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STEM CELLS

Sharing common factors for self-renewal

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> …ES cells and adult stem cells do have at least one factor in common.

Although the embryonic stem (ES) cells and the adult stem cells both exhibit the unique capacity for unlimited self-renewal, ES cells and adult stem-cell types have some strikingly distinct cellular and molecular features. However, a report by Boris Reizis and colleagues reveals that ES cells and adult stem cells do have at least one factor in common.

During early development, ES cells give rise to all cell types in the body. In adults, homeostasis is maintained by adult stem cells, which continuously generate all of the cell types that constitute a given tissue. Despite the fundamental differences between ES cells and tissue-specific adult stem cells, it remains unclear whether their self-renewal potential is regulated by common genes and pathways.

The transcription factor ZFX has previously been shown to be expressed at elevated levels in several stem-cell types, which prompted the authors to investigate the role of ZFX in stem-cell function. Loss of ZFX impaired the growth of ES cells *in vitro* and resulted in increased ES-cell apoptosis, particularly in serum-free conditions. Despite the growth and survival defect, *Zfx*-deficient ES cells remained undifferentiated and gave rise to all lineages, including the germ line. By contrast, ZFX overexpression favoured ES-cell renewal at the expense of differentiation. Taken together, these findings establish ZFX as a regulator of ES-cell self-renewal.

But what is the role of ZFX in adult stem cells? The authors showed that ZFX is not required for fetal haematopoiesis but is essential in adult haematopoietic stem cells, which failed to maintain their numbers or contribute to haematopoiesis after *Zfx* deletion. *Zfx*-deficient cells also showed increased apoptosis, which indicates a defect in long-term self-renewal owing to impaired survival. The survival and function of erythromyeloid progenitors were not affected, whereas loss of ZFX also resulted in impaired lymphopoiesis. So, it seems that ZFX controls both haematopoietic self-renewal and lymphoid differentiation, but not erythromyeloid differentiation.

The impaired self-renewal of *Zfx*-deficient ES cells and adult haematopoietic stem cells correlated with stem-cell-specific upregulation of stress-inducible and/or immediate-early genes. ZFX does not seem to regulate components of the NANOG, OCT4 and SOX2 transcriptional network, which regulates ES-cell self-renewal, but it might directly control the expression of other ES-cell self-renewal regulators such as TBX3 and TCL1.

This study provides evidence that embryonic and blood-generating haematopoietic stem cells share a common basis for self-renewal. Whether ZFX also regulates the self-renewal mechanisms of other stem-cell types remains to be seen. According to the authors, "…the high evolutionary conservation of ZFX raises the possibility that it may regulate stem-cell functions in other vertebrate species, including humans."

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ORIGINAL RESEARCH PAPER Galan-Caridad, J. *et al.* ZFX controls the self-renewal of embryonic and hematopoietic stem cells. *Cell* **129**, 345–357 (2007)

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