

# **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 PDGFR $\alpha$ <sup>+</sup> FLK1<sup>+</sup> 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<sup>+</sup> 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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# Contents List

<b>Abbreviations</b>	1
<b>1. Introduction</b>	4
<b>1.1 Primitive Streak and Mesoderm Patterning</b>	5
1.1.1.1 Hallmarks of Early Mesoderm Populations	7
<b>1.2 Developmental Haematopoiesis</b>	8
1.2.1 Haematopoiesis in the Mouse Embryo	8
1.2.1.1 Yolk Sac Haematopoiesis	8
1.2.1.2 Intra-Embryonic Haematopoiesis	12
1.2.2 Haematopoiesis in the Zebrafish Embryo	13
1.2.3 Markers of Haematopoiesis Development	15
1.2.4 Haematopoietic Transcription Factors	16
<b>1.3 Cardiac Development</b>	18
1.3.1 Cardiac Development in the Mouse Embryo	18
1.3.2 Cardiac Development in the Zebrafish Embryo	19
1.3.3 Markers of Cardiac Development	19
<b>1.4 Paraxial Mesoderm Lineages</b>	21
1.4.1 Markers of Paraxial Mesoderm Fate	21
<b>1.5 Embryonic Stem Cells as a Developmental Model</b>	22
1.5.1 Advantages of the ES/EB System	23
1.5.2 Weaknesses of the ES/EB System	24
1.5.3 Mesoderm Development	25
1.5.4 Blood Development	25
1.5.5 Cardiac Differentiation	28
<b>1.6 Cross-talk between Developing Mesoderm Lineages</b>	29
<b>1.7 The Transcription Factor SCL</b>	32
1.7.1 Expression of SCL in the Embryo	34
1.7.2 SCL Expression in the ES/EB System	35
1.7.3 SCL in Haematopoiesis	35
1.7.4 Direct DNA-Binding can be Dispensable for SCL Function	38

1.7.5	SCL in Other Lineages	39
1.7.6	SCL as an Activator and a Repressor of Gene Expression	40
<b>1.8</b>	<b>Project Aims</b>	<b>42</b>
<b>2.</b>	<b>Materials &amp; Methods</b>	<b>43</b>
<b>2.1.</b>	<b>Cell Culture Techniques</b>	<b>43</b>
2.1.1	Cell Lines	43
2.1.2	Maintenance of ES Cell Lines	43
2.1.3	<i>In vitro</i> Differentiation of ES Cells into EBs	44
2.1.3.1	Cell Suspension Method	44
2.1.3.2	Hanging Drop Method	45
2.1.4	Dis-aggregation of EBs	45
2.1.5	Re-aggregation of EBs	45
2.1.6	Haematopoietic Differentiation	46
2.1.6.1	Blast colonies	46
2.1.6.2	Haemoglobin Production	46
2.1.7	Cardiac Differentiation	46
2.1.7.1	Unsorted EBs	46
2.1.7.2	Sorted EB Populations	47
2.1.8	Osteogenic Differentiation	47
2.1.9	Chondrogenic Differentiation	47
2.1.10	Myogenic Differentiation	48
<b>2.2.</b>	<b>Cellular Staining Assays</b>	<b>48</b>
2.2.1	Alkaline Phosphatase Staining of ES Colonies	48
2.2.2	Alizarin Red Staining for Osteogenic Differentiation	49
2.2.3	Alcian Blue Staining for Chondrogenic Differentiation	50
2.2.4	Immuno-histochemistry for Myogenic Markers	50
<b>2.3.</b>	<b>Immuno-phenotypic Analysis and Cell Sorting</b>	<b>51</b>
2.3.1	Antibody Staining for Extracellular Proteins	51
2.3.2	Antibody Staining for Intracellular Proteins	52
2.3.3	Flow Cytometry	53

