SCL/Tal-1 transcription factor acts downstream of cloche to specify hematopoietic and vascular progenitors in zebrafish

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SCL/Tal-1 is a transcription factor necessary for hematopoietic stem cell differentiation. Although SCL is also expressed in endothelial and neural progenitors, SCL function in these cells remains unknown. In the zebrafish mutant cloche (clo), SCL expression is nearly abolished in hematopoietic and vascular tissues. Correspondingly, it was shown previously that clo fails to differentiate blood and angioblasts. Genetic analysis demonstrates that the clo mutation is not linked to the SCL locus. Forced expression of SCL in clo embryos rescues the blood and vascular defects, suggesting that SCL acts downstream of clo to specify hematopoietic and vascular differentiation.

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SCL (or Tal-1) is a basic helix-loop-helix (bHLH) transcription factor identified by its involvement in chromosomal translocations or upstream deletions associated with acute lymphocytic leukemia (Begley et al. 1989; Finger et al. 1989; Chen et al. 1990). During normal development the SCL gene is expressed in blood precursors (Green et al. 1991), endothelial progenitors (Kallianpur et al. 1994; Drake et al. 1997), and the brain (Green et al. 1992). Targeted disruption of the SCL gene in ES cells has established an essential role in hematopoiesis, acting at the stem cell level to specify all blood lineages (for review, see Green 1996; Shvidasani and Orkin 1996). Because the SCL−/− mice die during early embryogenesis, this precludes direct analysis of possible SCL function in other tissues where SCL is expressed, such as the endothelium and the brain.

Previous studies demonstrate an intimate relationship between blood and vascular development. Throughout vertebrate ontogeny, hematopoietic and vascular tissues arise in anatomical proximity (Sabin 1920; Pardanaud et al. 1987; Pardanaud et al. 1996). Blood and endothelial progenitors coexpress some molecular markers, such as CD34, c-kit, and flk-1 (Yamaguchi et al. 1993; Bernex et al. 1996; Kabrun et al. 1997; Shalaby et al. 1997; Wood et al. 1997). Targeted disruption of some genes, such as flk-1 and CBF, result in combined vascular and hematopoietic defects (Shalaby et al. 1995; Okuda et al. 1996; Wang et al. 1996). Furthermore, a zebrafish mutant cloche (clo) affects both blood and endothelial differentiation (Stainier et al. 1995). Because of the loss of endocardium, the clo mutant has enlarged cardiac chambers evident at 26 hr post-fertilization (hpf) (Liao et al. 1997). clo homozygotes have near undetectable expression of GATA-1 and flk-1, and complete loss of tie-1 (Liao et al. 1997). GATA-1 is a marker for differentiated red blood cells, whereas flk-1 and tie-1 are markers for endothelial cells (for review, see Mustonen and Alitalo 1995; Shvidasani and Orkin 1996). These and other studies suggest that interactions between hematopoietic and vascular tissue during early embryogenesis contribute to the proper differentiation of both tissues.

Here, we identify zebrafish SCL and examine its expression in hematopoietic and vascular progenitors during zebrafish embryogenesis.

Results

SCL is highly conserved across vertebrate species

A zebrafish SCL cDNA was identified (SCLa2.1) by hybridization using the bHLH domain of murine and Xenopus SCL cDNAs. Conceptual translation of SCLa2.1 sequence reveals that SCL is highly conserved across vertebrates (Fig. 1), where the bHLH domain (amino acids 188 to 243) is identical in zebrafish, Xenopus, chick, mouse, and human. Zebrafish SCL is most homologous to the chicken peptide (36% identity). Such high conservation of SCL among vertebrates implies a shared function during vertebrate development.

SCL expression delineates hematopoietic and endothelial progenitors

To examine patterns of SCL expression during zebrafish embryogenesis, RNA in situ analysis was carried out on whole embryos at various time points (Fig. 2). SCL transcripts are detected as early as the 1 somite stage in the anterior and posterior regions of the lateral plate mesoderm (data not shown). By 5 somites (12 hpf) SCL is expressed in the anterior (Fig. 2A), dorsal (Fig. 2B), and posterior (Fig. 2C) lateral plate mesoderm. As the embryo develops, SCL expression expands rostrally and caudally. The anterior lateral mesoderm cells contribute to form bilateral cranial marginal hematopoietic and angioblast progenitors (arrowhead, Fig. 2E).

