COLLEGE OF PHARMACY
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Pharmaceutical Sciences Sedman Lecture

"Pharmacoproteomics (PPx) of the CNS Barriers: Recent Advance and Prospect"

Presented by:

Tetsuya Terasaki

Division of Membrane Transport and Drug Targeting
Graduate School of Pharmaceutical Sciences
Tohoku University
Sendai, Japan

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Substrate exchange between blood and central nervous system (CNS) is strictly regulated by the function of brain barriers, *i.e.*, the blood-brain barrier (BBB), the blood-spinal cord barrier (BSB), the blood-cerebrospinal fluid barrier (BCB), and the blood-arachnoid barrier (BAB). Unbound drug concentration in the brain interstitial fluid (BIF) and/or the cerebrospinal fluid (CSF) is a key factor for the rational prediction of drug sensitivity to the CNS, while it is not so easy. Because the active transport function in these barriers generates the unbound drug concentration gradient between blood and BIF/CSF. Knowing location and amount of membrane transporter protein is crucial for the prediction of *in vivo drug* transport activity, therefore it is important to measure the transporter protein expression in the brain barriers. We have established a method to quantify proteins by LC-MS/MS combined with the *in silico* criteria of peptide selection among the peptides produced by tryptic digestion (1).

Similarity and difference of the transporter protein expression have been elucidated by comparing that of immortalized human BBB model (D3 cell line) *versus* isolated brain capillaries in human (2,3). Interspecies differences have also been exhibited for mouse (1), rat (4), dog (5), marmoset (4), cynomolgus monkey (6) and human (2). Assuming the intrinsic efflux transport activity of P-gp determined by in vitro *mdr1a* gene transfected cell line is same to that of *in vivo* BBB, we have succeeded to predict the unbound drug concentration gradient between BIF and plasma in the normal (7), epileptic mouse (8) and cynomolgus monkey (9) based on the pharmacokinetic model constructed. For the understanding of functional changes of the BBB transporter, we have examined the effect of tumor necrosis factor-α (TNF-α; an inflammatory mediator) on the BBB P-gp activity by phosphor-proteomics (10). Actin Filament-Associated Protein-1 (AFAP-1) is a key mediator in the inflammatory signaling-induced, translocation-independent rapid attenuation of P-gp efflux activity in human BBB, showing difficulties in the prediction of transport activity of in vivo BBB in the diseased states (10).

Contrary to the recent progress of the BBB research, lots of subjects remain to be clarified for the function of BCB, BSB and BAB. One of crucial subjects is, I believe, to clarify functional significance and regulation mechanism of BAB and BSB transport function for the reliable prediction of drug concentration in the CSF.

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