2.2.4	Analysis of Cell Cycle and Proliferation	53
2.2.5	Analysis of Apoptosis	53
<b>2.4.</b>	<b>Protein Expression</b>	<b>54</b>
2.4.1	Nuclear Extracts	54
2.4.2	Whole Cell Lysates	54
2.4.3	Immuno-Precipitation	55
2.4.4	Western Blots	55
<b>2.5.</b>	<b>Gene Expression Analysis</b>	<b>56</b>
2.5.1	RNA Preparation	56
2.5.2	cDNA Synthesis	57
2.5.3	Quantitative PCR	57
2.5.4	Statistical Analysis	58
2.5.5	Microarray and Bioinformatic Analysis	58
<b>2.6.</b>	<b>Chromatin Immuno-Precipitation (ChIP)</b>	<b>58</b>
2.6.1	$\alpha$ -SCL ChIP	58
2.6.2	Quantitative PCR Analysis of ChIP	60
2.6.3	ChIP-Sequencing	60
<b>2.7.</b>	<b>ES Cell Lines with Ectopic SCL or GATA4 Expression</b>	<b>61</b>
2.7.1	Constructs	61
2.7.2	Electroporation	62
2.7.3	Selection of ES clones by Antibiotic Resistance	62
2.7.4	DNA Lysis, Extraction and Precipitation	63
2.7.5	Selection of ES Clones by PCR and Western Blot	63
<b>2.8.</b>	<b>ES Cell Lines with Doxycycline Inducible SCL Expression</b>	<b>64</b>
2.8.1	Constructs	64
2.8.2	Generating tTA/ROSA26 ES Cells	64
2.8.2.1	Southern Blot	65
2.8.3	Introduction of Scl cDNA under the Control of a Tet- Promoter	65
2.8.3.1	Modification of the Cloning Vector	65
2.8.3.2	Lipofectamine Transfection	66
2.8.3.3	Selection of ES clones	66

<b>3. Results Chapter One:</b>	
<b>SCL Expression during Early Mesoderm Development</b>	70
<b>3.1 Characterising Wild Type Mesoderm Populations in EBs</b>	70
3.1.1 Flow Cytometry Protocol to Study Mesoderm Differentiation	70
3.1.2 Flk-1/PDGFR $\alpha$ Mesoderm Populations in Wild Type EBs	72
<b>3.2 Lineage Potential of Wild Type EB Mesoderm Populations</b>	77
3.2.1 Cell Fate Potential of Day 3.5 Flk-1/PDGFR $\alpha$ EB Cells	77
3.2.2 Mesoderm Gene Expression in Day 3.5 EBs	81
3.2.3 Haematopoietic and Cardiac Potential of Day 6 EBs	84
<b>3.3 Pattern of SCL Expression in Differentiating Wild Type EBs</b>	86
3.3.1 SCL Expression in Differentiating EBs	86
3.3.2 SCL Expression in Flk-1/PDGFR $\alpha$ Mesoderm Populations	88
3.3.3 <i>Scf</i> Gene Expression in Differentiating EBs	90
<b>3.4 Summary</b>	92
<b>4. Results Chapter Two:</b>	
<b>SCL is a Master Regulator of Mesoderm Specification</b>	94
<b>4.1 SCL Expression Affects Cell Fate Decisions in Flk-1/PDGFR<math>\alpha</math> Populations</b>	94
4.1.1 SCL Expression is Required for the Expansion of SP-F Populations	94
4.1.2 SCL Specifies Flk-1 <sup>+</sup> Lateral Mesoderm Lineages without Directly Binding DNA	97
4.1.3 Expansion of PDGFR $\alpha$ <sup>+</sup> Populations the Absence of SCL	100
4.1.4 Proliferation and Apoptosis are not affected in Flk-1/PDGFR $\alpha$ Populations <i>Scf</i> <sup>-/-</sup> EBs	101
<b>4.2 SCL is Essential for Correct Mesoderm Cell Fate Decisions</b>	103
4.2.1 SCL Expression is required for Lateral Mesoderm and Haematopoietic Commitment	103
4.2.2 Paraxial Mesoderm Lineage Potential of <i>Scf</i> <sup>-/-</sup> EBs	105
4.2.3 <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs have Increased Cardiac Potential	111

