Finding the origins of infant leukaemia

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Leukaemia arises as a result of genetic or epigenetic alterations in blood cells, leading to an aberrant accumulation of undifferentiated blasts. Understanding the molecular pathogenesis and aetiology of infant leukaemia induced by the MLL-AF4 fusion gene was the subject of the Leukaemogenesis project.

The mixed lineage leukaemia (MLL) gene is one of the most frequently mutated genes in infant acute leukaemias, leading to fusions that involve more than 50 different partners. Detection of MLL translocations at diagnosis is a strong negative prognostic marker of the disease.

In infant acute lymphoblastic leukaemia (ALL), MLL-AF4 is very common and arises in utero. However, very little is known about the nature of the target cell that becomes transformed in the embryo and the mechanisms accounting for its B cell lineage affiliation.

Although various murine models for MLL leukaemias exist, they fail to replicate many of the features of the human disease, suggesting that there are essential steps during early human development required for leukaemia onset. Seeking to address this issue, the EU Leukaemogenesis project was designed to determine the cell population that was most vulnerable to transformation by the MLL-AF4 gene.

As a first approach, scientists explored the in vitro and in vivo developmental impact of MLL-AF4 expression on haematopoietic stem progenitor cells (HSPCs) isolated from umbilical cord blood. MLL-AF4 seemed to augment the proliferation, clonogenic potential and in vivo multilineage haematopoietic engraftment of HSPCs. However, it was not sufficient to induce leukaemogenesis on its own, indicating that either additional hits were required to develop leukaemia or these cells were the inappropriate target.

In a similar way, MLL-AF4 expression was not sufficient to transform haematopoietic cells differentiated from human embryonic stem cells (hESC). Interestingly, a reduced production of haematopoietic cells was observed concomitant with an enhanced mature endothelial cell fate, suggesting that MLL-AF4 skewed the potential of common haemato-endothelial precursors towards a pronounced endothelial cell fate.

Scientists are hopeful that the precise mechanism of MLL-AF4–mediated cell transformation would be addressed by studying induced pluripotent stem cells (iPSCs) from infant patient blasts. Nonetheless, the platform generated during the Leukaemogenesis project constitutes an important tool for studying cellular and molecular

mechanisms during early embryonic development and could be further utilised for drug screening and toxicity.

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