

Genetic Architecture of Leukaemia

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Cancer clone expansion is a Darwinian, evolutionary process of genetic diversification and selection - in somatic cells inhabiting a tissue ecosystem. Childhood acute lymphoblastic leukaemia (ALL), though an intrinsically lethal malignancy, develops over a short time frame and has only modest genetic complexity. It is therefore amenable to interrogation of its pre-clinical evolutionary or natural history, i.e. the timing and sequence of critical mutational events and, ultimately, the causal basis of this process.

For the common variant, B cell precursor ALL, we have determined the temporal sequence of mutations. *ETV6-RUNX1* fusion (and hyperdiploidy) are commonly pre-natal and presumed initiating events followed by a modest set of secondary copy number alterations (CNA) or sequence-based mutations more proximal to diagnosis. Current whole genome sequencing screens should provide a complete audit of 'driver' mutations for ALL. Genetic studies on monozygotic twins with concordant and discordant ALL have been invaluable in these studies as has been modelling studies with murine and human cells.

Single cell analysis with multiplexed probes for *ETV6-RUNX1* fusion gene and CNA has enabled us to investigate the detailed genetic architecture of clones in ALL. This reveals that the evolutionary trajectory of this cancer (and we believe most others) is non-linear, and with a branching sub-clonal architecture of genetically distinct sub-clones, as anticipated on Darwinian principles. We have extended this analysis to show

that the 'stem' or propagating cells driving this process are themselves genetically diverse or variegated in individual patients. Current pan-genomic snapshots (SNP arrays or sequencing) of ALL and other cancer cells are largely blind to this underlying heterogeneity. These differing perspectives of genetic architecture in cancer are of some clinical consequence.

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