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DSICCR Tuesday Seminar Series

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Phylogenetic inference from single-cell RNA-seq data

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Tumors are comprised of subpopulations of cancer cells that harbor distinct genetic profiles and phenotypes that evolve over time and during treatment. By reconstructing the course of cancer evolution, we can understand the acquisition of the malignant properties that drive tumor progression. Unfortunately, recovering the evolutionary relationship of individual cancer cells linked to their phenotypes remains a difficult challenge. To address this issue, we have developed PhylinSic, a method that reconstructs the phylogenetic relationships among cells linked to their gene expression profiles from single cell RNA-sequencing (scRNA-Seq) data, and showed that it was robust to the low read depth, drop-out, and noisiness of scRNA-Seq data. This method called nucleotide bases from scRNA-Seq reads using a probabilistic smoothing approach, and then estimated a phylogenetic tree using a Bayesian modeling algorithm. We evaluated PhylinSic and showed that it identified evolutionary relationships resulting from selective events such as drug selection and metastasis and was sensitive enough to identify subclones from genetic drift. Finally, we applied methods of phylogenetic inference and found that breast tumors resistant to chemotherapies harbored two genetic lineages that independently manifested high predicted activity of K-Ras and β-catenin, potentially acquired by distinct mechanisms through convergent evolution. This suggested that therapeutic strategies may need to target multiple lineages to be durable. Taken together, these results demonstrated that PhylinSic provides a framework to model the evolution and link the genotypes and phenotypes of cells within a tumor or cohort of monophyletic tumors using scRNA-Seq.

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