<b>4.3 <i>Scf</i><sup>RER/RER</sup> EBs Exhibit Aspects of Wild Type and <i>Scf</i><sup>-/-</sup> Phenotypes</b>	117
<b>4.4 SCL Over-expression Favours Haematopoiesis over Cardiac Differentiation</b>	119
4.4.1 SCL Over-expressing ES Cell Lines	119
4.4.2 Haematopoietic Potential of SCL Over-expressing ES Cells	121
4.4.3 Cardiac Potential of SCL Over-expressing ES Cells	123
4.4.4 Phenotypic Rescue in <i>Scf</i> <sup>-/-</sup> /SCL EBs	126
<b>4.5 Summary</b>	129
<b>5. Results Chapter Three: An Inducible SCL Expression System</b>	132
<b>5.1 tTA/ROSA26 Knock-In ES Cells</b>	133
5.1.1 ES Cell Targeting	133
5.1.2 Characterisation of tTA/ROSA26 ES Cells	136
<b>5.2 ES Cell Line with Inducible SCL Expression</b>	140
5.2.1 ES Cell Targeting	140
5.2.2 Control of SCL Expression in WT/ <i>iScf</i> and <i>Scf</i> <sup>-/-</sup> / <i>iScf</i> ES Cells	143
5.2.3 SCL Expression in WT/ <i>iScf</i> and <i>Scf</i> <sup>-/-</sup> / <i>iScf</i> EBs	146
<b>5.3 Summary</b>	148
<b>5.4 Discussion: Using the Tet-Off System</b>	149
<b>6. Results Chapter Four: Mechanisms of Action; Investigating SCL Gene Targets</b>	152
<b>6.1 Differential Gene Expression in Wild Type and <i>Scf</i><sup>-/-</sup> EBs</b>	152
6.1.1 Microarray Analysis	152
6.1.2 Validation & Analysis of Microarray Data	160
6.1.2.1 Lateral Mesoderm Genes	161
6.1.2.2 Cardiac Mesoderm Genes	161
6.1.2.3 Paraxial Mesoderm Genes	162
6.1.2.4 Other Genes of Interest	163

6.1.3	Lateral Mesoderm Gene Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	164
6.1.4	Cardiac Mesoderm Gene Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	166
6.1.5	<i>Sox9</i> Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	168
<b>6.2</b>	<b>GATA4 in Cardiac and Haematopoietic Differentiation</b>	<b>170</b>
6.2.1	GATA4 Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EB	172
6.2.2	GATA4 Expression in SCL Over-expressing EBs	177
6.2.3	Creation of a GATA4 Over-expressing ES Cell Lines	179
6.2.4	Cardiac Potential of GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	181
6.2.5	Haematopoiesis in GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	183
6.2.6	SCL Expression in GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	185
<b>6.3</b>	<b>Investigating Direct Targets of SCL</b>	<b>187</b>
6.3.1	SCL does not directly bind the GATA4 Proximal Promoter	188
6.3.2	Genome-Wide Mapping of Regions Bound by SCL	191
6.3.3	ChIP Optimisation	198
<b>6.4</b>	<b>Summary</b>	<b>200</b>
<b>7.</b>	<b>Discussion</b>	<b>202</b>
<b>7.1</b>	<b>Using the ES Cell System to Model Development</b>	<b>203</b>
<b>7.2</b>	<b>Defining Mesoderm Populations</b>	<b>204</b>
7.2.1	Refining Mesoderm Patterning During EB Differentiation	205
7.2.2	SCL Expression Marks Lateral Mesoderm-Primed Populations	208
7.2.3	GATA4 Expression Marks Cardiac Progenitors	210
<b>7.3</b>	<b>SCL is required for Lateral Mesoderm Specification: New Insights into SCL Function</b>	<b>211</b>
<b>7.4</b>	<b>SCL Negatively Regulates Cardiac Development</b>	<b>213</b>
<b>7.5</b>	<b>Reciprocal Antagonism between Cardiac Development and Haematopoiesis during Mouse Development</b>	<b>214</b>
7.5.1	GATA4 Expression Affects Cardiac and Blood Development	215
7.5.2	Drawing Parallels with Zebrafish Development	216

