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Chapter 6

Gene Polymorphisms of Immunosuppressants in Solid Organ Transplantation

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Abstract

The rapid development of immunosuppressants (IS) has already improved the prognosis of recipients post solid organ transplantation (SOT) in the past decades. However, the individual difference in IS metabolism may lead to either rejection or drug toxicity, thus suggesting the importance of personalized therapy. Gene polymorphisms (GP) regarding metabolic enzymes and medication transporters of the IS consist the footstone for personalized therapy, which are the hotspots in recent years. However, although a great of efforts have been put into researching the association between GP and pharmacokinetics (PK) or pharmacodynamics (PD), controversial results still remained. The only consensus that has been reached is the use of GP-based IS therapy could help the recipients to reach target concentration faster with less dose adjustment. Whether the GP-based IS therapy could improve the clinical long-term outcome needs further confirmation. In our chapter, we would summarize the information associated with GP of IS, and discuss the potential impact of GP on clinical practice to provide new insights into guiding tailored therapy of IS in SOT.

Keywords: gene polymorphisms, immunosuppressants, solid organ transplantation, pharmacokinetics, pharmacogenetics

1. Introduction

SOT has prominently reduced mortality and morbidity when facing conditions of end-stage organ failure [1]. To prevent rejection of SOT, the use of IS is essential. And with the continuous development of medical technology, individualized treatment has been paid much more attention. With the advent of new drugs, more choices of IS combination are available in present clinical practice, and the most widely used of which is a calcineurin inhibitor (CNI) + an

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antiproliferative agent + corticosteroid. Tacrolimus (Tac) and ciclosporin (CsA) are both CNI, and Tac has held most of the market in recent years. Mycophenolate (MMF) is the most widely used antiproliferative agent, which is a prodrug of mycophenolic acid (MPA) that has immunosuppressive activity [2]. There is also a monosodium salt of MPA that was developed to overcome the gastrointestinal side effects of MMF. Ahead of the "triple immunosuppressive therapy", many maintenance regimens also have induction therapy, which consists of antibodies to lymphocytes. The mammalian target of rapamycin (mTOR) is a more recent IS, which includes sirolimus (SRL) and everolimus (EVE). They were first envisaged as a primary IS in regimens without CNI [1, 3, 4], while now, most of the time they are used at low doses in CNI-sparing regimens [5, 6].

To achieve the target blood concentration fast with less dose adjustment is clinically important, for the therapeutic window of these IS is narrow, which may lead to either acute rejection or over-immunosuppression [7–9]. There are also numerous drug-specific adverse effects, CNI has a closer relation to high blood pressure hypertension, nephrotoxicity, and new-onset diabetes after transplantation (NODAT) [10], steroids may also lead to NODAT [11], and the mTOR inhibitors are often associated with delayed wound healing and hyperlipidemia [8]. In the majority of cases, these adverse effects are associated with high drug concentrations in the blood, but this is by no means universal [12].

In consideration of inter-individual variation in PK of IS, monitoring the blood concentration has been essential. Therapeutic drug monitoring (TDM) has been widely used to ensure the blood concentration of CNI and SRL [13]. In daily clinical practice, the blood sample is taken and measured at a single time-point immediately before the next dose (called C_0 or trough concentration). Although recent studies have suggested that, for measurement of CsA, 2 h after dosing (C_2) correlates better with the area under the concentration-time curve (AUC) compared to C_0 [9]. This may also apply for Tac, but the practice has not been adopted widely [12, 14, 15].

TDM is no doubt powerful and indispensable in the current management of IS, while many patients may still experience a significant delay in achieving target blood-concentrations, and drug dosage need to be adjusted repeatedly, which could significantly increase the risk of acute graft rejection [9, 16]. The narrow therapeutic window of the IS makes it impossible to use a higher initial dose for all patients, and here comes an unmet need for a strategy, which can lead to the fast achievement of IS target blood concentration in the period immediately following transplantation for all the patients. Fortunately, the investigation of GP combined with critical patient data and concomitant medications may help and thus potentially reduce the adverse events related to over- or under-exposure. In addition, studies may also possibly reveal the association between GP and IS PD, which may help clinicians to choose a better combination of IS for the specific group. A strategy based on GP is most likely to be effective when a single gene has a major influence on the absorption, disposition, elimination or tissue compartmentalization of a drug [12].

