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Emerging Role of Pharmacogenetic in Organ Transplantation

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Abstract

The currently used immunosuppressive drugs have a narrow therapeutic index which required to individualize the dose regimen for different recipients. Pharmacogenetic is the use of genetic screening to prevent metabolic responses to different immunosuppressive drugs. Since the oxidative enzymes cytochrome P450 CYP3A and the drug efflux pump P-glycoprotein (P-gp) play a pivotal role in immunosuppressive drugs metabolism, pharmacogenetic studies have been mainly focused on these two enzymes. This would provide an important aid toward drug regimen individualization during the post-transplant therapy and has potential to improve graft outcome.

Keywords: Pharmacogenetics; Calcineurine inhibitors; Organ transplantation; *CYP3A5*; *ABCB1*

Introduction

Organ transplantation is becoming the optimal therapy strategy for end stage renal, liver heart and lung diseases. The introduction of better and more specific immunosuppressive drugs have enable organ replacement to obtain its current place. In fact, a gradual improvement in short-term graft survival has occurred over the last 10 years and extensive use of the calcineurine inhibitors (CI) tacrolimus and cyclosporine, have played a not negligible role [1]. However, there has been minimal improvement in long term graft survival over the same period partly due to drug side effects [2,3]. It is well recognized that response to CI has significant inter and intra individual variation in transplant patients. Both over and under-dosage of CI influence the life span of the graft and of the recipient [4,5]. Several factors such as organ function, drug interaction and the nature of the disease may influence the effects of CI. Recently, the role of genetic factors has been also pointed out since genetic polymorphisms are implicated in the inter-individual variability of the pharmacokinetic and pharmacodynamic characteristics of many drugs. Pharmacogenetic is the study of genetic variations that give rise to different drug responses and theoretically represents a very promising tool. A genetic screening prior to transplantation should allow to forecast the individual response to a given immunosuppressive drug therefore to tailor immunosuppressive regimen in order to optimized short and long term outcomes.

Metabolic Pathways as Possible Targets for a Pharmacogenetic Strategy

The genes that are primarily involved in metabolizing immunosuppressant are those encoding cytochrome P450 (CYP) 3A family enzymes and multidrug resistance P-glycoprotein 1 (the *ABCB1*gene). As many drugs undergo substantial intestinal and liver metabolism after absorption from the gut lumen, it is believed that CYP3A and P-glycoproteinare are lagely responsible for the poor oral bioavailability of calcineurin inhibitors [6]. The CYP3A subfamily is a cluster consisting of four isoenzymes. *CYP3A4* and *CYP3A5* are the main genes involved in the metabolism of cyclosporine and tacrolimus [7]. *CYP3A5* is expressed more variably and at a relatively higher level in the proximal renal tubules [8]. *CYP3A5*1* encodes an active protein and is responsible for the increased metabolism of many drugs including tacrolimus but not cyclosporine [6]. During the transcription phase, the *CYP3A5*3* (6986 A>G) allele introduces an alternative splicing site leading to protein truncation, thus resulting in the absence of full-length protein expression [9,10]. *CYP3A4* is abundantly and constitutively expressed in hepatic and intestinal epithelia, so the reported increase in transcriptional activity shown by the *CYP3A4*1B* allele *in vitro* would theoretically also reflect significant enzymatic activity *in vivo* [11]. P-gp, which is encoded by the *ABCB1* gene, is a large ATP-dependent transmembrane protein involved in the extracellular extrusion of many xenobiotics and drugs including calcineurin inhibitors (CNIs) [12]. Cyclosporine is a typical *ABCB1* substrate and intestinal P-gp may be responsible for the reduced intestinal absorption of cyclosporine [13]. More than 700 variations in the nucleotide sequences have been described and although nothing is known about the clinical impact of most of the sequence variations on P-gp function, some seem to be functionally relevant and substantially influence the pharmacokinetics of substrate drugs. The most extensively investigated SNPs of *ABCB1* are 3435C > T (rs1045642) in exon 26, 1236C > T (rs128503) in exon 12 and 2677G > T/A (rs 2032582) in exon 21 [14]. The 3435C > T polymorphism is a silent polymorphism that may be in linkage disequilibrium with other functional polymorphisms in the *ABCB1* gene, including 2677G > T/A. The 3435C > T polymorphism may also reduce *ABCB1* mRNA stability in the liver and it could change protein folding and activity [15]. Another interesting SNP is IVS21+49 T > C (rs2032583) in intron 21 of *ABCB1*, which is involved in the pharmacokinetics of many drugs including antidepressants and methadone [16].

