LEUKAEMIA STEM CELLS

Self-renewal-associated signature

Leukaemia stem cells acquire the ability to self-renew by activating only a portion of the genes that are typically expressed by HSCs.

The presence of a population of stem cells in leukaemias and other cancers that can self-renew is crucial for cancer formation and maintenance, and destroying these cells is thought to be necessary for effective cancer therapy. Andrei Krivtsov, Scott Armstrong and colleagues compared the gene-expression profiles of leukaemia stem cells (LSCs) and normal haematopoietic stem cells (HSCs), and found that LSCs acquire the ability to self-renew by activating only a portion of the genes that are typically expressed by HSCs.

To impart stem-cell properties on committed haematopoietic progenitors, the authors expressed

the mixed-lineage leukaemia (MLL)–AF9 fusion protein in granulocyte–macrophage progenitors (GMPs). When these cells were injected into sublethally irradiated mice, the mice developed acute myeloid leukaemia (AML). Leukaemic cells with GMP-like characteristics (L-GMPs) were then isolated using cell-surface markers, and, based on their ability to induce AML in secondary recipient mice at a high frequency, the authors determined that this cell population was enriched for LSCs. In culture, L-GMPs were able to generate differentiated progeny that were unable to induce AML, further indicating that L-GMPs possessed stem-cell properties.

Are the genes expressed by L-GMPs different from those expressed by GMPs, normal HSCs or other haematopoietic progenitors? Analysis of expression profiles using microarrays showed that L-GMPs are most similar to GMPs, but that they also highly express a group of genes found in the HSC population. In addition, when L-GMPs were allowed to differentiate in culture, most of the HSC-associated genes reverted to expression levels found in GMPs. This group of 363 genes expressed in cells with self-renewal potential is only a subset of the 1,137 genes that are typically highly expressed in HSCs.

Furthermore, the authors found a hierarchy of gene expression.

Only a subset of the 363 leukaemia self-renewal signature genes were expressed ‘immediately’ following MLL–AF9 expression in GMPs, including *Mef2c* (myocyte enhancer factor 2C), *Runx2* (runt related transcription factor 2) and the Wnt pathway gene *Tcf4*, and some genes previously associated with MLL translocations, such as *Hoxa* cluster genes and *Meis1*. Serial replating assays showed that retroviral expression of *Hoxa6*, *Hoxa7*, *Hoxa9* or *Hoxa10* was sufficient to immortalize GMPs. By contrast, the expression of *Mef2c* was not sufficient for immortalization, but suppression of *Mef2c* using short hairpin RNAs in L-GMPs indicated that the expression of this gene is crucial for AML development in mice.

Is this murine leukaemia self-renewal signature relevant to human AML? The authors found significant overlap (91 of 363 genes) between previously published human MLL-rearranged AML-expression profiles and their murine self-renewal-associated signature.

The data presented by Krivtsov, Armstrong and colleagues indicate that there are phenotypic differences between LSCs and HSCs, which might make it possible to develop cancer therapies that specifically target LSCs.

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ORIGINAL RESEARCH PAPER Krivtsov, A. V. et al. Transformation from committed progenitor to leukaemia stem cell initiated by MLL–AF9. *Nature* 16 July 2006 (doi: 10.1038/nature04980)

FURTHER READING Huntly, B. J. & Gilliland, D. G. Leukaemia stem cells and the evolution of cancer-stem-cell research. *Nature Rev. Cancer* 5, 311–321 (2005)

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