This chapter discusses the published genetic associations with IS PK and PD, and their potential use in clinical practice to guide drug dosing in SOT.

2. GP and Tac

Tac is a 23-membered macrolide lactone isolated from *Streptomyces tsukubaensis* in 1987 for the first time [17], and in 1994, the US Food and Drug Administration firstly approved Tac for liver transplantation. Due to its excellent efficacy, Tac has been extended as a first-line regimen for kidney, heart, lung, intestinal and bone marrow transplantation. Genetic factors including CYP3A5*3, CYP3A4*1B, CYP3A4*22, ABCB1, and POR*28 have been reported frequently for their influence on Tac dose requirement, which reveals the importance of GP of Tac.

2.1. CYP3A5 and Tac

Reportedly, polymorphisms in the CYP3A5 gene may explain 40–50% of the variability in Tac dose requirement [18, 19]. The hottest SNP studied in CYP3A5 is CYP3A5*3, which is an A to G transition at position 6986 within intron 3 (rs776746) [20]. This mutation leads to alternative splicing, and truncation of the protein, which decreases the function of the CYP3A5 enzyme [21]. As a result, CYP3A5 expressers (CYP3A5*1/*1 or CYP3A5*1/*3 genotype) have significantly lower dose-adjusted C_0 compared to CYP3A5 non-expressers (CYP3A5*3/*3 genotype), and the requirement of Tac dose is CYP3A5*1/*1 > *1/*3 > *3/*3 [20]. A large number of retrospective studies have shown that kidney graft recipients who are CYP3A5 expressers require an approximately 2-fold higher Tac dose compared with non-expressers [22–24]. In addition, no matter in adult or pediatric heart recipients [25, 26], in lung transplantation recipients [27], as well as in liver transplantation recipients [28], the same relationship has also been observed.

Other CYP3A5 SNPs include CYP3A5*6 (rs10264272) and CYP3A5*7 (rs41303343). CYP3A5*6 encodes a G to A transition at position 14,690, causing a splice variant mRNA and deletion of exon 7, resulting in nonfunctional CYP3A5 protein [21, 29]. CYP3A5*7 denotes a single base insertion at codon 346, causing a frame shift and resulting in a truncated mRNA and nonfunctional CYP3A5 [30].

As for the association between CYP3A5 and the early prediction of the risk of acute rejection, the results are quite inconsistent. Some studies involving Tac therapy did not find any significant association [23, 31–34], while some other studies reported that CYP3A5 expressers had a higher risk of experiencing biopsy-proven acute rejection (BPAR) [35, 36].

As for other kidney transplantation outcomes involving Tac therapy, such as chronic allograft nephropathy or delayed graft function (DGF). Some studies reported that CYP3A5 expressers had a higher risk of experiencing biopsy-proven Tac-related nephrotoxicity [37, 38] and reduced renal function during the first year after transplantation [36], and CYP3A5 non-expressers were more likely to develop DGF [39] and early renal graft injury as assessed by the urine test [40].

2.2. CYP3A4 and Tac

As for CYP3A4 gene, two SNPs in relation to Tac PK have been investigated extensively: CYP3A4*1B SNP (rs2740574) and CYP3A4*22 SNP (rs35599367).

The CYP3A4*1B SNP involves an A to G transition at position −392 in the promoter region of CYP3A4 and is associated with an increase of CYP3A4 activity [41]. It showed that the C_0/D ratio of Tac in patients with the *1B mutation was reduced by 35% compared with that of wild-type homozygotes [42]. However, there is a linkage disequilibrium (LD) between CYP3A4*1B and rs776746 of the CYP3A5 gene. It is possible that the effect of CYP3A4*1B on Tac PK and PD is caused by rs776746, which has been shown in several published studies [43, 44]. Therefore, the exact effect of CYP3A4*1B alone on Tac is still unclear.

