twist and snail as positive and negative regulators during Drosophila mesoderm development

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The mechanisms by which the mesoderm is determined during early development vary in different species. For example, in vertebrates, soluble factors secreted by non-mesodermal cells induce mesoderm formation (for review, see Slack 1991), whereas in Drosophila, the nuclear concentration of a maternal transcription factor, the dorsal protein, determines mesodermal fate (Rushlow et al. 1989; Steward 1989; Roth et al. 1989). However, early mesoderm-specific genes, such as twist, snail, or MyoD, which are expressed after the initial mesoderm determination and probably regulate further mesoderm development, appear to be remarkably homologous even between insects and vertebrates (Davis et al. 1987; Hopwood et al. 1989; Michelson et al. 1990; Paterson et al. 1991; Wolf et al. 1991; A. Nieto and D.G. Wilkinson, pers. comm.). This suggests that once the mesoderm is determined, different species use similar regulatory molecules to govern its further development.

In Drosophila, the mesoderm arises from the ventral region of the embryo. A group of maternal genes, the dorsal group genes and cactus, define positional values along the dorsoventral axis of the embryo by the nuclear concentration of the dorsal gene product (Roth et al. 1989; Rushlow et al. 1989; Steward 1989). The dorsal nuclear protein directly or indirectly regulates the activation or repression of zygotic genes. Differences in the expression of zygotic genes along the dorsoventral axis are visible as early as 2 hr after fertilization, which is ~1 hr before the invagination of the mesoderm begins. At least four domains along the dorsoventral axis can be distinguished by their fates and their gene-expression patterns. The region next to the mesoderm is occupied by the ventral ectoderm, followed more dorsally by the dorsolateral ectoderm, and finally, by the amnioserosa.

Two zygotic genes, twist and snail, are known to be required for the formation of the mesoderm (Nüsslein-Volhard et al. 1984). Embryos mutant in these genes gastrulate abnormally, form no mesodermal germ layer or mesodermal derivatives, and die at the end of embryogenesis (Simpson 1983; Grau et al. 1984). The lateral and dorsal parts of the embryo are not affected in the mutants. The products of the twist and snail genes are members of the helix-loop-helix and zinc-finger protein families, respectively (Boulay et al. 1987; Thisse et al. 1988) and are therefore probably involved in transcriptional regulation. They are expressed in the mesoderm anlage (Thisse et al. 1988; Leptin and Grunewald 1990). Their structure and expression patterns, and the mutant phenotypes suggest that twist and snail play a role in determining the differentiation and morphogenesis of the mesoderm, probably by regulating the transcription of other genes.

Although neither twist nor snail mutant embryos develop a mesoderm, their phenotypes are different (Leptin and Grunewald 1990). In twist mutants, the ventral furrow (the early invagination of the mesoderm) is only half the width of the wild-type furrow, suggesting that the mesoderm anlage might be narrower than in the wild-type embryo. In snail mutants, which make no furrow, the ventral epithelium buckles irregularly over the normal width of the mesoderm anlage. The phenotype of embryos mutant for both genes is much stronger than that of either single mutant alone, the ventral epithelium is indistinguishable from the neighboring ecto-
This indicates that twist and snail do not act exclusively in the same pathway but have at least partly independent functions. Because they act most likely as transcriptional regulators, we tested their roles in mesoderm development by examining their effects on the expression of a number of genes normally expressed in the mesoderm and at its borders. As representative examples, we used PS2α, expressed in the mesoderm [Bogaert et al. 1987]; single-minded (sim), expressed in mesectodermal cells that lie at the border of the mesoderm [Crews et al. 1988] and do not contribute to the mesoderm, but become part of the nervous system [Campos-Ortega and Hartenstein 1985]; and crumbs, expressed outside the mesoderm, in the ventral and more dorsal ectoderm [Knust et al. 1987]. These genes are required for the proper development of the cells in which they are expressed, i.e., for the differentiation of mesectodermal cells [sim], the attachment of mesodermal cells to the ectoderm [PS2α], and for the organization of the epidermis (crumbs). Under the control of twist and snail, respectively, these genes are activated in or their expression is confined to the areas in which they are destined to be active.

Results

Expression patterns of twist and snail

Because the temporal and spatial limits of twist and snail expression are important for this study, they were analyzed and compared in detail.

As reported previously (Thisse et al. 1988; Leptin and Grunewald 1990), both twist and snail RNA are expressed in the prospective mesoderm at the cellular blastoderm stage [Fig. 1A,B]. However, when first detectable (during nuclear cycle 12), they appear in a diffuse band only half the width of the prospective mesoderm [Fig. 1C,D].

