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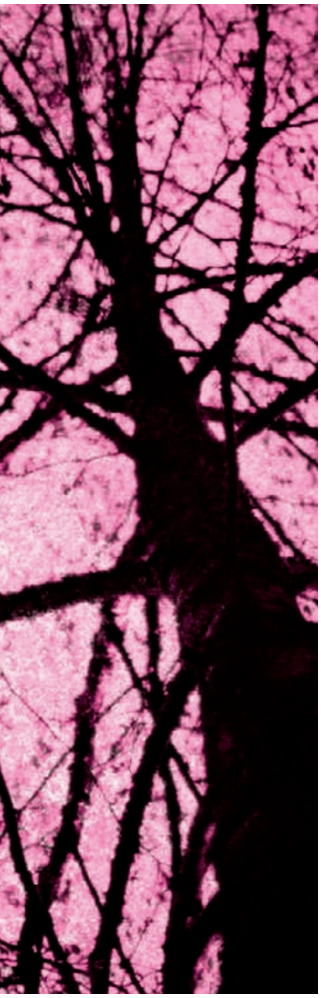
CANCER GENETICS

Initially complex, always heterogeneous



The genetic complexity and heterogeneity of cancer is becoming increasingly appreciated through genomic and histological analyses. Two recent studies add further weight to this concept, revealing that even the subpopulation of leukaemia-initiating cells in individual patient samples can have surprising genetic heterogeneity.

Acute lymphoblastic leukaemia (ALL) is particularly amenable to studies of genetic subpopulations owing to the ease of single-cell analyses, its limited genomic instability and its variety of well-characterized, recurrent mutations. Anderson and colleagues studied samples of childhood ALL that have an *ETV6–RUNX1* translocation and used fluorescence *in situ* hybridization to detect other mutations (driver mutations) that are known to be involved in the development of ALL. In a separate study, Notta and colleagues studied genome-wide copy number alterations (CNAs) in adult ALL cases with a breakpoint cluster region (*BCR*)–*ABL1* translocation. By analysing individual leukaemic cells in each sample population, both groups found that the leukaemia-initiating cell subpopulation (defined by cell surface markers or by serial xenotransplantation in mice) maintained a genetic heterogeneity that was similar to the population of leukaemia cells in the sample. This suggests that the linear clonal succession model of cancer evolution, in which cancers progress through single-cell clone bottlenecks, might be an oversimplification. The genetic heterogeneity and the branching evolutionary trajectories evident in the samples evoke a remarkably Darwinian perspective of the evolution of leukaemia-initiating cells.

Interestingly, a comparison of multiple leukaemia samples from individual patients during disease progression and post-treatment relapse revealed that shifts can occur in the dominance of the subclones, although the subclonal diversity is generally maintained.

In a further experiment, Notta *et al.* classified their ALL samples into aggressive versus non-aggressive types based on their ability to engraft a variety of immunodeficient mice. This aggressive versus non-aggressive classification correlated with the survival of the patients from whom the samples were taken and with specific genetic lesions. In the aggressive samples, the frequencies of leukaemia-initiating cells were higher and the numerically dominant subclones maintained their dominance of the population after xenotransplantation. These findings suggest that assays to quantify leukaemia-initiating cells and the observation of shifts in subclonal dominance during transplantation assays could form predictive biomarkers for patient survival.

It will be interesting to see whether these diverse subclones of cancer-initiating cells equally fulfil all the biological properties of cancer stem cells. Another key question is whether the extent of genetic complexity seen for ALL-initiating cells will be mirrored in other cancers, given that acute leukaemias have a greater proportion of cancer-initiating cells compared with some solid tumours. Finally, this genetic heterogeneity suggests that the therapeutic targeting of cancer-initiating cells will be a considerable challenge. However, the ability to isolate and study rare subclones in xenografts opens a pathway to developing therapies that would target all subclones.

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ORIGINAL RESEARCH PAPERS Anderson, K. *et al.* Genetic variegation of clonal architecture and propagating cells in leukaemia. *Nature* **469**, 356–361 (2011) | Notta, F. *et al.* Evolution of human BCR–ABL1 lymphoblastic leukaemia-initiating cells. *Nature* **469**, 362–367 (2011)