The CYP3A4*22 SNP (rs35599367) contains a transition of C to T in intron 6 and is associated with reduced CYP3A4 mRNA expression and CYP3A4 enzyme activity in vitro [45]. In clinic observation of kidney transplantation, the CYP3A4*22 required less Tac dose to achieve the target exposure. What's more, it was not influenced by the CYP3A5 genotype [46]. However, it should be noted that the frequency of CYP3A4*22 is relatively low. About 5% of the Caucasian population, 3% in the American population, and not found in Asians or Africans [47].

Other CYP3A4 SNPs such as CYP3A4*18 (rs28371759) may also have an impact on Tac PK. This SNP is located in intron 10, with a transition of T to C at position 878. This mutation may increase the activity of the CYP3A4 enzyme and thereby increase the Tac clearance rate and plasma drug concentration [48].

There is also a new and rare CYP3A4 variant, which is now designated as CYP3A4*26. This variant is an 802C>T transition and results in a premature stop codon at position 268 in exon 9 (R268*) [49]. The truncated CYP3A4 protein is non-functional.

When combining CYP3A4 and CYP3A5 genotypes, Elens et al. [50] were able to predict Tac dose requirements better compared with the CYP3A4 or CYP3A5 genotype alone. Based on these observations, it has been proposed to prescribe different Tac doses for ultrarapid (CYP3A5 expressers and CYP3A4 *1/*1), intermediate (CYP3A5 non-expressers and CYP3A4*1/*1) and poor (CYP3A5 non-expressers and CYP3A4*22 carriers) CYP3A metabolizers, respectively [51].

2.3. ABCB1 gene and Tac

P-gp, also known as ABCB1 or MDR1 is a glycoprotein encoded by the human ABCB1 gene, which serves as drug transporter of Tac, and plays an important role in Tac PK. Recently, P-gp has been found to contain more than 50 SNPs. Among them, the ABCB1 3435C>T (rs1045642), 1236C>T (rs1128503) and 2677G>T/A (rs2032582; Ala893Ser/Thr) SNPs have drawn the most attention after intensive investigation [52–54].

The ABCB1 3435C>T (rs1045642) might be the hottest locus among all the ABCB1 gene SNPs. Reportedly, the frequency of this mutation in orientals is 37–49% [55]. The variation of rs1045642 locus might reduce the expression and function of P-gp in the duodenum, and thus potentially affect the bioavailability of Tac [56].

As for ABCB1 2677G>T/A SNP, wild-type patients required 40% higher Tac dose compared with homozygous carriers of 2677G>T/A SNP ($P \leq 0.05$), while the concentration/dose ratio was 36% lower in the wild-type patients ($P \leq 0.02$). The haplotype analysis further confirmed the

results and suggested that 3435C>T and 2677G>T/A SNPs were associated with daily Tac dose requirements. In addition, the study of these three SNP haploids (1236C>T, 2677G>T/A and 3435C>T, which are in linkage disequilibrium) found that C-G-C (haplotype 1) and T-T/A-T (haplotype 2) accounted for 45.4 and 36.2% of the haplotypes, respectively; individuals with haplotype 1 required significantly higher daily doses of Tac than those with haplotype 2 [57].

Although there are many studies on the association of ABCB1 GP with Tac PK or PD, the results remain inconsistent. To further confirm the association, large-scale genotype-phenotype correlation trials are encouraged.

2.4. POR and Tac

POR is essential for CYP-mediated drug oxidation as an electron donor [58]. POR*28 (rs1057868; A503V) is a coding variant in POR gene, which is believed to be effective in increasing the activity of POR and thus leads to the increasing activities of CYP3A4 and CYP3A5 [59, 60].

it has also been reported frequently that POR*28 carriers have lower adjusted Tac C_0 and Tac C_0/Tac dose in heart or kidney transplantation, no matter for the adult or the pediatric [61–64]. Although the strength of this association seems weak and has a limited clinical impact on Tac dose requirements (15–20%), POR*28 may explain a part of Tac variability, and POR*28 carriers may experience faster Tac metabolism [61, 63, 65].

