

# The Stem Cell Leukaemia Gene: Establishing the Transcriptional Programme for Blood

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## Abstract

One of the central issues of metazoan biology concerns the mechanisms whereby a multipotent stem cell gives rise to distinct mature cell types and there has been considerable interest in the clinical applications of manipulating stem cell plasticity. Haematopoiesis is the best characterised stem cell system and a close link has long been recognised between the development of blood and endothelium. The Stem Cell Leukaemia (SCL) gene encodes a bHLH transcription factor with a pivotal role in the formation of blood and endothelium. Loss-of-function and gain-of-function studies by our laboratory and others have demonstrated that SCL is essential for establishing the transcriptional programme responsible for the formation of haematopoietic stem cells and have focused attention on the regulation of SCL itself. We have therefore systematically characterised the transcriptional regulation of the murine SCL gene using a combination of long range genomic sequence comparisons, chromatin studies and transgenic analysis of reporter constructs. Our results have defined a chromosomal domain sufficient for normal SCL transcription and have revealed a panel of spatially distinct enhancers, each of which directs expression to a sub-domain of the normal SCL expression pattern. Of particular note, a SCL 3 enhancer specifically targets expression to haematopoietic stem cells, progenitors and endothelial cells throughout ontogeny, suggesting that this enhancer functions at a nodal point for signals that establish the transcriptional programme for blood and endothelium. Molecular characterisation of this enhancer is illuminating the mechanisms that control formation of haematopoietic stem cells and is providing novel tools for stem cell manipulation.

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