The expression patterns of twist and snail differ in a number of aspects. Along the anterior–posterior axis, twist RNA and protein extend farther anterior and posterior than snail RNA and protein [Fig. 2A–D]. snail RNA and protein form a sharp posterior boundary [Fig. 2B,D]. [snail protein like twist [Thisse et al. 1988], is nuclear [Fig. 2J], consistent with the role suggested by the zinc-finger motifs in its sequence.] Although twist continues to be expressed in the mesoderm throughout germ-band extension [Fig. 2E], snail products completely disappear from the mesoderm halfway through germ-band extension and appear in a subset of cells in the neural ectoderm, which by their distribution and shape are probably neuroblasts [Figs. 2F and 6E].

The lateral boundaries of twist and snail expression are not identical. Both snail RNA and protein have a discrete lateral boundary, whereas twist RNA and protein form a gradient at the edge of the prospective mesoderm [Fig. 2G–J]. The fainter part of this gradient extends beyond the sharp snail boundary into the territory of the prospective ectoderm. Figure 2 shows this difference at its most extreme point, in mid-cellularization. Much earlier, the snail boundary is slightly more diffuse than shown here, and later, during gastrulation, the twist boundary sharpens.

Expression domains of other genes along the dorsoventral axis

The expression of a number of genes normally expressed in and around the mesoderm in embryos lacking twist and snail function was examined. The localization of the expression domains of some of these genes relative to each other and relative to twist and snail was established in double-labeling experiments [in cases where the subcellular localization of the RNAs differ, e.g., Fig. 4B] and by comparisons on serial sections. Their expression patterns are summarized in Figure 3. sim is expressed in mesectodermal cells at the border of the mesoderm [Fig. 4A,B; Crews et al. 1988]; crumbs is expressed outside the mesoderm, in the ventral and more dorsal ectoderm [Knust et al. 1987; Fig. 4B]. Its expression domain includes the mesectodermal cells. PS2α is expressed in the mesoderm [Fig. 4C; Bogaert et al. 1987]; like snail, it is expressed only in the region between the two lines of mesectodermal cells. The snail and PS2 expression domains do not overlap the sim expression domain. In contrast, twist expression is not confined to this region at the blastoderm stage. The sim-expressing cells lie within the region of the graded distribution of twist protein. Thus, at this stage, low levels of twist protein are found in mesectodermal and some ectodermal cells. During late germ-band extension, however, twist products disappear from nonmesodermal cells, and when the mesoderm has invaginated fully, the mesectodermal cells no longer express twist [Leptin and...
Grunewald 1990). Other genes expressed in the prospective mesoderm or ectoderm are listed in the legend to Figure 3.

Expression patterns in twist and snail mutants

In snail embryos, PS2 and twist are activated in the same pattern as in the wild type (Fig. 4C,F; Leptin and Grunewald 1990). This is also the case of other early mesodermal genes (see Fig. 4 legend). In contrast, the expression patterns of sim and of ventrolateral genes are altered. crumbs and sim are expressed in the mutant mesoderm [Fig. 4G,H; for sim, see also Leptin and Grunewald (1990); Nambu et al. (1990); Rushlow and

Figure 2. (See facing page for legend.)
prospective amnioserosa. Other genes expressed in the mesoderm at this stage are restricted to more lateral regions [t48 (data not shown); Delta [M. Haenlin and J. Campos-Ortega, pers. comm.], mesectodermal genes [Nambu et al. 1990]]. This indicates that snail is not required to activate mesodermal genes, but to repress ventrolateral genes in the mesoderm territory. However, during germ-band extension, twist and PS2 disappear earlier than during wild-type development, suggesting a direct or indirect late role of snail in the maintenance of the expression of these genes (see Discussion).

In twist mutants, the two sim lines lie closer together than in the wild type, at the edge of the region that forms the mutant ventral furrow (Fig. 4D). The crumbs expression domain also extends farther ventrally in twist mutant embryos (Fig. 4B,E), as do those of two other genes expressed in the lateral and dorsal regions at this stage [t48, not shown; Delta, M. Haenlin and J. Campos-Ortega, pers. comm.]. Thus, the mutant mesoderm anlage in twist embryos is narrower than in the wild type, consistent with the finding that the ventral furrow in twist embryos is narrower. PS2 is not expressed in these embryos, nor are other genes that are expressed in wild-type mesoderm at this stage (string, B. Edgar, pers. comm.; msh-2, Bodmer et al. 1990; t48, data not shown). Thus, twist is required for the activation of early mesodermal genes but not for the repression of lateral genes.