SCL expression in the anterior lateral mesoderm cells is evident at 26 hr post-fertilization (hpf) (Liao et al. 1997). The anterior lateral mesoderm cells contribute to form bilateral cranial vascular plexi (arrowhead, Fig. 2E); dorsal cells contribute to the dorsal aorta primordium. The posterior cells begin to fuse by 20 somites (arrowhead, Fig. 2I).

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enter circulation (arrowhead with asterisk, Fig. 2I). By 2 days postfertilization (dpf), SCL expression in vascular primordia subsides and hematopoietic expression is reduced to a few circulating cells (arrowhead, Fig. 2I). By 3 dpf, SCL expression is most intense in the developing brain but can also be detected weakly in the posterior tail (arrowhead, Fig. 2J). At the same time, c-myb transcripts are detected more strongly in this posterior tail region (Fig. 2K); c-myb is associated with definitive hematopoiesis in mice (Mucenski et al. 1991). SCL expression in the posterior tail region becomes evident by 4 dpf (Fig. 2L). Interestingly, SCL expression is also localized to the heart (Fig. 2L). Transverse histological section of the heart reveals that both cardiac chambers are filled with SCL-positive cells (arrowhead, Fig. 2N). SCL-positive cells are also consistently observed within the dorsal aorta (arrowhead, Fig. 2O) and axial vein (arrowhead with asterisk, Fig. 2O) throughout the embryo. We suggest that these SCL-positive cells in the heart lumen represent pooled blood in the fixed day 4 embryo. However, the posterior tail SCL expression is not restricted to the vessel (Fig. 2P). Here, SCL transcripts are detected strongly in a group of cells ventrally to the axial vein [ventral vein region (VVR)], bound anteriorly by the end of the pro-nephric duct, and posteriorly by the end of notochord. By 5 dpf, SCL expression in the VVR subsides.

The zebrafish clo mutation abrogates SCL expression RNA in situ analysis in the clo mutant reveals that SCL expression is abrogated in the lateral plate mesoderm at 5-somites (Fig. 3A). By 24 hpf, SCL transcripts are detected in the hindbrain and spinal neurons (Fig. 3B). However, the clo mutant fails to express SCL in any of the angioblast populations described previously (cf. Fig. 3B with Fig. 2, E, F, and G). Previous work suggests that most endothelial cells are deleted by the clo mutation, where only a small population in the posterior tail is spared (Stainier et al. 1995; Liao et al. 1997). Moreover, the hematopoietic progenitors fail to form in the embryo. At 24 hpf, very few cells (5-10) with SCL transcripts can be detected in the ICM (arrow, Figure 3B). These rare hematopoietic precursors can differentiate and give rise to a very small number of GATA-1-positive cells, which remain in the tail (Liao et al. 1997). These GATA-1-positive blood cells persist into 36 hpf (data not shown) but are not detected with GATA-1 (Fig. 4) or SCL (Fig. 3C) in situ later at 2 dpf. SCL expression in the developing brain appears unperturbed by clo.

Because SCL expression is severely affected by the clo defect, it was important to ascertain whether the SCL locus represents the clo mutation. A single-strand length polymorphism (SSLP) was defined in the SCL cDNA. In-

Figure 1. Zebrafish SCL peptide sequence compared with that of Xenopus, chick, mouse, and human (amino acids identical across species is in dark blue, with decreasing similarity in lighter shades).

with asterisk, Fig. 2D) and form the intermediate cell mass (ICM) by 24 hpf (arrowhead, Fig. 2G). The ICM contributes to both hematopoiesis and vasculogenesis (Detrich et al. 1995; Pardanaud et al. 1996).

