Metabolic flux analysis of mantle lymphoma cells upon Bruton tyrosine kinase inhibition

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Ibrutinib, a Bruton tyrosine kinase inhibitor, is being popularly used for treatment of relapsed/refractory mantle cell lymphoma (MCL) as well as chronic lymphocytic leykemia/ small lymphocytic lymphoma (CLL/SLL). We are working on metabolic pathway analysis of MCL cells upon ibrutinib treatment using novel 13C NMR and mass spectrometry technique and flux analysis methods. Ibrutinib sensitive MCL-RL cells and ibrutinib less sensitive Jeko-1 cells were studied. Cells were incubated in the medium containing 1,6-13C glucose, 1,2-13C glucose or U-13C glutamine for 8 hours to reach steady state of labeling enrichment of intracellular metabolites, and 13C labeling information was obtained using NMR or liquid chromatography mass spectrometry (LC-MS) techniques. Bonded cumomer and fragmented cumomer analysis methods were employed for analysis of NMR and LC-MS data. Significant changes were observed in the fluxes of glycolysis, glutaminolysis, reductive carboxylation and fatty acid syntheis in MCL-RL cells after ibrutnib treatment while less or no changes in JeKo-1 cells. Glycolytic flux changed to 1/4 in MCL-RL cells while to 1/2 in in JeKo-1 cells. Glutaminolysis changed by 90% in MCL-RL cells while no change in JeKo-1 cells. When a glutaminase inhibitor, CB-839, was added to medium, JeKo-1 cells exhbited remarkable response in cell growth while MCL-RL cells did not. This study demonstrates that metabolic flux analysis provides an important clue of what pathway is being affected and what pathway is not to specific kiniase inhibitors and which metabolic pathway should be further targeted with additional drugs.

Speaker Biography

Seung-Cheol Lee has finishes his BS (Physics) from Korea Advanced Institute of Science and Technology in 1993 and MS (Solid State Physics) from Korea Advanced Institute of Science and Technology in 1995. After that, he did his Post-Graduate Training (Postdoc in Biophysics) from Korea Basic Science Institute (2001-2004) and Postdoc in Radiology from University of Pennsylvania (2004-2007). He has expertise in MRI and MRS of cancer cells, animal models and human patients' prediction and early detection of therapeutic response in non-Hodgkin's lymphoma.

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