<b>7.6 SCL in Paraxial Mesoderm Development</b>	220
7.6.1 Chondrogenic Differentiation	220
7.6.2 Osteogenic Differentiation	222
7.6.3 Myogenic Differentiation	222
<b>7.7 SCL Direct Gene Targets</b>	223
<b>7.8 Concluding Remarks</b>	225
<b>7.9 Future Plans</b>	226
7.9.1 Tracking Cell Fate Changes in the Absence of SCL	226
7.9.2 Determining the Temporal Window of SCL Activity	227
7.9.3 Further Investigation into SCL Direct Gene Targets	227
7.9.4 Uncovering Additional Direct Gene Targets of SCL	228
7.9.5 Action of SCL through DNA-Independent Mechanisms	229
7.9.6 Verification in the Mouse Embryo	230
<b>References</b>	232

# List of Figures

## Chapter 1

1.1 Mouse Embryonic Mesoderm and Haematopoietic Development	6
1.2 Haematopoietic & Cardiac Development in the Mouse Embryo	11
1.3 Haematopoietic & Cardiac Development in the Zebrafish Embryo	14
1.4 Using the Mouse ES/EB System to Model Development	26
1.5 The Haematopoietic Transcription Factor SCL	33

## Chapter 3

3.1 Mesoderm Populations in Wild Type EBs	71
3.2 Immuno-phenotypic Differentiation Potential of Day 3.5 Flk-1/PDGFR $\alpha$ Populations	74
3.3 Cellular Fate Re-plating Assays	78
3.4 Cell Fate Potential of Day 3.5 Flk-1/PDGFR $\alpha$ Populations	80
3.5 Gene Expression in Day 3.5 Flk-1/PDGFR $\alpha$ Populations	82
3.6 Cell Fate Potential of Day 6 Flk-1/PDGFR $\alpha$ Populations	85
3.7 SCL Expression in Differentiating EBs	87
3.8 SCL Expression within Flk-1/PDGFR $\alpha$ Populations	89
3.9 Comparison of <i>Scf</i> Gene and SCL Protein Expression	91

## Chapter 4

4.1 Mesoderm Populations in <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	95
4.2 SCL and CD41 Expression in <i>Scf</i> <sup>RER/RER</sup> EBs	99
4.3 Apoptosis and Cell Cycle Analysis of Day 3.5 Flk-1/PDGFR $\alpha$ Populations in Wild Type and <i>Scf</i> <sup>-/-</sup> EBs	102
4.4 Haematopoietic Potential of Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	104
4.5 Chondrogenic Potential of Wild Type and <i>Scf</i> <sup>-/-</sup> EBs	106
4.6 Osteogenic Potential of Wild Type and <i>Scf</i> <sup>-/-</sup> EBs	108
4.7 Myogenic Potential of Wild Type and <i>Scf</i> <sup>-/-</sup> EBs	110
4.8 Cardiac Potential of Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	112
4.9 Cardiac Troponin T Expression in Cardiac Colonies	113
4.10 Cardiac Populations in Differentiating EBs	115
4.11 Haematopoietic and Cardiac Potential in Temporally Distinct Flk-1 <sup>+</sup> Populations	116
4.12 Gene Expression in Flk-1 Wild Type, <i>Scf</i> <sup>-/-</sup> and <i>Scf</i> <sup>RER/RER</sup> EBs	118
4.13 SCL Over-Expressing ES Cell Lines	120

<b>4.14</b> Mesoderm Differentiation of SCL Over-Expressing EBs	122
<b>4.15</b> Haematopoietic Potential of SCL Over-Expressing EBs	124
<b>4.16</b> Cardiac Potential of SCL Over-Expressing EBs	125
<b>4.17</b> Rescue of <i>Scf</i> <sup>-/-</sup> Haematopoietic Phenotype	127
<b>4.18</b> Rescue of <i>Scf</i> <sup>-/-</sup> Cardiac Phenotype	128