When both twist and snail function are removed (in twist snail double mutants), no mesodermal or mesectodermal genes are expressed, and the genes of the ventral ectoderm are expressed over the whole ventral surface [data not shown, as crumbs expression in the double mutants looks like Fig. 4H, and PS2 expression looks like Fig. 4F. Double-mutant embryos do not express the sim gene [data not shown; Rushlow and Arora 1990]).

snail and twist expression in twist mutants

The normal expression pattern of twist protein in snail mutants [Leptin and Grunewald 1990] shows that snail function is neither required for turning on twist expression nor for its early maintenance. Specifically, the width of the mesodermal territory can be defined in the absence of snail.

However, if twist is required for the expression of all early mesodermal genes, expression of snail and possibly even of twist itself should depend on twist activity. This is indeed the case. snail transcription is never established over the whole mesodermal territory in twist mutant embryos. Its early expression in a narrow band is the same as in the wild type, but it does not become expressed in a wider band [Fig. 5C]. Instead, it disappears at the cellular blastoderm, usually by first breaking up into patches [Fig. 5E]. Thus, the initial transcription of snail
**Figure 4.** Expression of mesodermal, mesectodermal, and ectodermal genes in wild-type embryos and in twist and snail mutants. (A,D,G) Ventral views of in situ hybridizations of whole-mount embryos at cellular blastoderm; all other panels are transverse sections of embryos during early gastrulation, dorsal side up. In wild-type embryos (B,C), the ventral furrow has begun to form. (A,D,G) sim is expressed in two lines, each one cell wide, at the edge of the mesoderm. In twist mutants, these lines lie closer together (D); in snail mutants, the gene is expressed over the whole width of the mesodermal territory (G). (B,E) Embryos hybridized simultaneously with probes for sim and crumbs. Because crumbs RNA is localized only in the apical part of each cell and sim is distributed over the whole cytoplasm, their expression domains can be distinguished in sectioned embryos (B,E). In twist embryos, both the sim cells and the edges of the crumbs domain lie farther ventrally and closer to each other than in the wild type. (H) snail mutant embryo hybridized with a crumbs probe. crumbs is expressed around the whole periphery of the embryo. Two other genes expressed in the ectoderm, t48 (Gould et al. 1990) and Delta, show the same changes of expression patterns in the mutants as crumbs (results not shown; M. Haenlin and J. Campos-Ortega, pers. comm.). (C,F,I) Embryos hybridized with a PS2 probe. PS2 is not expressed in twist embryos (F) but is expressed normally in snail mutants (I). Other early mesodermal genes that behave in this way are twist, the early ventral expression of t48 (Gould et al. 1990, results not shown), and msh-2 (Bodmer et al. 1990). In embryos mutant for both twist and snail, the crumbs expression pattern looks like that in H, and PS2 looks like that in F.

In a narrow band is independent of twist, probably directly activated by the maternal genes, but its maintenance and later expression across the whole width of the mesoderm require twist function. The late expression of snail in neuroblasts is entirely independent of twist (Fig. 6F).

Twist function appears also to be required for the maintenance of expression of its own RNA. The effects of four strong twist alleles on twist expression were tested. In embryos mutant for any of them, twist RNA is initially transcribed normally, first in a narrow band, then over the whole width of the mesoderm. During cellularization, however, the RNA begins to fade [see Fig. 5D,F] and finally disappears at the beginning of gastrulation [see Fig. 5H]. Thus, the early twist transcription pattern is established, but its expression cannot be maintained in the absence of detectable twist function.

**Late fate changes**

Many mesodermal and ventral-ectodermal genes are only expressed during or after germ-band extension, at least 3 hr later than the genes analyzed above. Late mesodermal genes, such as β-tubulin [Leiss et al. 1988; Kimble et al. 1990], pox meso [Bopp et al. 1989], and the embryonic muscle actin Act57A (Tobin et al. 1990) are neither expressed in twist nor in snail mutants (Fig. 6A–D; Leiss et al. 1988). Although this suggests that snail may have a role in the activation of these genes, it should be noted that in snail mutants, twist also disappears early. Furthermore, even in the wild type, snail disappears from the mesoderm before β3-tubulin, pox meso, and Act57A are expressed. Therefore, the failure of snail mutants to express late mesodermal genes is consistent with a direct requirement for twist for the activation of these genes and an indirect role for snail.

The transient expression of snail in twist mutant embryos is not sufficient to repress late ventrolateral genes. The mutant mesodermal region in twist embryos begins to show aspects of ventrolateral behavior after germ-band extension, in that cells delaminate from it. These cells have the typical shape of delaminating neuroblasts and express genes normally expressed by neuroblasts at this stage [as with hunchback and the late, neuroblast-specific snail, Fig. 6C–E]. This suggests that the presence of snail is required continually to repress all lateral characteristics in the mesodermal region.

