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Proteomics atlas of cancer cells' death and survival

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Mass-spectrometry based proteomics is widely used to profile proteome changes in cancer cells in response to different anticancer treatments. The proteome changes are expected to follow one of the established death pathways. Until 2008, three such mechanisms have been widely recognized. In 2012, the Nomenclature Committee on Cell Death (NCCD) has listed 13 distinct mechanisms of cellular death. However, in the 2015 NCCD report this classification has effectively been disavowed, because new research has shown that programmed death pathways previously believed to be unidirected are actually reversible. To differentiate between different modes of cell death, we mapped the proteome changes occurring in three attached cell lines treated with 50 different anticancer agents. Upon 24 hours incubation at a dose at which 50% cells are tested as dead, the still-attached cells and the floating cells were separately collected with the floating population showing the majority of dead cells while the attached cells consist of preferentially living cells. Proteome comparison of the surviving and dying cells with the untreated cells reveals the specific mechanisms of drug action as well as the pathways of death and survival that are common for all tested cell lines and drugs. Thus created proteomics atlas of cancer cell death and survival will serve as a reference in fundamental studies as well as in drug development.

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Introducing epigenomics in systems biology: Cross-talk between cell signal transduction and epigenetic mechanisms

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Integrating omics strategies is becoming a new frontier in systems biology, since disciplines like genomics and proteomics are now established. However, the traditional view of how these disciplines interplay, i.e., genomics→transcriptomics→proteomics→metabolomics, is too static to exhaustively represent a biological system. Events like early response to stimulus (protein phosphorylation) and structural gene regulation (epigenetic mechanisms) must enter in the equation. We investigated the development of larvae from *Drosophila melanogaster* upon treatment with kinase inhibitors. By integrating proteomics, phosphoproteomics, histone modification analysis and chromatin immunoprecipitation coupled with DNA sequencing (ChIP-seq) we reconstructed links between drug treatment and phenotypic abnormalities during development. Larvae from wild type (OregonR) hatched and grew from eggs laid on food w/o inhibitors for the kinases EGFR and c-Met. Considering the phosphoproteome as indicative of early response to stimulus we characterized pathways of proteins with regulated phosphorylations connecting the inhibitor target with nuclear receptors and histone modifier enzymes. Specifically, we found down-regulated phosphosites in both inhibitor treatments on the ecdysone nuclear receptor and the interacting trithorax complex, which last catalyzes methylation on histone H3 lysine 4 (H3K4me). This modification, enriched in actively transcribed genes, globally decreased upon inhibitor treatment. ChIP-seq analysis mapped H3K4me on genes coding for proteins involved in translational initiation in wild type, which we found expressed in lower abundance in treated larvae. Collectively, our preliminary data indicate how drug treatment might be related to developmental abnormalities (slower growth), using epigenomics to link early response to proteome regulation.

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