GESELLSCHAFT DEUTSCHER CHEMIKER

KOLLOQUIUM

Sommersemester 2018

Titel

A combined chemical biology and proteomics approach to elucidate polypharmacology mechanisms of targeted drugs

Vortragender

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Abstract

Targeted drugs, in particular kinase inhibitors, can have widely varying selectivity profiles. This is usually considered a concern due to potential toxicity, but can also result in unexpected anticancer activity. However, elucidation of the underlying mechanisms of action (MoAs) of such unexpected activity, a critical requirement for drug repurposing, is a major challenge. We here describe an integrated, mass spectrometry-based chemical and phosphoproteomics approach that can elucidate complex MoAs of multikinase inhibitors and lead to identification of novel drug combinations. Through an unbiased cell viability screen against multiple non-small cell lung cancer (NSCLC) cell lines we identified anticancer activity of several multikinase inhibitors, namely ceritinib, midostaurin and foretinib, which displayed efficacy in cell line panels with partial overlap. Importantly, comparison with appropriate control compounds indicated that in many of these NSCLC cell lines this activity was independent of the intended drug targets. We therefore applied an unbiased chemical proteomics approach that revealed several new kinase targets of these compounds. In parallel, global and tyrosine phosphoproteomics determined their proteome-wide signaling effects. Integration of these datasets nominated several targets/pathways with substantial signaling crosstalk as functionally relevant. Combined gene silencing and chemical probe treatment identified complex polypharmacology MoAs of all three inhibitors involving multiple different off-targets, also in cells that are sensitive to two different compounds. This mechanistic understanding led to the rational design and validation of synergistic drug combinations with the microtubule inhibitor paclitaxel (ceritinib), the PLK1 inhibitor BI-2536 (midostaurin) and the Aurora kinase B inhibitor barasertib (foretinib) in different lung cancer cells. In summary, the multikinase inhibitors ceritinib, midostaurin and foretinib display anticancer activites in NSCLC cells also independently of their intended targets. Through an integrated chemical biology and functional proteomics approach we elucidated their complex polypharmacology MoAs and identified novel rational drug combinations. Comparison of the different MoAs of these compounds furthermore revealed novel insight into context dependence and plasticity of polypharmacology.

Ort

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Zeit

Dienstag, 28.08.2018, 13:00 Uhr

Meet the Prof. für Studierende im Anschluss an den Vortrag

gez. Professor Dr. Daniel Rauh
Gesellschaft Deutscher Chemiker
Ortsverband Dortmund