CYP3A5 and *ABCB1* Genotypes and Tacrolimus

The expression of *CYP3A5* is associated with reduced tacrolimus exposure following oral administration in both pediatric and adult population [17,18]. *CYP3A5* expressors exhibit a significant delay in achieving target blood concentration [19]. Therefore, an increased incidence of acute rejection episodes in the early post-transplant period has been reported [20]. Recently, the first study to show the prospective adaptation of tacrolimus daily dose based on *CYP3A5* patient's genotype, confirmed that pre-transplant genetic screening increased significantly the proportion of patients reaching the therapeutic target range. In fact, in this multi-center randomized controlled trial, patients receiving tacrolimus daily dose according to their *CYP3A5* genotype,

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achieved the target concentration more rapidly with lesser dose modification and in an higher percentage (>75%) when compared to those in whom tacrolimus was managed with a concentration-control strategy [21]. *ABCB1* polymorphisms do not seem to influence tacrolimus pharmacokinetic and research into this association has yielded mixed results [22,23]. Nevertheless, in our series we observed a significant reduction in tacrolimus concentration and dose-adjusted tacrolimus concentrations in the early post-transplant period for the TT polymorphism of C1236T; this suggests that there is higher metabolism of the drug in subjects with this genotype [24]. This could be substantiated by the fact that 1236 and 3435 polymorphisms of *ABCB1* influence the shaping and stability of mRNA and, consequently, gene expression [25]. Interestingly, a recent study on pediatric liver transplantation demonstrated a significant association between *ABCB1* polymorphisms and tacrolimus-related nephrotoxicity [26]. This suggests that *ABCB1* polymorphisms in the gastrointestinal tract do have an influence on tacrolimus dose requirement and exposure.

CYP3A5 and *ABCB1* Genotypes and Cyclosporine

There are a number of conflicting reports regarding the *CYP3A* genotype influence on cyclosporine pharmacokinetic [27,28]. Therefore, a clear role of this polymorphism on cyclosporine metabolism has not been demonstrated. However, it is necessary to bear in mind that the drug is simultaneously both a substrate and an inhibitor of *ABCB1* [29] which is why the influence of *ABCB1* polymorphisms is rather controversial. In our series, we found that *ABCB1* polymorphisms affected cyclosporine pharmacokinetics in the immediate post-transplant period rather later [24]. The time-related effect of *ABCB1* polymorphisms may be explained by the fact that the drug's potent inhibitory effect on P-gp function requires an adequate pharmacological load before it is fully expressed [30]. Another possible explanation should be related to the age of the recipients. Recently, Fanta and colleagues suggested that age-related polymorphisms of *ABCB1* could explain the different oral bioavailability of cyclosporine among different age groups [31].

The Effect of Donor Genetic Polymorphisms on the Transplant Outcome

Among the genetic variables that might affect immunosuppressive drug metabolism, consideration should be given to the possible role of donor genotype. In fact, grafts from donors may carry different genotypes from *CYP3A5* and *ABCB1*. However very few data are available on whether and how much the donor graft genetic background influence absorption and metabolism of immunosuppressive drugs. This would mainly apply to liver transplantation where particular receptors in the donor's graft have been reported to substantially affect tacrolimus metabolism [32,33]. In the kidney transplant setting there have been relatively few studies looking at the role of polymorphisms in graft donors and their conclusions remains unclear. Woillard et al. [34] reported that the presence of *ABCB1* polymorphisms in donors influenced long-term graft outcome of renal transplant patients. Nevertheless, Hauser et al. [35] reported that in adult renal transplant recipients the incidence of cyclosporine nephrotoxicity was significantly higher when the donor rather than the recipient, had the *ABCB1* 3435TT genotype. Obviously, intra-graft *ABCB1* expression is related to donor's genotype and possibly responsible for cyclosporine accumulation in renal tubular cells. Further studies are required to evaluate the role of donor polymorphisms although it is likely that in pediatric and adult renal transplantation the role of recipient polymorphisms will be more important.

Conclusions

In organ transplantation the poor bioavailability and the large intra and inter-individual variability in the administration of immunosuppressive drugs limit the postoperative drug therapy, which may subsequently affect the function and lifespan of grafts. The individualization of the therapeutic regimens in different patients is mandatory in order to balance clinical efficacy and toxicity. CYP3A and P-gp are the two key enzymes which greatly influence the absorption, disposition, metabolism and clearance of immunosuppressive drugs. Many genetic factors have been identified to affect the expression of CYP3A and P-gp and up to day there is a large evidence base relating to genetic influences on the pharmacology of calcineurine inhibitors. The pre-transplant screening of the most relevant polymorphisms should therefore be considered in order to tailor immunosuppressive therapy to an individual patient's metabolism.

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