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Quantitative Membrane Proteomics and its Application in Translational Pharmacology

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The drug development process is expensive, time-consuming and of high attrition. Often in spite of the efforts on improving drug discovery ability and the excellent preclinical results, a significant number of candidate drugs failed during clinical trial because of the unfavorable efficacy and/or safety properties. To aim at improving success rates in the crucial preclinical stage of development, scientists in the pharmaceutical industry identify a number of fundamental elements to guide decision making in drug discovery and development. The elements are referred as three pillars of Phase II survival [1], which include: 1) a drug is present at the target site of action. 2) a drug binds to the pharmacological target. 3) pharmacological activity is expressed associated with the shown target exposure and target binding.

Membrane proteins including transporters, receptors and channels are expressed on cellular membrane and play essential roles in the transport of nutrients, ions and physiological compounds to sustain cell survival. A subset of membrane proteins called drug transporters also transport therapeutical xenobiotics across cellular barrier to regulate the exposure on the site responsible for their effect and/or toxicity. Accordingly membrane transporters become potential pharmacological targets, biomarkers, carriers for drug delivery and regulators of drug absorption, disposition, metabolism and elimination (ADME) that may be involved in clinical drug-drug interactions and adverse effects.

Since the predictive information allows extrapolation to human from in vitro or preclinical results, model based predictions, e.g. physiologically-based pharmacokinetics (PBPK) model, become emerging approaches used to predict complex drug disposition in a way of holistic perspectives and are essential tools in the translational research for the systemic and quantitative integration of diverse preclinical information for the sake of rational drug design [2,3]. Rapid advance in this regard requires analytical tools that can quantitatively determine the components associated with biological processes and measure the differences between two or more physiological states of a biological system. Toward this end, technologies for characterizing membrane proteins at different molecular levels such as transcriptomics, proteomics, and metabolomics have been a growing field, and proteomics in particular becomes a key enabling technology and is continuing to evolve rapidly. While tissues selective expressions at mRNA level are well-addressed in the literatures [4-6], quantitative expressions of membrane proteins in human organs at protein level are still missing.

Liquid chromatography tandem mass spectrometry (LC-MS/MS)-based proteomics address two shortcomings from classical proteomics quantifications technologies---resolution of separation provided by gels and identity of the underlying protein, and offer considerable opportunities for biological understanding and translational pharmacology in drug discovery and development. While global proteomics can be used to indentify thousands of proteins in cells or other biological samples, targeted proteomics quantifications use peptides unique to the protein of interest, which can be readily obtained from commercial sources and serve as surrogate standards to overcome the absence of protein standards, to assess quantitative protein expressions in various biological matrices by way of a sensitive and selective method that is amenable to high-throughput formats [7]. However, despite of advances in protein analytical technologies have been offering broad applications in drug discovery programs, significant analytical challenges in quantitative membrane proteomics remain, as membrane proteins are expressed at relatively low levels and often comprise multiple hydrophobic domains that resist exposure to aqueous environments leading to solubilization and denaturation limitations with respect to facilitating protease access and digestion efficiency. To overcome aforementioned hurdles, optimizations tailored to a specific protein often include membrane solubilization strategies, in which the organic solvents, detergents, and chaotropic agents are examined to be compatible with the route of digestion and subsequent MS analysis. The released proteolytic peptides are also monitored over the course of the digestion to attain the optimized digestion condition. The combination of proteases, example Lys-C and trypsin, and the use of isotope labeled internal standards at different level, e.g. stable isotope label by amino acid in cell culture (SILAC), are commonly applied for addressing the incomplete digestion [8,9]. New tools are continually being explored. For example, recently lipid-based protein immobilization that offer immobilization and digestion of bilayer-embedded native membrane proteins is used to rapidly probe the solvent exposed domains in a flow cell format [10].

Quantitative membrane proteomics is now beginning to learn for which type of study these methods can be meaningfully applied; however, significant further improvements to experimental strategies are required particularly for the quantitative analysis of post-translational modifications. Improvement in sample preparation is equally important in order to differentiate the sub-cellular components for investigating proteomes of intracellular membranes. As such, significant technological advances and method optimizations that affect quantification in bottom-up proteomic workflows for membrane proteomics are further required to improve detection and accuracy through addressing the sample handling, digestion efficiency, and separation challenges.

References

1. Morgan P, Van Der Graaf PH, Arrowsmith J, Feltner DE, Drummond KS, et al.

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(2012) Can the flow of medicines be improved? Fundamental pharmacokinetic and pharmacological principles toward improving phase II survival. Drug Discov Today 17: 419-424.

2. Atkinson AJ Jr, Smith BP (2012) Models of physiology and physiologically based models in clinical pharmacology. Clin Pharmacol Ther 92: 3-6.
3. Smith BJ (2012) An industrial perspective on contemporary applications of PBPK models in drug discovery and development. Biopharm Drug Dispos 33: 53-54.
4. Nishimura M, Naito S (2005) Tissue-specific mRNA expression profiles of human ATP-binding cassette and solute carrier transporter superfamilies. Drug Metab Pharmacokinet 20: 452-477.
5. Nishimura M, Naito S (2008) Tissue-specific mRNA expression profiles of human solute carrier transporter superfamilies. Drug Metab Pharmacokinet 23: 22-44.
6. Nishimura M, Suzuki S, Satoh T, Naito S (2009) Tissue-specific mRNA expression profiles of human solute carrier 35 transporters. Drug Metab Pharmacokinet 24: 91-99.
7. Kamiie J, Ohtsuki S, Iwase R, Ohmine K, Katsukura Y, et al. (2008) Quantitative atlas of membrane transporter proteins: Development and application of a highly sensitive simultaneous LC/MS/MS method combined with novel in-silico peptide selection criteria. Pharm Res 25: 1469-1483.
8. Balogh LM, Kimoto E, Chupka J, Zhang H, Lai Y (2012) Membrane protein quantification by peptide-based mass spectrometry approaches: Studies on the organic anion-transporting polypeptide family. J Proteomics and Bioinformatics S4: 003.
9. Wu CC, Yates JR 3rd (2003) The application of mass spectrometry to membrane proteomics. Nat Biotechnol 21: 262-267.
10. Sui P, Miliotis T, Davidson M, Karlsson R, Karlsson A (2011) Membrane protein digestion - comparison of LPI hexalane with traditional techniques. Methods Mol Biol 753: 129-142.