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How do cellular selection and diversity contribute to leukemic progression? Seeking answers using computational and mathematical analyses

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Many cancers can be treated with therapies that target pathways enriched because of driver mutations. In acute leukemia recent developments target IDH2 and FLT3 mutations. Almost inevitably, the rapidly evolving tumors develop resistance to targeted therapy. Intraleukemic heterogeneity serves as a reservoir for this resistance evolution, which often occurs due to selection of minor cellular sub-populations during therapy— high levels of heterogeneity can persist undetected over long times. Especially in Acute Myeloid Leukemia, the cellular diversity can hardly be captured by genomic heterogeneity alone. Although bulk RNA sequencing can also associate this diversity with outcomes, its true 'clonal' architecture on the level of identifiable sub-populations can only be revealed by high-dimensional single cell methods. We seek leverage the fact that single-cell RNA-sequencing data from individual patient samples can be used to describe intraleukemic heterogeneity in AML. We argue that this description can especially become useful when clinical sampling is combined with computational and statistical modeling. We developed a pipeline that can be used to analyze single cell data, via recursive normalization, clustering and mathematical interpretation, and seek to verify this platform in the clinic. We develop and use metrics of inter- and intra-sample heterogeneity in AML and link these new metrics to disease evolution. These analyses are possible due to exciting new technologies and can be used to point to new therapies that directly reduce tumor heterogeneity in order to minimize chances of resistance evolution in the clinic.