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Metabolic flux analysis of mantle lymphyoma 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 techniques 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 exhibited 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 drugss.

Biography

Seung-Cheol Lee has completed his PhD from Korea Advanced Institute of Science and Technology in 2001 and has completed his Post-doc at the Korea Basic Science Institute and the University of Pennsylvania. He is a Research Assistant Professor of Radiology at the University of Pennsylvanis since 2011. His research focus is on imaging cancer metabolism in the cellular level, animal models and human patients using NMR and mass spectrometry.

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