molecules and innate immune system proteins which are the frontline contributors to rejection (or conversely to immune tolerance). This panel of cytokines provide a long list of less explored candidate genes in the search for polymorphisms that might be used to predict clinical outcomes, and thus tailor therapy based on risk.

Several excellent reviews exist on the topic of genetic polymorphisms in immune system genes and their impact on graft outcomes in solid organ transplantation [2–5]. The following review aims to highlight the loci that have been studied specifically in kidney transplantation related to outcomes of success (acute rejection, graft survival chronic allograft nephropathy, among others), and to present an update

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Table 1
Genes coding for the main proteins related to the immune response in the context of allograft transplantation.

Chromosome location	Gene	Name	Other names	Main function[a]
Genes related to initial T cell activation				
Co-stimulatory molecules				
2	*CD28*	CD28 molecule		Binds CD80/86 expressed by antigen-presenting cells to provide a co-stimulatory signal (T-cell activation, proliferation and a proinflammatory response)
3	*CD80*	CD80 molecule		
2	*CTLA4*	Cytotoxic T-lymphocyte-associated protein 4	CD152	Downregulates the immune system (acts as an "off" switch by stimulating the CD28 receptor on the T cell)
20	*CD40*	CD40 molecule	TNFRSF5	Mediates a broad variety of immune and inflammatory responses including T
X	*CD40LG*	CD40 ligand	CD154, CD40L	cell-dependent immunoglobulin class switching and memory B cell development
Regulatory molecules				
1	*PTPN22*	Protein tyrosine phosphatase, non receptor type 22		Negative regulator of TCR-signal
16	*CIITA*	Class II, major histocompatibility complex, transactivator		Master regulator of the HLA class II
Genes related to cytokines and receptors				
2	*IL1A*	Interleukin-1 alpha (IL-1α)		Produced by monocytes and macrophages, involved in inflammatory processes and hematopoiesis
2	*IL1B*	Interleukin-1 beta (IL-1β)	IL1F2, catabolin	Produced by activated macrophages (as a proprotein), involved in the inflammatory response (cell proliferation, differentiation, apoptosis)
2	*IL1R1*	Interleukin 1 receptor, type 1	CD121A, IL1RA	Receptor for interleukin-1 alpha, interleukin-1 beta, and interleukin-1 receptor antagonist
2	*IL1RN*	Interleukin-1 receptor antagonist (IL-1RA)		Inhibits the activities of interleukins 1, alpha and beta
4	*IL2*	Interleukin 2 (IL-2)	Lymphokine	Proliferation of T and B lymphocytes
22	*IL2RB*	Interleukin-2 receptor subunit beta (IL-2Rβ)	CD122	Component of intermediate and high affinity IL2-receptor, Involved in endocytosis and transduction of mitogenic signals from IL-2
5	*IL3*	Interleukin-3 (IL-3)		Potent growth promoting cytokine (mainly hematopoietic cells)
5	*IL4*	Interleukin 4 (IL-4)		Produced by activated T cells, immunoregulation (differentiation in TH2 cells)
16	*IL4R*	Interleukin 4 Receptor alpha	CD124	Binds IL-4 (to promote differentiation of Th2 cells) and IL-13 (to regulate IgE production)
7	*IL6*	Interleukin 6 (IL-6)	IFNB2	Functions in inflammation and the maturation of B cells also capable of inducing fever in people with autoimmune diseases or infections
1	*IL10*	Interleukin-10 (IL-10)		Produced primarily by monocytes, immunoregulation (differentiation in TH2 cells)
5	*IL12B*	Interleukin 12, subunit beta (IL12-B)		Expressed by activated macrophages, an essential inducer of Th1 cells development
6	*IL17A*	Interleukin 17 (IL-17)	CTLA8, IL-17A	T helper 17 (Th17) cells activation
11	*IL18*	Interleukin 18 (IL-18)	IGIF (IFNγ inducing factor)	Augments natural killer cell activity in spleen cells. Stimulates interferon gamma production in T-helper type I cells
4	*IL21*	Interleukin 21 (IL-21)		Role in both the innate and adaptive immune responses (differentiation, proliferation and activity of macrophages, natural killer cells, B cells and CTLs)
6	*TNFA*	Tumor necrosis factor (TNFα)	Cachexin, cachectin	Secreted by macrophages, proinflammatory cytokines (cell proliferation, differentiation, apoptosis)
6	*LTA*	Lymphotoxin alpha	TNFB (Tumor necrosis factor-beta)	Involved in inflammatory, immunostimulatory, and antiviral response, role in apoptosis, role in formation of secondary lymphoid organs during development
19	*TGFB1*	Transforming growth factor beta (TGF-β)		Regulates proliferation, differentiation, adhesion, migration, and other functions in many cell types
Genes related to the innate immune response				
4	*TLR2*	Toll-like receptor 2	CD282	Role in pathogen recognition and activation of innate immunity
9	*TLR4*	Toll-like receptor 4	CD284	
3	*TLR9*	Toll-like receptor 9	CD289	
19	*C3*	Complement component 3	C3b	Central role in the activation of complement system, antimicrobial activity
5	*CD14*	CD14 molecule		Expressed on monocytes/macrophages, cooperates with TLRs to mediate the innate immune response to bacterial lipopolysaccharide
Genes related to the effector phase of rejection (graft infiltration and injury)				
4	*CXCL8*	Chemokine (C–X–C motif) ligand 8	IL8	Chemoattractant for neutrophils, also a potent angiogenic factor
2	*CXCR1*	Chemokine (C–X–C motif) receptor 1	IL8RA, IL8R1, CD128, CD181	Interleukin 8 receptor (high affinity)
2	*CXCR2*	Chemokine (C–X–C motif) receptor 2	IL8RB, IL8R2, CD182	Interleukin 8 receptor (high affinity)
17	*CCL2*	Chemokine (C–C motif) ligand 2	MCP-1 (monocyte chemotactic protein 1)	Chemoattractant for monocytes and basophils
17	*CCL5*	Chemokine (C–C motif) ligand 5 (CCL5)	RANTES	Chemoattractant for blood monocytes, memory T helper cells and eosinophils
3	*CCR2*	C–C chemokine receptor type 2	CD192	CCL2 receptor
3	*CCR5*	C–C chemokine receptor type 5	CD195	CCL5 receptor
10	*CXCL12*	Chemokine (C–X–C motif) ligand 12	SDF1 (stromal cell-derived factor 1)	Ligand of chemokine (C–X–C motif) receptor 4, role in immune surveillance, inflammation response, tissue homeostasis, and tumor growth and metastasis
Other adhesion Molecules				
1	*VCAM1*	Vascular cell adhesion molecule 1 (VCAM-1)	CD106	Leukocyte-endothelial cell adhesion and signal transduction
19	*ICAM1*	Intercellular Adhesion Molecule 1 (ICAM-1)	CD54	Expressed on endothelial cells and cells of the immune system. Binds to integrins of type CD11a or CD11b (CD18)