Although SCL expression is similar to that of flk-1 during early zebrafish development, there are two significant differences. SCL transcripts are not detected in the rostral bilateral flk-1-positive cells at 20 somites, which represent the precardiac angioblasts that form the endocardium (Stainier et al. 1993; Liao et al. 1997). Instead, a more caudal set of bilateral stripes are SCL positive, representing those lateral mesoderm cells that do not converge to form the ICM (arrowhead, Fig. 2D). These bilateral cells persist dorsally to 24 hpf (arrowhead, Fig. 2F), and are located immediately lateral to the dorsal aorta primordium. Furthermore, SCL expression in the ICM differs from that of GATA-1 (Detrich et al. 1995). Although both SCL and GATA-1 transcripts are detected at high levels in the ICM, SCL expression extends more posteriorly (arrowhead, Fig. 2G).

As circulation commences ~26 hpf, SCL-positive blood cells begin to leave the ICM and enter the primitive vascular network. Circulating blood is evident in the cardinal vein (arrowhead, Fig. 2H). However, it is not clear whether the blood progenitors in the posterior ICM
SCL specifies hematopoiesis and vasculogenesis

Forced expression of SCL in clo rescues both the hematopoietic and vascular defects.

To determine whether SCL can rescue the clo defect, we expressed the full-length SCLα2.1 cDNA (cmv-SCLα2.1) in embryos microinjected at the one- to four-cell stage. Embryos were scored and fixed at 2 dpf, when GATA-1 (Fig. 4B) and tie-1 (Fig. 4E) transcripts are absent in clo−/− embryos, and flk-1 expression is undetectable in the head and trunk (mut, Fig. 4D). Because CMV promoter expression is unrestricted, cmv-SCLα2.1-injected embryos exhibit ectopic expression of SCL at high levels persisting into 2 dpf (Fig. 4A).

For microinjection experiments, embryos were obtained from either adult clo heterozygote mating pairs or wild-type mating pairs as control. The embryos were scored at 2 dpf, separated with respect to wild-type or mutant enlarged heart phenotype, and fixed for in situ analysis. SCL forced expression in embryos had no effect on normal development (Fig. 4A). When SCL is expressed in clo−/− embryos, red blood cells are evident in the trunk of the live 2 dpf embryos, whereas none are seen in the uninjected clo−/− (data not shown). These red cells are better demonstrated by in situ for GATA-1 (Fig. 4B). Alternatively, o-dianisidine staining for complexed hemoglobin specifically demonstrates differentiated erythrocytes in the clo wild type and rescued clo−/− embryos (Fig. 4C). The number of red cells rescued by injection appears to be lower than that observed in uninjected clo wild-type embryos, suggesting that the rescue of hematopoietic defect is incomplete. SCL expression also rescued the expression of flk-1 and tie-1 in the injected clo−/− embryos (Fig. 4D,E). The rescue of flk-1 expression in the cranial (Fig. 4D, arrowhead in rsc1, rsc2) and trunk vasculature (Fig. 4D, arrow with asterisks in rsc2) is mosaic among the injected embryos, and near complete rescue has been observed. Rescue of tie-1 expression is partial and is restricted to vasculature of the posterior tail (Fig. 4E, arrowhead). The pattern of tie-1 expression in the rescued clo−/− embryos also appears disorganized, lacking discrete sprouting of intersomitic vessels that are present in clo wild type (compare rsc and wt in Fig. 4E). Of the 502 embryos (381 clo−/−, 121 clo−/−) injected with cmv-SCLα2.1 and analyzed by RNA in situ for molecular rescue, 42/121 were rescued (35%). Of the 473 uninjected embryos (349 clo−/−, 124 clo−/−) similarly analyzed, none were rescued. Control injection of cmv-GFP into 75 embryos (55 clo−/−, 21 clo−/−) also failed to rescue the molecular markers in the mutants. Collectively, these experiments suggest that SCL acts downstream of clo to specify hematopoietic and angioblasts precursor formation.

