Genetic Architecture of Leukaemia: Cancer's Dark Darwinian Secret

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Contemporary cancer research has two prominent paradigms:

- That whole genome sequencing will identify the mutational spectrum of each patient's cancer cells and facilitate a new era of targeted or 'personalised' therapy;

- That a subset of cells in each cancer – the cancer 'stem' cells drive and sustain the disease and it is these cells (and their specific mutations) that provide the 'bull's eye' for therapy.

Currently these two strands of research – genetics and stem cells, have not been combined and, when they now are, a striking and disconcerting result emerges.

We have interrogated the evolution of cancer clones in childhood lymphoblastic leukaemia (ALL) and identified the dynamic architecture of disease, i.e. the timing and sequence of acquisition of mutations and the distribution of mutations in sub-clones and stem cells. To achieve this, we exploited the unusual situation of leukaemia in identical twins and analysed the genetic make-up of individual leukaemic cells. This enabled us to designate certain mutations as initiating or primary events, usually occurring pre-natally, *in utero*, and a 'set' of additional secondary mutations arising post-natally closer to the clinical diagnosis. Strikingly, the full set of mutations does not accumulate in a linear fashion in sequentially dominant sub-clones (as widely anticipated) but rather via a complex, branching architecture of clonal evolution. Moreover, separate branches of the clonal, evolutionary tree are sustained by genetically distinct stem cells.

These data are entirely consistent with the concept of cancer clone development as a Darwinian evolutionary process. They highlight that the so-called 'bull's eye' in cancer is, in fact, a dynamically diverse and moving target which may provide an explanation of why advanced disease is so difficult to eradicate. Cancer needs a Darwinian by-pass?

1. Anderson K, Lutz C, van Delft FW, Bateman CM, Guo Y, Colman SM, Kempski H, Moorman AV, Titley I, Swansbury J, Kearney L, Enver T, Greaves M (2011) Genetic variegation of clonal architecture and propagating cells in leukaemia. Nature, 469: 356-361.

2. Greaves M (2010) Cancer stem cells: back to Darwin? Seminars in Cancer Biology, 20: 65-70.