A010 · A Single-Cell Analysis of State-Restricted and Uniform Collateral-Lethality Dependency Signatures in Pancreatic Ductal Adenocarcinoma

Presenter: Om Rajesh — The Woodlands High School

Authors: Om Rajesh, The Woodlands High

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Pancreatic ductal adenocarcinoma (PDAC) has a five-year survival rate of nearly 13%. Most tumors contain a mutation in the KRAS gene, which has proved to be difficult to target directly. As a result, researchers have turned to the idea of collateral lethality - when the deletion of one gene also results in the loss of another neighboring 'passenger' gene, this creates a dependency on a different gene to survive. These targets have been identified through bulk screens of numerous cell lines. which average these into a single profile. However, PDAC tumors are not uniform because their malignant cells exist in two states: classical and basal. Therefore, targeting a gene that is only essential to one of these states will leave the other untreated. Here, we investigate whether three known collateral lethality targets: VPS4A, PRMT5, and MAT2A, are evenly distributed between these two states in two independent cohorts of single-cell RNA sequencing. For each target, we derived a dependency signature from the Cancer Dependency Map, scored it in every malignant cell, and tested whether it tracked the classical state using a within-patient partial Spearman correlation. VPS4A and PRMT5 signatures did not favor either state, while the MAT2A signature was concentrated in classical cells in both cohorts. This pattern was not explained by generic gene essentiality. These findings demonstrate that single-cell analysis can show when a collateral-lethality dependency signature is confined to part of the tumor, a question bulk screens cannot answer.

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