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EPIGENETICS

Separate paths for epigenomes and genomes in cancer evolution?

Cancers typically evolve during tumorigenesis and therapy response, but the contributions of genomic versus epigenomic changes (and their interplay) are incompletely characterized. A new study identifies substantial independence between the evolutionary trajectories of genomes and epigenomes in acute myeloid leukaemia (AML).

Li, Garrett-Bakelman *et al.* investigated the clinical evolution of AML. As the genetic mutation load is low in AML relative to most solid tumours (and often those genetic mutations affect epigenetic-modifier genes), an altered epigenome is likely to be important for AML pathology.

The team assembled a collection of paired diagnosis and post-treatment relapse AML samples from 138 patients (accompanied by clinical outcome data), as well as normal bone marrow samples from 14 donors. Using enhanced reduced-representation bisulfite sequencing (ERRBS) to profile 5-methylcytosine (5mC) in GC-enriched regions, they then calculated the 'epigenetically shifted loci per million loci' (EPM), which is a metric for the degree of global change in DNA methylation heterogeneity between pairs of samples. Relative to normal bone marrow, all AML samples showed significant changes in epigenetic heterogeneity. As support for the biological and clinical relevance of these changes, high EPM scores for AML diagnosis samples were predictive of poorer clinical outcomes than were lower EPM scores, and the predictive power increased when analysis was restricted to 5mC at promoter CpG sites (where methylation is most likely to alter gene expression).

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When comparing AML diagnosis samples to the subsequent paired relapse sample, there was substantial variability in the degree of epigenetic change, ranging from no significant change to changes as substantial as those seen between AML and normal bone marrow. Looking beyond the EPM metric of the degree of overall change, the authors clustered the samples based on whether the AML-associated epigenetic states were generally acquired between diagnosis and relapse (relapse-specific), lost between diagnosis and relapse (diagnosis-specific) or had a more balanced set of changes. To determine whether there was a clear genetic underpinning of these differential epigenome trajectories, the authors carried out exome sequencing on paired samples from 48 of the patients. Overall, there was a remarkable disconnect between the epigenomic and genetic data. Increases or decreases in epigenomic diversity between diagnosis and relapse were not accompanied by equivalent changes in genetic diversity, and the acquisition of epigenomic diversity did not correlate with mutations in known epigenetic-modifier genes.

The evolutionary dynamics of the epigenome and genome were studied in more detail in a patient for whom five serial AML samples were available, from diagnosis and four relapse time points. ERRBS and whole-genome sequencing showed highly distinct trajectories of the epigenome and genome, in terms of the kinetics of when significant alterations occurred during the treatment course, the stability of the alterations and their clonal heterogeneity. Transcriptomic analyses of cell populations and single cells showed that epigenetic heterogeneity changes are associated with changes (and intercellular variability) of gene expression, but their contribution to AML pathology remains to be seen.

It will be interesting to determine whether mechanistic links between evolving genomes and epigenomes will be so elusive for other cancer types, and whether genomic or epigenomic analysis (or a combination of both) will provide the greatest prognostic value as biomarkers.

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ORIGINAL ARTICLE Li, S., Garrett-Bakelman, F. E. *et al.* Distinct evolution and dynamics of epigenetic and genetic heterogeneity in acute myeloid leukemia. *Nat. Med.* http://dx.doi.org/10.1038/nm.4125 (2016)
FURTHER READING Feinberg, A. P., Koldobskiy, M. A. & Göndör, A. Epigenetic modulators, modifiers and mediators in cancer aetiology and progression. *Nat. Rev. Genet.* **17**, 284–299 (2016)