Role of the Haematopoietic Transcription Factor SCL in Mesoderm Development

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Abstract

During embryonic development, precursor cells commit to specific cell fates in response to environmental cues through the establishment of lineage-specific gene expression programmes. Transcription factors are important downstream effectors of signalling pathways that initiate and maintain cell fate decisions. The haematopoietic transcription factor SCL (TAL-1) is an essential regulator of embryonic blood development. However, the exact stage at which SCL is required, its mechanisms of action, and its genomic targets are poorly understood. Characterising how SCL functions during haematopoietic development will provide insights into how stem cells are specified.

Using the embryonic stem cell/embryoid body (ES/EB) system to model early mouse development, we describe a critical role for SCL in mesoderm patterning. SCL is first expressed in PDGFRα^+ FLK1$^+$ mesoderm populations which contain lateral, paraxial and cardiac precursors. Through loss- and gain-of-function studies, we show that SCL drives lateral mesoderm specification and activates the haematopoietic programme in a direct DNA-binding independent manner, while actively repressing alternative mesodermal fates, specifically cardiac development, in a DNA-binding dependent manner. At a molecular level, we have identified direct genomic targets of SCL in Flk-1$^+$ mesoderm populations. These include haematopoietic and cardiac transcription factors, cardiac-specific structural proteins, signalling proteins and general transcriptional repressors; thereby strengthening the dual function of SCL in mesoderm patterning. Finally, we have shown that the cardiac transcription factor GATA4 acts in a reciprocal manner, specifying cardiac precursors while repressing a lateral mesoderm fate.

Collectively, this implicates SCL as a critical transcriptional regulator of cell fate decisions in early mesodermal precursors, employing distinct molecular mechanisms to impose a blood programme. Moreover, and extending earlier reports, we document the existence of an antagonistic cross-talk between haematopoietic and cardiac lineages during mesoderm patterning. In conclusion, this work offers a cellular and molecular platform to begin to dissect the network of genetic interactions involved in these developmental processes.

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