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Understanding landscape of chemically induced cell death phenotypes

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FACILITATOR	**: Dr. LI Fangfei**

Abstract

Dysregulation of cell death machineries is a major cause of age-associated diseases, such as cancers or neurodegenerative diseases. Cell death is not a singular event. To this date, apoptosis and multiple non-apoptotic cell death phenotypes, such as necroptosis and ferroptosis, have been reported. Most of our knowledge about cell death comes from detailed studies of each cell death phenotype; we have come to know more about each phenotype, however, we have little systematic view as to comparison of cell death phenotypes so far. It remains elusive how similar these cell death phenotypes are. In this seminar, I will introduce my two recent projects performing machine-learning analysis of large datasets to achieve comparative analysis of chemically induced cell death phenotypes *in vitro* and *in vivo*.

In the first part, I will discuss analysis of a large-scale compound profiling across cancer cell lines (NCI-60). Cluster analysis of cellular sensitivity of compounds across 60 cancer cell lines *in vitro* discovered multiple mechanisms of action of lethal compounds simultaneously. Further, basal transcriptome of the same cell lines helped us to discover robust biomarkers for drug sensitivity, including basal NADPH level in cells as a biomarker for ferroptosis-inducing compounds, which was later experimentally validated.

In the second part, I will focus on analysis of a large toxicogenomic dataset (Open TG-GATEs). Unsupervised characterization of systemic physiological and histological changes from the dataset revealed nine discrete toxin-induced disease states, which correspond to both known and novel pathology. Analysis of dynamics revealed transitions between disease states at constant toxin exposure, mostly towards decreased pathology, implying induction of tolerance. Tolerance correlated with induction of known xenobiotic defense genes and decrease of novel ferroptosis sensitivity biomarkers, suggesting ferroptosis as a druggable driver of tissue pathophysiology.
These two examples will give insights for how we should conceive chemically induced cell death in the context of *in vitro* and *in vivo* physiology in the modern data science era.

****All are Welcome****