Multidrug resistant transporter MDR1/P-glycoprotein, the gene product of \textit{MDR1}, is a glycosylated membrane protein of 170kDa, belonging to the ATP-binding cassette superfamily of membrane transporters. MDR1 was originally isolated from resistant tumor cells as part of the mechanism of multidrug resistance, but over the last decade, it has been elucidated that human MDR1 is also expressed throughout the body to confer intrinsic resistance to the tissues by exporting unnecessary or toxic exogeneous substances or metabolites. A number of various types of structurally unrelated drugs are substrates for MDR1, and MDR1 and other transporters are recognized as an important class of proteins for regulating pharmacokinetics and pharmacodynamics. It has been accepted that intestinal MDR1 located in the brush border membrane of enterocytes limits the oral absorption of the drugs, which are the substrates for MDR1, and the interaction of drug candidates with MDR1 has attracted a great deal of attention, when developing an oral medicine within a short time period. However, the analysis of molecular and pharmacokinetic properties of 222 commercially available oral drugs suggests that being a substrate for MDR1 does not always result in poor bioavailability; that is, the average molecular weight for MDR1 substrates is $479\pm240$Da ($\pm SD$) and their bioavailability is $47.2\pm21.7\%$, whereas they are $311\pm115$Da and $67.0\pm28.9\%$, respectively, for non-substrates [1]. The average value of bioavailability is certainly lower for substrates, but the difference of bioavailability can be explained by that of molecular weight, suggesting that intestinal MDR1 might not act as a barrier for oral absorption of drugs. The potential role of MDR1 in oral absorption of drugs has been established through considerable efforts using in vitro cell culture systems including Caco-2 cell line, however, it is recently that the expression level of MDR1 in Caco-2 cells is quantitatively compared with human enterocytes. We compared the expression levels of mRNAs for MDR1, MRP1, MRP2 and CYP3A in Caco-2 cells, kindly supplied by several laboratories in Japan, with those in human normal duodenal enterocytes, normal colorectal tissues and colorectal adenocarcinomas, which were obtained as biopsy samples [2]. It was demonstrated that the expression levels for MDR1, MRP1, MRP2 and CYP3A were about 12-, 3-, 7- and 8000-fold lower in Caco-2 cells than in human normal duodenal enterocytes, respectively [2]. It is important to pay attention to the difference of their expression, when expecting the oral absorption in vivo from the in vitro data obtained using Caco-2 cells. Recently, we have conducted a cross-over study in which the serum concentration-time profiles of digoxin, a typical substrate for MDR1, was compared between after conventional oral administration of a tablet and after direct intraduodenum administration as a saline solution [3]. Absorption rate of digoxin from duodenum depended on the \textit{MDR1} C3435T genotype, indicating that it was regulated by MDR1, and it was found that digoxin was absorbed very rapidly from duodenum, and serum concentrations after conventional oral administration of a tablet was significantly affected by disintegration, dissolution and gastric emptying [3]. Collectively, it can be said that intestinal MDR1 might not act as a barrier for oral absorption of drugs in vivo. The in vitro studies using Caco-2 cells have certainly demonstrated that intestinal MDR1 limits the oral absorption, and thus further examinations should be addressed on the factors regulating the MDR1 function and the role of intestinal MDR1.

References: