1-Alpha, 25-dihydroxyvitamin D3 alters the pharmacokinetics of mycophenolic acid in renal transplant recipients by regulating two extrahepatic UDP-glucuronosyltransferases 1A8 and 1A10

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Mycophenolic acid (MPA) is an important immunosuppressant broadly used in renal transplantation. However, the large inter-patient variability in mycophenolic acid (MPA) pharmacokinetics (PK) limits its use. We hypothesize that extrahepatic metabolism of MPA may have significant impact on MPA PK variability. Two intestinal UDP-glucuronosyltransferases 1A8 and 1A10 plays critical role in MPA metabolism. Both *in silico* and previous genome-wide analyses suggested that vitamin D (VD) may regulate intestinal *UGT1A* expression. We validated the VD response elements (VDREs) across the *UGT1A* locus with chromatin immunoprecipitation (ChIP) and luciferase reporter assays. The impact of 1-alpha,25-dihydroxyvitamin D3 (D3) on *UGT1A8* and *UGT1A10* transcription and on MPA glucuronidation was tested in human intestinal cell lines LS180, Caco-2 and HCT-116. The correlation between transcription levels of VD receptor (VDR) and the two UGT genes were examined in human normal colorectal tissue samples (n = 73). PK alterations of MPA following the parent drug, mycophenolate mofetil (MMF), and D3 treatment was assessed among renal transplant recipients (n = 10). Our ChIP assay validate three VDREs which were further demonstrated as transcriptional enhancers with the luciferase assays. D3 treatment significantly increased transcription of both UGT genes as well as MPA glucuronidation in cells. The *VDR* mRNA level was highly correlated with that of both *UGT1A8* and *UGT1A10* in human colorectal tissue. D3 treatment in patients led to

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about 40% reduction in both AUC_{0-12} and Cmax while over 70% elevation of total clearance of MPA. Our study suggested a significant regulatory role of VD on MPA metabolism and PK via modulating extrahepatic UGT activity. (Translational Research 2016;178:54–62)

Abbreviations: AcMPAG = acyl mycophenolic acid glucuronide; ChIP = chromatin immunoprecipitation; Cmax = maximum concentration; DR = direct repeat; MMF = mycophenolate mofetil; MPA = mycophenolic acid; MPAG = mycophenolic acid glucuronide; PK = pharmacokinetics; PD = pharmacodynamics; TDM = therapeutic drug monitoring; UGT = UDP-glucuronosyltransferase; VDR = Vitamin D3 receptor; VDRE = Vitamin D response element

AT A GLANCE COMMENTARY

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Background

Mycophenolic acid (MPA) is an important immunosuppressant, but the large inter-patient variability in its pharmacokinetics (PK) limits its use. Our study found that 1-alpha,25-dihydroxyvitamin D3 (VD) regulates the transcription of two intestinal UDP-glucuronosyltransferases *UGT1A8* and *UGT1A10* which are involved in glucuronidation of MPA, which has a significant impact on MPA pharmacokinetics in kidney transplant recipients.

Translational Significance

Our study identified a novel mechanism underlying the inter-patient variability in MPA pharmacokinetics, and suggests co-administration of VD with MPA may potentially result in drug-drug interaction and lead to inter- and intra-patient difference in clinical response to MPA treatment.

INTRODUCTION

Mycophenolate mofetil (MMF) is increasingly used as an important immunosuppressant to prevent acute rejection after kidney transplantation. Recent clinical studies have consistently suggested that including MMF is superior to other immunosuppressant combinations in maintaining renal function, in the development of adverse effects, as well as in graft and patient survival.[1-4] However, inter-patient variability in its pharmacokinetics (PK) limits its full potential in clinical applications.[5,6] MMF is a prodrug which is hydrolyzed into its active form mycophenolic acid (MPA) after oral intake.[5] It has been shown that the extent of MPA exposure is highly correlated with acute allograft rejection.[7] About 20% of patients discontinue the medication due to the adverse events such as gastrointestinal disorders and bone marrow suppression which were suggested to be associated with the free MPA fraction.[7,8] In spite of numerous studies to date, the mechanism underlying this inter-patient PK variability of MMF/MPA has not been completely elucidated.[6] In order to individualize the MMF dosage, current MMF administration protocols increasingly apply therapeutic drug monitoring (TDM).[7,9] Therefore, identifying factors affecting MMF/MPA PK is of particular importance to achieve more effective and safer use of this drug.

Inter-patient PK variability are largely attributed to the variable activities of drug metabolism pathways. Previous studies have demonstrated that MPA is mainly metabolized via glucuronidation by UDP-glucuronosyltransferases (UGTs) in both the liver and intestine, which produces a major phenolic glucuronide, mycophenolic acid glucuronide (MPAG), and a minor acyl glucuronide (AcMPAG).[10-14] UGTs catalyze the formation of hydrophilic glucuronides, which is one of the important detoxification processes in human metabolism.[15] The human UGTs consists of 4 families, UGT1, UGT2A and 2B, UGT3, and UGT8, of which, UGT1, UGT2A and UGT2B are primarily involved in drug metabolism and are encoded by genes located on chromosome 2 and 4, respectively.[15-17] Variability in UGT activity has been significantly associated with inter-individual differences in metabolism of a broad array of endogenous and exogenous compounds including many therapeutic agents.[18] Previous studies have revealed that glucuronidation of MPA mainly involves UGT1A8 and UGT1A9, with UGT1A10 and UGT2B7 playing a minor role.[10-14] While UGT1A9 and UGT2B7 are important hepatic UGTs whose roles in MPA metabolism have been widely investigated, UGT1A8 and UGT1A10 are the only two UGT1A enzymes expressed in human intestinal tissue including the small intestine, colon and rectum,[15,19] and their roles in MPA PK variability has drawn only limited attention. It has been suggested that intestinal UGTs are also critical to the metabolism of many