Stony Brook University

Biomedical Informatics Grand Rounds

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Feedback Pathways Regulating Drug Interaction and Resistance in Lung Cancer

Wednesday, September 4, 2019 3 pm—4 pm
Health Science Center L2-3B

Abstract:

Multiple signal transduction pathways can be concurrently active within a single cell, and extensive crosstalk can occur between receptor tyrosine kinases (RTKs). Additionally, tumor tissues can be comprised of a heterogeneous collection of cell states utilizing distinct RTKs for maintenance of tumor cell growth and survival. As a consequence of this complexity, many tumors may be only partially sensitive to single agent therapies and would require the interdiction of multiple RTKs and other protein signaling targets for optimal anti-cancer therapy. Understanding pathway crosstalk is vital to guide the rational combination of approved and experimental anti-cancer agents. Co-option of diverse kinase signaling networks by a single RTK is observed in the NSCLC H1993 cell line. Here, exposure to small molecule Met tyrosine kinase inhibitors attenuated both Met and Met-associated SH2/PTB domain adapter proteins as well as more distantly related RTK signaling networks. Exposure of H1993 epithelial carcinoma cells to Met inhibitors (2hrs) markedly inhibited ~250 Met substrates, both known and unknown, including the cell surface signaling proteins Met, Ron, EGFR, ErbB2, DDR1, CSFR2, ITG4, ITG6, EphA2, EphB4. This in turn results in a comparatively complete dephosphorylation of a wide array of signaling adaptors, cell-cell junction proteins, cytoskeletal reorganizing elements and folding chaperones. While marked attenuation of EGFR was observed in response to Met inhibition alone, the combination of both Met and EGFR inhibitors was required for full dephosphorylation of both Erk1/2, pS6 and pPRAS40. In erlotinib resistant mt-EGFR HCC827 (HCC827ER) cell line, Met becomes active but cell inhibition, both proliferative and apoptotic, requires the combination of Met and EGFR inhibitors. Several conclusions can be drawn. First, Met is the principle source of phosphotyrosine in H1993, and the cell line is likely onco-addicted solely to Met. Second, effective blockade of Erk activation was only observed with the two Met/erlotinib combinations suggesting synergy relies on erlotinib directed Erk inhibition in the H1993 model. Third, Met essentially 'highjacks' EGFR, ErbB2, CSF1R2, Ron and EphR as signaling adapters. The mechanism by which EGFR inhibitors, with no single agent activity, can synergize with Met inhibitors is being further examined by phospho-profiling and metabolic-profiling of H1993 and HCC827ER cell lines.

Bio:

Dr. Haley earned a Ph.D. in Molecular Endocrinology from the Howard Florey Institute for Experimental Physiology and the University of Melbourne and completed postdoctoral research fellowships at the Howard Florey Institute in Melbourne and at the Imperial Cancer Research Fund and the Ludwig Institute for Cancer Research in London. He returned to the U.S. to join Oncogene Science Inc. as Program Manager for Cancer Therapeutics and was subsequently recruited to OSI Pharmaceutical Inc. in 1992. At OSI, Dr. Haley served as Senior Director for Exploratory Cancer Research, Senior Research Director for Translational and EMT Research, and Senior Research Director for Discovery Research. Dr. Haley has worked in the area of biological mass spectrometry since 1995, notably pioneering the field of phosphoproteomics from 2000 - 2004. He has published on the exploration of cancer drug resistance and cancer biomarkers, and has organized and chaired several AACR symposia and mini-symposia on the subject. His current expertise is in the quantitation of post-translational modifications coupling stable isotope labeling and mass spectrometry.

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