Discussion

We found that SCL is expressed in early hematopoietic and vascular progenitors during normal development and is nearly absent in the clo mutant. Genetic analysis demonstrates that SCL is not linked to clo. In the 2 dpf clo mutant embryos, GATA-1 and tie-1 transcripts are not detected; flk-1 is expressed only in a small number of cells in the posterior tail (Liao et al. 1997) but is absent in the head and mid-trunk. clo−/− embryos fail to initiate normal hematopoiesis and vasculogenesis (Stainier et al. 1995; Liao et al. 1997). When SCL is expressed in the clo−/− embryo, expression of GATA-1, flk-1, and tie-1 are restored at 2 dpf. However, the rescue is incomplete, perhaps because of mosaicism of the injected embryos. It is also possible that the clo defect cannot be entirely

Figure 2. SCL expression in vascular and hematopoietic progenitors during early development. SCL RNA in situ hybridization at 5-somites stage (A–C), 18-somites stage (D), 24 hpf (E–G), 26 hpf (H), 2 dpf (I), 3 dpf (J), 4 dpf (K,L), and 5 dpf (M). Transverse histological sections (6 µm) from 4 dpf embryos are shown in N–P, corresponding to labeled lines in L. All are in situ done with SCL, except K, which is with c-myb. All are viewed laterally, with anterior to the left and dorsal up, except A which is an anterior view, B and D, which are dorsal views, and C, which is a posterior view. (See text for details.)
SCL, flk-1, never detected. Interestingly, those few cells expressing tie-1 detected in a very small number of cells, and 

Our rescue of flk-1 expression in the clo−/− mutant suggests that SCL acts upstream or in parallel to flk-1 in the zebrafish embryo.

Analysis of SCL expression during embryogenesis also provides insight into how the hematopoietic and vascular tissues may be specified. In the posterior ICM, SCL, LMO-2, and GATA-2 are expressed, but not GATA-1 (Detrich et al. 1995; M.A. Thompson and L. Zon, unpubl.). In mice, GATA-2 is involved in hematopoietic progenitor proliferation (Tsai et al. 1994), LMO-2 in blood progenitor differentiation (Warren et al. 1994), and GATA-1 in erythroid differentiation (for review, see Shivdasani and Orkin 1996). Morphologically, the hematopoietic cells in the posterior ICM are less differentiated than those of the anterior ICM (Detrich et al. 1995). Collectively, these results suggest that the posterior ICM hematopoietic cells represent a population of hematopoietic progenitors. Although most SCL-positive blood cells of the ICM enter circulation, we believe some SCL-positive progenitors remain in the posterior ICM. The posterior ICM contributes to form the VVR of the posterior tail. More anteriorly, SCL expression is detected in dorsal bilateral stripes at 24 hpf. These SCL-positive cells migrate toward the trunk midline as development progresses. Preliminary studies suggest that these cells colonize the AGM (aorta–gonad–mesonephros) region, a site of definitive hematopoiesis in vertebrates (M.A. Thompson and L. Zon, unpubl.). At 4 dpf, SCL and c-myb are coexpressed at high levels in the VVR. In mice, c-myb is associated with definitive hematopoiesis (Mucenski et al. 1991). We propose that the VVR represents a larval site of definitive hematopoiesis in zebrafish. AGM formation (at 36 hpf) precedes that of the VVR (4 dpf), and we believe both regions form niches for definitive blood. The relative contribution of VVR and AGM to definitive blood remains to be elucidated by detailed transplantation and cell lineage studies.

Our data also support the notion of angioblast heterogeneity. We find SCL expressed in cranial angioblasts and in the ICM but not in precardiac angioblasts that contribute to the endocardium. The ICM has been implicated to contain angioblast potential (Pardanaud et al. 1996), and may be involved in forming the dorsal aorta and axial vein of the trunk and tail. The lack of SCL transcripts in the precardiac angioblasts suggests a molecular difference in the developmental programs that specify different vascular structures.

Our experiments suggest an instructive role for SCL in specifying both hematopoietic and vascular progenitors during zebrafish embryogenesis. Recent evidence from Xenopus animal cap assays suggests that SCL is sufficient to specify the hematopoietic mesoderm (P. Mead and L. Zon, unpubl.). The dual role of SCL acting in hematopoiesis and yolk sac vitelline vessel angiogenesis has also been implicated by mouse chimera and transgenic studies (Visvader et al. 1998). These lines of evi-
SCL specifies hematopoiesis and vasculogenesis

