Tracking clonal structure from AML diagnosis to relapse using mitochondrial variants

Derek Tam, MSc

Bioinformatics Graduate Program, UBC; Karsan Lab, Michael Smith's Genome Sciences Centre, BC Cancer Research Institute

Scientific Abstract:

Background and rationale: Acute myeloid leukemia (AML) is a clonally heterogenous disease despite its low mutational burden, with a relapse rate of over 60% within five years of diagnosis. Clonal heterogeneity among cancer cells provides a reservoir of genetic and epigenetic diversity from which variations in fitness emerge in response to treatment. This reservoir is an important factor in the recalcitrance of cancer cells to treatment and eventual cancer relapse. An important step in understanding how therapy resistance occurs is studying how different clones respond to treatment and characterizing the differences between them. Recently, a novel method for assaying clonal structure *in vivo* using mitochondrial DNA variants was reported. This approach could provide a way to study longitudinal changes in clonal structure in parallel with recurrent mutations in AML.

Objective(s): We aimed to (1) develop a method to simultaneously capture the mutational and clonal landscape of an AML sample and (2) apply it to longitudinally paired samples from relapsed AMLs to characterise response to treatment at a clonal resolution and to examine clone dynamics.

Methods and Results: A scDNA-seq panel was designed to simultaneously capture genomic regions of interest in myeloid disorders and stochastic mutations in the mitochondrial genome. The use of mitochondrial variants to infer clonal relatedness was validated in a cell-line mixture experiment. This panel was subsequently used to assay longitudinal bone marrow sample pairs from AML patients (n = 26) at the diagnostic and relapse time-point after treatment by induction chemotherapy. Clones identified using variants detected in the myeloid panel before and after treatment were compared. This revealed that perturbation of the clonal structure in response to treatment varied between individuals, with some relapses demonstrating little or no change in clonal composition after a period of remission. Further investigation of these cases reveals that a subclonal change can be detected using mitochondrial DNA variants, suggesting that additional factors in clone fitness may be present beyond known recurrent mutations in myeloid diseases.

Conclusion(s): Differential response to induction chemotherapy between clones is not fully described by genetic mutations, suggesting that non-genetic factors play an important role in determining resistance.

Anticipated Impact: Understanding how therapy resistance occurs through both genetic and non-genetic factors could identify novel avenues of treatment that target multiple facets of resistance, improving overall patient outcomes.

Plain Language Abstract:

Background and rationale: Acute myeloid leukemia (AML) is a type of blood cancer that has been found to evolve into many biologically varied groups of cancer cells, or clones. The diversity allows the cancer to adapt to treatment, contributing to relapse in 60% of AML patients within five years of diagnosis. To better understand why some cancer clones are resisting treatment, researchers need methods to track these cell groups over time. A recent study introduced a new way of identifying clones that uses natural changes in mitochondrial DNA as markers which accumulate over time. This approach could help researchers study how the makeup of these clones change in patients in response to treatment and identify the differences in their biology.

Objective(s): This study aimed to (1) develop a way to measure genetic changes relevant to AML and capture cancer clones at the same time, then (2) to apply this method to samples from the same patients before treatment was received and after the cancer returned to see how the makeup of the cancer clones changed.

Methods and Results: We developed a DNA-sequencing test that looks at important parts of the genome in AML as well as the natural changes in mitochondrial DNA that accumulate over time. We applied this test to samples from 26 AML patients in the Marathon of Hope cohort, taken at cancer diagnosis and again after the cancer returned following therapy. This data was then used to identify cancer clones in each patient. Comparing the size of these clones before and after treatment, we found that in some patients a large change could be seen, revealing that the clone which caused the cancer initially is different from the clone that caused the cancer to return. In some cases, however, almost no change could be seen until the mitochondrial DNA markers were used. This suggests that there are other factors in treatment response than genetic mutations in AML.

Conclusion(s): The way that different groups of cancer cells respond to treatment cannot be fully explained by genetic mutations and suggests that other regulatory changes also help some clones resist treatment.

Anticipated Impact: By more completely understanding how cancer cells evade and resist treatment, new therapies can be identified that target each of the ways in which cancer cells survive, leading to improved responsiveness to treatment and better patient outcomes.