## Chapter 5

<b>5.1</b> Knock-in of a Tetracycline Responsive Element	134
<b>5.2</b> Screening for tTA/ROSA26 ES Cells	135
<b>5.3</b> tTA/ROSA26 Wild Type ES Cells	137
<b>5.4</b> tTA/ROSA26 <i>Scf</i> <sup>-/-</sup> ES Cells	139
<b>5.5</b> An Inducible SCL Expression System	141
<b>5.6</b> Selection of ES Cells with Inducible SCL Expression	142
<b>5.7</b> Doxycycline Control of SCL Expression	144
<b>5.8</b> Doxycycline Control of SCL Expression in ES Cells	145
<b>5.9</b> Inducible SCL Expression in EBs	147

## Chapter 6

<b>6.1a</b> Differential Gene Expression between Wild Type & <i>Scf</i> <sup>-/-</sup> Flk-1 <sup>+</sup> Cells	153
<b>6.1b</b> Functional Gene Ontology of Differentially Expressed Genes in Wild Type & <i>Scf</i> <sup>-/-</sup> Flk-1 <sup>+</sup> Cells	154
<b>6.2</b> Lateral Mesoderm Gene Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> & <i>Scf</i> <sup>RER/RER</sup> EBs	165
<b>6.3</b> Cardiac Mesoderm Gene Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> & <i>Scf</i> <sup>RER/RER</sup> EBs	167
<b>6.4</b> Sox9 Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> & <i>Scf</i> <sup>RER/RER</sup> EBs	169
<b>6.5</b> GATA4 Expression in Wild Type, <i>Scf</i> <sup>-/-</sup> & <i>Scf</i> <sup>RER/RER</sup> EBs	173
<b>6.6</b> GATA4 Expression in Differentiating EBs	175
<b>6.7</b> GATA4 Expression in Day 6 SCL Over-Expressing & <i>Scf</i> <sup>-/-</sup> /SCL EBs	178
<b>6.8</b> Generation of a Gata4 Over-Expressing ES Cell Line	180
<b>6.9</b> Cardiac Potential of GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	182
<b>6.10</b> Haematopoietic Potential of GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	184
<b>6.11</b> SCL Expression in GATA4 Over-expressing & <i>Gata4</i> <sup>-/-</sup> EBs	186
<b>6.12</b> SCL does not directly bind the <i>Gata4</i> Proximal Promoter	190
<b>6.13a</b> Genome-wide Mapping of Regions Bound by SCL in Day 3.5 EBs	192

<b>6.13b</b> Gene Ontology of Regions Bound by SCL in Day 3.5 EBs	193
<b>6.14</b> Optimisation of $\alpha$ -SCL ChIP on Day 3.5 Flk-1 <sup>+</sup> EB Cells	199

## Chapter 7

<b>7.1</b> Model of Mesoderm Development during EB Differentiation	206
<b>7.2</b> Cross-Antagonism between Haematopoietic and Cardiac Lineages during Mouse Development	217

## List of Tables

<b>Table 1:</b> PCR Primers for Gene Expression Analysis	68
<b>Table 2:</b> PCR Primers for ChIP Analysis	69
<b>Table 3:</b> PCR Primers for Cell Line Generation	69
<b>Table 4:</b> Expansion of Flk-1/PDGFR $\alpha$ Populations	75
<b>Table 5:</b> Total Cell Numbers for Flk-1/PDGFR $\alpha$ Populations	96
<b>Table 6:</b> Differential Gene Expression Exhibited by Flk-1 <sup>+</sup> <i>Scf</i> <sup>-/-</sup> EBs Compared to Wild Type	156
<b>Table 7:</b> Percentage of Total Cells Co-expressing GATA4 with Flk-1 and/or PDGFR $\alpha$	176
<b>Table 8:</b> Genes Associated with Genomic Regions Bound by SCL in Day 3.5 Wild Type EBs	194