Materials and methods

Zebrafish strains and maintenance

Zebrafish were maintained as described (Westerfield 1993), and staged as described (Kimmel et al. 1995). Embryos raised to time points beyond 24 hpf were treated with 0.003% phenylthiourea (PTU) to prevent melanization (Sigma). The spontaneous clo allele, clo<sup>m<99</sup> (Stainier et al. 1995), was obtained from Mark Fishman, MGH (Charlestown). The clo<sup>m<99</sup> allele was outcrossed to the standard wild-type strain (AB) for two generations. Heterozygotes carrying AB clo<sup>m<99</sup> allele were crossed to a wild-type strain in the isogenic DAR genetic background to generate a AB/DAR mapping strain. Embryos used for in situ and microinjection experiments were collected from pairwise matings between identified clo<sup>m<99</sup> heterozygotes. Haploids used for linkage analysis were generated essentially as described (Westerfield 1993).

Isolation of zebrafish SCL cDNA

Full-length zebrafish SCL cDNA was isolated by low stringency hybridization using the bHLH domain of mouse and Xenopus SCL as the labeled probe. The SCL bHLH fragments were generated by PCR with the following primers: murine SCL (5'-TTTTGTGGGACACCGATG, 3'-CTCTCTCCTGCTCATGGAG), Xenopus SCL (5'-TTGGTGACCCACACCC, and 3'-ATCGAGAAGTTTGCCAAG). An adult zebrafish kidney cDNA library (provided by) J. Rast, Children’s Hospital, St. Petersburg, FL) was screened, and one full-length clone (SCLa2.1) was sequenced (DNA Sequencing Core Facility, Children’s Hospital, Boston) and used in the experiments described herein (GenBank accession no. AF045432). Sequence analysis using BLAST, BESTFIT, and PILEUP programs was done with the UWGCG software package. Peptide sequence alignment was done with Gene Inspector (Textco).

In situ hybridization, Dianisidine staining, and histological analysis

In situ hybridization and riboprobe synthesis were performed as described (Schulte-Mmerker et al. 1992), with modifications: Proteinase K digestion was extended to 2 min in 20 µg/ml, and hybridization steps were carried out at 65°C. The GATA-1 (Detrich et al. 1995), flk-1, and tie-1 (M.A. Thompson and L. Zon, pers. comm.) probes were prepared as described previously. O-dianisidine staining was done as described (Detrich et al. 1995). Embryos for histological sections were treated with acetic and embedded in epon-araldite (Polysciences, Inc.) plastic resin, for histological sections. Sections of 6 µm were cut on LKB microtome and counterstained with 0.5% eosin, as described (Hyatt et al. 1996).

Mapping of SCL and polymorphism analysis in clo

A SSLP was amplified with the following primers (forward, GGGATTCCAGCCCTCTATC; reverse primer, GCAGGGCTAAAGTTGGGAT(T/G)). The 100-bp (AB) or 188-bp (DAR) product was resolved on 8% denaturing urea-polyacrylamide gel. This SSLP was used to type clo<sup>m<99</sup> and clo<sup>m<99</sup>-DAR haploid individuals, and 96 individuals of a diploid AB/DAR genetic background to generate a AB/DAR mapping strain. Embryos used for in situ and microinjection experiments were collected from pairwise matings between identified clo<sup>m<99</sup> heterozygotes. Haploids used for linkage analysis were generated essentially as described (Westerfield 1993).

SCLa2.1 full-length cDNA defined by BamHI and XhoI sites was subcloned into BamHI and XhoI sites of the pC52<sup>V</sup>-vector, containing the CMV promoter (D. Turner (Fred Hutchinson Cancer Research Center, Seattle, WA) and R. Rupp (Friedrich-Miescher Laboratory, Tübingen, Germany)). The injection construct (cmv-SCLa2.1) plasmid DNA was diluted to 100 ng/µl in sterile ddH<sub>2</sub>O. A control plasmid (cmv–GFP) was constructed with the green fluorescent protein (B. Seed, MGH, Boston), gene inserted into C1al and Xbal sites of the pC52<sup>V</sup>-vector, and diluted to 125 ng/µl. Microinjection was performed essentially as described (Westerfield 1993), utilizing Nikon picoinjector and Narishige micromanipulator.
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