ESTIMATION OF THE CONTRIBUTION OF P-GLYCOPROTEIN TO INTESTINAL ABSORPTION OF VARIOUS DRUG CANDIDATES: ACTIVITY REPORT FROM WORKING GROUP FOR THE DRUG TRANSPORTERS
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As indicated by Professor Yamashita’s overview, it is very important to develop a high-throughput screening method for evaluating the intestinal absorption properties of new drug candidates during the R&D process. On the consortium for evaluating intestinal absorption in the R&D, organized by Professor Shinji Yamashita, Setsunan University, three projects are in progress to predict drug absorption in human based on in vitro data. Among the three projects, “assessment of the contribution of P-glycoprotein (P-gp) to intestinal absorption of new drug candidates” has been selected as Project 3 and our members are investigating this issue. The ultimate goal of this investigation is to construct a simple method of evaluating the extent of the P-gp contribution to intestinal absorption of new drug candidates. If drug candidates are a P-gp substrate, these agents do not always show a low permeability across the intestinal membrane. Actually, Sakaeda et al analyzed the molecular and pharmacokinetic properties of 222 commercially available oral drugs and suggested that being a substrate of P-gp does not always result in poor bioavailability1). These results can be easily understood because drugs showing relatively good bioavailability have been screened among numerous drug candidates source as oral drugs. The intestinal permeability of these drugs might be determined by various factors such as diffusivity for absorptive direction, affinity for P-gp, and transport ability to blood vessels across the basolateral membrane as well as other factors. Therefore, we must also investigate whether P-gp is one of determinant factors for intestinal absorption of drug and drug candidates.

Recently, Troutman and Thakker2) suggested that the use of Efflux Ratios could be misleading in predicting the extent to which P-gp attenuates the absorptive transport of substrates because greater difference between their $K_m$ values of P-gp-mediated efflux activities appear to be observed in absorptive and secretory directions, respectively. This report indicates that estimate the precise contribution of P-gp on intestinal absorption of drugs, at least three factors such as, luminal concentration of the drugs, their affinity to P-gp, and their intrinsic apical-to-basal permeability, must be estimated by appropriate methods. As a first step to characterize the above issues, we are investigating (i) to determine Caco-2 permeability of well-known P-gp substrates with diverse intestinal permeability, and to compare the differences of data from each pharmaceutical company, and (ii) to classify the relationship between their Efflux Ratios (= $P_{app,BA}/P_{app,AB}$) and their $F_a$ values in vivo (Fig. 1). In the present symposium, we will present data for the above two issues obtained from pharmaceutical companies in Japan including our laboratory and will discuss how to estimate the contribution of P-gp to intestinal absorption, and which factors are major determinant for intestinal absorption of P-gp substrates.