

New insights into P-glycoprotein as a multidrug transporter

Mi Sun Jin¹, Michael L. Oldham², Qiuju Zhang², and Jue Chen^{2,3}

¹*Department of Life Sciences, Gwangju Institute of Science and Technology,* ²*Department of Biological Sciences, Purdue University and* ³*Howard Hughes Medical Institute, West Lafayette, Indiana 47907, USA.*

P-glycoprotein (P-gp) is an ATP-binding cassette (ABC) transporter that confers multidrug resistance in cancer cells. It also affects the absorption, distribution, and clearance of cancer unrelated drugs and xenobiotics. For these reasons, the structure and function of P-gp have been studied extensively for decades. Here we present biochemical characterization of P-gp from *C. elegans* and its crystal structure at 3.4 Å resolution. This work provides the following new information towards a mechanistic understanding of P-gp: (1) The apparent affinities of P-gp for anticancer drugs actinomycin D and paclitaxel are approximately 4,000 and 100 times higher, respectively, in the membrane bilayer than in detergent. This affinity enhancement highlights the importance of membrane partitioning when drug accesses the transporter in the membrane. (2) The transporter in the crystal structure opens its drug pathway at the level of the membrane's inner leaflet. In the helices flanking the opening to the membrane we observe extended loops that may possibly mediate drug binding and/or function as hinges to gate the pathway. (3) The interface between the transmembrane and nucleotide-binding domains, which couples ATP hydrolysis to transport, contains a ball-and-socket joint and salt bridges similar to the ABC importers, suggesting that ABC exporters and importers may share a similar mechanism to achieve alternating access for transport.

Keywords: P-glycoprotein, ABC transporter, Multidrug transporter, Drug resistance, X-ray crystallography

Curriculum Vitae

Name: Mi Sun Jin
Office Address: Department of Life Sciences
GIST(Gwangju Institute of Science and Technology)
123 Chumdangwagi-ro Buk-gu
Gwangju 500-712 South Korea
Phone and E-mail: 82-62-715-3562
misunjin@gist.ac.kr

Education

1998. 3 ~ 2002.2 B.S., Sogang University, Department of Chemical Engineering
B.S., Sogang University, Department of Chemistry
2002. 3 ~ 2004. 2 M.S., KAIST, Department of Chemistry
2004. 3 ~ 2008. 8 Ph.D., KAIST, Department of Chemistry
2008. 9 ~ 2009. 9 Postdoc, KAIST, Department of Chemistry
2009. 10 ~ 2013. 9 Postdoc, Purdue University, Department of Biological Sciences
2013. 10 ~ 2014. 03 Research Specialist, Purdue University

Current Status

2014. 07 ~ present Assistant Professor, GIST

Awards

2008 Department of Chemistry Excellent Thesis Award
2008 Agawal Award

Postdoctoral Fellowships

2009 National Research Foundation of Korea
2010 - 2013 The International Human Frontier Science Program

Publications

1. **Mi Sun Jin**, Michael L. Oldham, Qiuju Zhang, and Jue Chen (2012), Crystal structure of the multidrug transporter P-glycoprotein from *C. elegans*, *Nature*, 490(7421), 566-569
2. Jin Young Kang, Xuehua Nan, **Mi Sun Jin**, Suk-Jun Youn, Young Hee Ryu,

- Shinji Ma, Seung Hyun Han, Sang-Gi Paik, Hayyoung Lee, and Jie-Oh Lee (2009), Recognition of lipopeptide patterns by TLR2-TLR6 heterodimer, *Immunity*, 31(6): 873-84
3. **Mi Sun Jin**, Sung Eun Kim, Jin Young Heo, Mi Eun Lee, Ho Min Kim, Sang-Gi Paik, Hayyoung Lee and Jie-Oh Lee (2007), Crystal structure of the TLR1-TLR2 heterodimer induced by binding of a tri-acylated lipopeptide, *Cell*, 130(6): 1071-1082
 4. **Mi Sun Jin** and Jie-Oh Lee (2008), Structures of the Toll-like Receptor Family and Its Ligand Complexes, *Immunity*, 29(2): 182-191
 5. **Mi Sun Jin** and Jie-Oh Lee (2008), Structures of TLR-ligand complexes, *Curr Opin Immunol.*, 20(4): 414-419
 6. **Mi Sun Jin** and Jie-Oh Lee (2008), Application of hybrid LRR technique to protein crystallization, *BMB reports*, 41(5): 353-357
 7. Jin Hee Ahn, Mi Sik Shin, Mi Ae Jun, Sun Ho Jung, Seung Kyu Kang, Kwang Rok Kim, Sang Dal Rhee, Nam Sook Kang, Sun Young Kim, Sang-Kwon Sohn, Sung Gyu Kim **Mi Sun Jin**, Jie-Oh Lee, Hyae Gyeong Cheon and Sung Soo Kim (2007), Synthesis, biological evaluation and structural determination of beta-aminoacyl-containing cyclic hydrazine derivatives as dipeptidyl peptidase IV (DPP-IV) inhibitors, *Bioorg Med Chem Lett.*, 17(9): 2622-2628
 8. Hyun Jung Oh, Kyung-Kwon Lee, Su Jung Song, **Mi Sun Jin**, Min Sup Song, Joo Hyun Lee, Chang Rak Im, Jie-Oh Lee, Shin Yonehara and Dae-Sik Lim (2006), Role of the Tumor Suppressor RASSF1A in Mst1-Mediated Apoptosis, *Cancer Res.*, 66(5): 2562-2569
 9. Jung-In Kim, Chang Jun Lee, **Mi Sun Jin**, Cherl-Ho Lee, Sang-Gi Paik, Hayyoung Lee and Jie-Oh Lee (2005), Crystal structure of CD14 and its implications for lipopolysaccharide signaling, *J. Biol. Chem.*, 280(12): 11347-11351