As for the association between POR*28 allele and BPAR after Tac or CsA therapy, no significant evidence was found [63]. As for other graft clinical outcomes, the POR*28 allele was not found to be associated with the higher risk of DGF after Tac therapy in patients with renal transplantation [63]. While it should be noted that one study in recipients with kidney transplantation demonstrated a higher risk of post-transplantation diabetes mellitus (PTDM) in patients carrying the POR*28 allele [60].

2.5. PXR and Tac

As a nuclear transcription, the human pregnane X receptor (PXR), which is encoded by NR1I2, regulates the expression of CYP3A and ABCB1. Polymorphisms of NR1I2 have been reported, but the results regarding their association with Tac dose requirement are conflicting [18, 66, 67].

2.6. PPAR-α and Tac

The expression and activity of CYP3A are also related to the nuclear receptor peroxisome proliferator-activated receptor alpha (PPAR-α). Two sequence variants in the PPAR-α gene (PPARA), PPARA c.209-1003G>A and c.208+3819A>G, can reduce the PPAR-α expression and contribute to the intra- and inter-individual variability of CYP3A [68]. At present, PPARA c.208+3819A>G appears to have the strongest influence on Tac PK, though it still needs confirmation.

As for graft clinical outcome, one study in kidney transplant recipients demonstrated a higher risk of PTDM who carry the rs4253728 SNP [59].

2.7. Other SNPs and Tac

The multidrug resistance-associated protein 2 (MRP2), which is encoded by the ABCC2, may also be associated with Tac metabolism [69].

The CYP2C8 enzyme, which is highly expressed in the liver, can also be found in extrahepatic tissues like kidney [70]. Reported by Suarez-Kurtz et al. [71], the CYP2C8*3 was associated with higher Tac C_0/D, but only in CYP3A5 non-expressers. Furthermore, CYP2C8*3 and CYP2J2 -76G>T SNPs were reported to influence the renal function of the patients and the occurrence of adverse events during treatment with Tac and mycophenolate sodium [72].

Genetic polymorphisms in IL-18 (e.g., rs5744247) and IL-10 (e.g., −819 C/T and −592 C/A) can also affect Tac dose requirements [50, 62]. However, the exact mechanism by which they affect Tac dose requirements is unknown [73, 74].

Recently, it was also reported that IL-3 rs181781 and CTLA4 rs4553808 genetic polymorphisms probably influence the Tac dose requirements in Chinese kidney transplant recipients [75].

3. GP and CsA

Both CsA and Tac are CNI. The GP that closely related to Tac as mentioned above could have more or less the effect on CsA, and as it should be, the effect is not exactly the same. In recent years, Tac gradually replaces the use of CsA, and here we will not make an in-depth introduction.

Reportedly, the influence of the CYP3A5*3 and CYP3A4*22 variants on the PK [19, 42, 50, 76–80] or PD [33, 81–84] of CsA are controversial. The effect of CYP3A5*3 on the CsA PK appears to be weaker than observed for TAC, while the CYP3A4*22 allele appears to be stronger, which would decrease the clearance of CsA by 15%. As stated in [47], for the time being, no precise dose adjustment has been proposed based on these variants.

4. GP and SRL

Both SRL and EVE are the mammalian target of rapamycin inhibitors (mTORi). SRL was not used as IS until the late 1990s. SRL can form a complex with the tacrolimus-binding protein (FKBP), which binds to mTOR. It inhibits the entry of cells from G1 phase to S phase and inhibits T lymphocyte activation (proliferation) [85, 86].

Despite the potential advantages of sirolimus, such as antitumor activity [87–89] and antiviral activity [90–92], there are also a number of side-effects that result in a limit use of mTORi in clinical trials and practice, including PTDM, hyperlipidemia, anemia, proteinuria, oral ulcers, diarrhea, impaired wound healing, interstitial pneumonitis and edema [93].

4.1. CYP3A5 and SRL

At least 2 studies found no association between the CYP3A5*3 allele and SRL trough levels (C_0), dose requirement, C_0/dose [94, 95]. On the contrary, several other studies described

significant associations between SRL exposure and the CYP3A5*3 genotype [96–99]. The difference between the two kinds of results may be caused by the co-treated use of CNI. The effect of CYP3A5*3 genotype on SRL may only be notable in the patients taking no CNI [100].

