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In-depth quantification of signaling pathways for advancing cancer personalized therapies

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Abstract

All cancers deregulate the activity of kinase-driven signaling pathways. These enzymes are therefore drug targets for the treatment of different malignancies. However, not all cancer patients respond to these drugs to the same extent, meaning that there are different signaling routes by which cancer cells can sustain the malignant phenotype. In order to shed light into this complexity and to identify biomarkers of response for patient stratification, we developed methods to quantify signaling as comprehensively as possible. These techniques are based on quantification of protein phosphorylation by mass spectrometry. The presentation will summarize our efforts to develop robust workflows for label-free quantitative phosphoproteomics, which involved the optimization of extraction procedures, normalization of MS data and the design of a computer program that allows efficient implementation of the workflow. We also developed a computational approach to obtain readouts of pathway activation from phosphoproteomics data. These techniques were used to quantify kinase activities and thus profile signaling pathways in leukemia cell lines and primary tissues. Fitting quantitative values of kinase activities into mathematical models allowed us to identify the activities that predicted responses to several kinase inhibitors. We observed that pathways parallel to those being targeted predicted sensitivity to inhibitors that target PI3K signaling nodes. The most frequently deregulated pathways in primary leukemia cells (20 cases analyzed) were driven by the activity of kinase such as PI3K, cyclin dependent kinases, casein kinases and PAK. In conclusion, in-depth quantification of phosphorylation by MS represents a general tool to profile signaling and to identify biomarkers of response to inhibitors that target the signaling network.

Biography

Pedro R. Cutillas completed his PhD at University College London and his postdoctoral work at the Ludwig Institute for Cancer Research (London Branch). In 2007 he obtained a lectureship in Barts Cancer Institute, where he set up a research group focusing on the analytical aspects of cancer cell signaling. He has recently moved to the MRC Clinical Sciences Centre at Imperial College London to head the Biological MS and Proteomics Laboratory. In the last 5 years Dr Cutillas has published 19 papers and filed 5 patent applications.