Targeting cancer therapy with phosphoproteomics

May 11 2015

Winner of the Louise Eisenhardt Traveling Scholarship Award, Teresa Purzner, MD, presented her research, Quantitative Phosphoproteomics for Targeted Cancer Therapy.

Medulloblastomas (MB), the most common malignant pediatric brain tumor, originate from dysregulation of developmental signaling pathways. To discover important drug targets within these pathways, researchers have undertaken the first quantitative mass spectrometry-based phosphoproteomic approach to identify important phosphorylation events, using the Hh signaling pathway as the model.

Quantitative phosphoproteomic analysis was performed using SILAC (Stable Isotope Labeling with Amino acids in Cell culture), combined with strong cation exchange fractionation and phosphopeptide enrichment by immobilized metal affinity chromatography (IMAC), followed by multiplexed quantitative mass spectrometry.

The study revealed changes in phosphorylation of 94 proteins only 25 minutes after Shh exposure. Motif analysis revealed a novel and critical role for the kinase, CK2, in mediating 45 percent of all early phosphorylation events. Importantly, CK2 affects terminal Hh signaling components, circumventing challenges of emergence of resistance and a priori resistance commonly encountered with existing small molecule inhibitors developed for medulloblastoma. CK2 inhibitors demonstrated early and sustained inhibition of Hh signaling across several mammalian cell types, including MB cells. In vivo, mice harboring flank MB

allografts derived from Ptch+/−;Tpr53−/− tumor harbouring a point mutation in Smo that renders them resistant to other Hh pathway inhibitors, showed near-complete cessation of tumor growth in response to TBB, a highly potent and selective inhibitor of CK2.

This quantitative phosphoproteomic approach to Hh signaling has provided a perspective that was unattainable with previous transcription and genome-based efforts. This success using one pathway will set the foundation for others to apply a similar approach in different tumor initiating pathways.

Provided by American Association of Neurological Surgeons