4.2. CYP3A4 and SRL

The CYP3A4*22 allele was found to be associated with a moderately lower SRL hepatic metabolism in vitro, which, is inconsistent with another study [101]. A 113 stable recipients post renal transplantation switched from a CNI to SRL and found no significant association between this allele and SRL PK.

As for CYP3A4*1B allele and SRL PK, a study including 149 recipients with renal transplantation confirmed a significant association between this allele and SRL C_0/dose in the subgroup of 69 patients taking no CNI [96, 97], as the same case in CYP3A5*3. However, another study reported differently [97].

4.3. ABCB1 and SRL

As for ABCB1 gene, two studies showed no significant association between the ABCB1 c.3435C>T SNP and the SRL C_0/dose [96, 98]. In another study, no association was found between SRL C_0/dose and any of the ABCB1 exon 12, exon 21, and exon 26 SNPs, nor with their haplotype [94].

On the other hand, some reported that ABCB1 haplotype combination has a significant influence on SRL PK [44]. According to the report, the mean SRL C_0/dose was approximately 30% lower in Chinese renal transplantation recipients carrying ABCB1 CGC/CGC as than those carrying the CGC/TTT or TTT/TTT combinations (no effect of ABCB1 individual SNPs was found).

4.4. Other SNPs and SRL

As for the POR*28 allele, the PPARA rs4253728 SNP, and CYP2C8*3, no significant association was found between these SNPs and SRL PK [60, 68, 102–104].

Reported data about the influence of P450 or ABCB1 gene variants on the PK/PD of SRL are inconsistent [96, 97, 101, 105, 106]. CYP3A5*3 genotyping might be potentially useful in kidney transplant recipients with no CNI because of the possible competition for CYP3A5 metabolism [100]. As was stated in [47], at the present time, data are insufficient to recommend any genotype test for this immunosuppressant.

5. GP and EVE

EVE is the hydroxyethyl derivative of SRL, with a similar mechanism of action but much more predictable PK. Clinical trials using EVE followed, first in combination with CNI then in CNI-sparing regimens [100].

Again, the reported data about the association between SNP polymorphisms (including CYP3A5*3, CYP3A4*22, ABCB1 c.3435C>T, CYP2C8 and PXR) and the PK/PD of EVE are

inconsistent [26, 104, 107, 108]. For more details, readers may refer to [100, 109], one of which was specifically devoted to EVE.

6. GP and mycophenolic acid (MPA)

MMF is the most widely used antiproliferative agent [2], after administration, MMF is hydrolyzed to form MPA, which is in turn glucuronidated by several members of the uridine diphosphate-glucuronosyl transferase (UGT) family to form the main metabolite 7-O-MPA-glucuronide (MPAG). MPAG is excreted into bile by ABCC2 (or MRP2) and undergoes enterohepatic circulation [100]. Organic anion transporting polypeptides (OATPs, encoded by the SLCO genes), ABCB1 (P-glycoprotein, encoded by the ABCB1 gene), and cytochrome P450 (CYP) 2C8 and CYP3A4/5 are also involved in the PK of MPA [110].

6.1. UGT1A9 and MPA

As mentioned above, the UGT family plays an important role in the metabolic process MMF, of which, UGT1A9 is the most important family member that may affect the PK of MPA [110]. Reportedly, there a significant influence of the UGT1A9-2152C>T (rs17868320) and −275T>A (rs6714486) SNPs on MPA PK, while this conclusion seems to depend on the MPA dose, type of concomitant CNI (CsA or Tac), and time after transplantation [111–114].

Another UGT1A9 SNP, −98T>C (or UGT1A9*3) has also been found to be associated with higher MPA exposure in healthy volunteers and kidney transplantation recipients [111, 113–115].

As for the association between MPA PK and genetic variants in UGT1A8 or UGT2B7, reported results remain conflicting. Further investigation is needed to reveal the associations between MPA PK and UGT genotype [110, 116].

6.2. ABCC2 and MPA

ABCC2 is responsible for the biliary and renal excretion of MPAG and is inhibited by CsA [117]. According to the reports, the ABCC2 -24C>T has been studied most extensively among the SNPs that have been identified in the ABCC2 gene [110]. Some studies did find a significant relationship between various ABCC2 SNPs and MPA PK [118, 119], while many other studies have reported differently [110, 112, 113].

6.3. SLCO1B1 gene, SLCO1B3 gene, and MPA

The OATPs 1B1 (SLCO1B1 gene) and 1B3 (SLCO1B3 gene), 2 uptake transporters located on the sinusoidal side of the hepatocytes, are involved in the uptake of circulating MPAG in hepatocytes [112], which contributes to MPA enterohepatic circulation.

Among the SNPs that have been described in SLCO1B1, the nonsynonymous 521T>C (Val174Ala) and 388A>G (Asn130Asp) SNPs are associated with altered transport activity. These 2 SNPs are in LD and form haplotypes designated as SLCO1B1*1A (388A-521T),

SLCO1B1*1B (388G-521T), SLCO1B1*5 (388A-521C), and SLCO1B1*15 (388G-521C) [120]. In the studies of [112, 121], no significant association was found between the SLCO1B1 SNPs or haplotypes and MPA PK in renal transplantation recipients. In another study, SLCO1B1*15 allele carriers are found to be related to a lower level of MPAG than in noncarriers [122], suggesting a decreased hepatic uptake of the metabolite.

As for the various of SNPs in SLCO1B3, the most frequent are a T>G substitution at position 334 and a G>A substitution at position 699 (in complete LD), which result in 2 amino acid changes (Ser112Ala and Met233Ile). In a study of renal transplant recipients receiving MMF with no CsA immunosuppressive regimen, the SLCO1B3 334G allele was found to be associated with a significantly lower MPA dose-normalized exposure, Whereas in the group of MMF + CsA, no significant effect was observed [112].

6.4. Inosine monophosphate dehydrogenase (IMPDH) and MPA

The mechanism of action of MPA is the inhibition of the rate-limiting enzyme in de novo purine synthesis, inosine monophosphate dehydrogenase (IMPDH). Followed by the characterization of 2 isoforms in humans, IMPDH1 and IMPDH2 [123], many other genetic variants of both isoforms have been identified. Although a few of them seem to have an effect on the expression or the enzyme activity directly, most of the genetic variants are either rare or ineffective on enzyme activity [124, 125].

As for the potential influence of IMPDH variants on IMPDH activity, a study in a group of renal transplantation recipients on MPA demonstrated that the enzyme activity over 12 h was 49% higher in patients with the IMPDH2 variant rs11706052 than in patients with the wild-type. While in the group with no MPA, no difference was found [126]. In addition, for the IMPDH2 variant rs121434586, which has only been reported at a very low frequency, the enzyme activity is reduced to approximately 21% of wild-type activity, probably because of accelerated protein degradation. For the IMPDH1 variant only found in the Han Chinese-American group (rs72624960), the enzyme activity is as low as 10% compared with the wild type, also explained by accelerated degradation [124].

7. Conclusions

Tremendous efforts have been made in order to better understand the individual differences of IS. The genetics polymorphisms mentioned above are more or less related to the variability of IS PK/PD. To date, our knowledge of GP associated with IS in SOT is insufficient. It is still not sure whether genotype testing of these alleles would improve clinical outcome of SOT, this technique is definitely effective in depicting the PK parameters of IS, and has the potential to increase the chance of determining the best drug and the correct initial dose. A benefit of genotyping as a predictive test is that this is a fixed characteristic that will not change with pharmacological and physiological status [12]. Algorithms based on multiple genotypes may have a better performance in predicting the required dose, which helps recipients achieve target IS concentration faster with fewer dose adjustments. The Clinical Pharmacogenetics Implementation Consortium (CPIC) has also published Tac dosing guidelines based on

CYP3A5 genotype expression [127], which is inspiring that the transplant community devotes such great efforts to the PG research.

Whatever, based on the present literature, a study of initial tacrolimus dosing based on the CYP3A5 genotype would be logical. And according to [47], the French National Network of Pharmacogenetics (Réseau national de pharmacogénétique [RNPGx]) considered CYP3A4 (CYP3A4*22) genotyping would be potentially useful.

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Conflict of interest

No conflict of interest.

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