**Discussion**

Together, the results shown here suggest the following early functions for twist and snail (Fig. 7). twist responds to maternal positional information defining the boundaries of the mesoderm. Within this territory, it is respon-
Figure 5. Expression of twist and snail RNA in twist mutants. (A,B) Expression pattern of snail RNA in wild-type embryos at cellular blastoderm (A, ventral view) and early gastrulation (B, lateral view). Apart from the differences described in Fig. 1, twist is expressed in the same patterns. (C-H) Expression patterns of snail and twist RNA in twist mutant embryos. (C,G,E) twist mutant embryos [from the null allele Df(2R)twi s6°] hybridized with a snail probe. (D,F,H) twist mutant embryos [allele twi HE] hybridized with a twist probe. (C,D) Syncytial blastoderm at the beginning of cellularization (ventral views); (E,F) Cellular blastoderm (ventral views); (G,H) early gastrulation (lateral views).

Possible for activating and maintaining the expression of early mesoderm-specific genes, including itself and snail. The expression patterns of mesodermal genes in snail mutants show that twist can perform this function in the absence of snail. snail represses genes in the mesodermal territory that are destined to be active only in more lateral or dorsal regions. snail, too, can perform its function alone, as in twist mutants lateral genes are off in the region where snail is expressed early. The comparison of twist and snail twist double mutants shows that the early snail expression has an effect on downstream genes. Because a narrow ventral band of cells differs from lateral cells in behavior and gene expression patterns in twist, but not in the double mutant, and as the only difference between twist and the double mutant is the early presence of snail RNA, it must be the function of this early snail RNA that makes the twist phenotype different from the double-mutant phenotype. Therefore, the narrow band of snail, itself, represses lateral genes in the mutant mesodermal region in twist embryos.

The combined presence of both twist and snail is required to achieve both activation of mesodermal and repression of lateral genes, and proper development of the mesoderm. Thus, neither gene is sufficient to regulate the whole repertoire of gene expression required to allow mesodermal development, but each alone can regulate the expression patterns of some genes. Only in the absence of both twist and snail do all mesodermal qualities disappear from the ventral region of the embryo. This situation also resembles that of dorsal fate determination, where the function of zygotic dorsal-specific genes appears to be to repress lateral fates and allow the expression of dorsal fates [Irish and Gelbart 1987]. Thus, in the absence of any region-specific dorsoventral zygotic gene activity the ground state of the blastoderm appears to be the expression of neural ectoderm fates.

This model for the roles of twist and snail as mesoderm gene activators and lateral gene repressors, respectively, is necessarily preliminary. It is possible that mesodermal or lateral genes might be discovered that do not obey the rules described for the genes analyzed here. Furthermore, interactions between genes might complicate the interpretation of mutant expression patterns. For example, a gene under negative control of lateral genes [which are repressed ventrally by snail] would be expressed in the mesoderm but depend on snail for its expression. It is also not possible to distinguish whether the disappearance of twist in snail mutants indicates that snail is normally directly responsible for the maintenance of twist expression, or whether the disappearance is due to effects of ventrolateral genes normally repressed by snail. The latter seems more likely. First, snail protein itself disappears from the mesoderm during germ-band extension in the wild type, and it is therefore difficult to see how it could be directly responsible for the late maintenance of twist expression. Second, even during wild-type development, twist disappears from...
cells expressing *sim* and ventrolateral genes [i.e., from mesectoderm cells] during germ-band extension [Leptin and Grunewald 1990]. At this time, therefore, it is possible that genes active in this region repress or destabilize *twist*, which they would also do over the whole mesodermal region in *snail* mutants.

The transformation of the *twist* mutant mesoderm into something resembling neural ectoderm is interesting with respect to neuroblast differentiation. The mutant mesodermal region does not express ventrolateral genes early. This shows that neuroblasts do not require a wild-type ectodermal environment to differentiate and delaminate. Furthermore, as neuroblasts can delaminate in *twist* mutants, an underlying mesoderm is not required for their differentiation.

**Definition of the mesoderm boundaries**

The differences in the lateral boundaries of *twist* and *snail* expression domains might reflect the differences in the way the domains are set up. Although the boundary of *twist* initially appears to be determined by the maternal gradient of nuclear dorsal concentration alone, *snail* clearly requires *twist* activity to be expressed in the...
whole mesoderm. It is possible that twist responds to dorsal activity in a more or less linear way, whereas snail responds to a combination of dorsal and twist protein in a cooperative way, thus creating a sharper boundary. The late sharpening of the twist boundary might interact to sharpen the twist activity in a more or less linear way, whereas snail responds to a combination of dorsal and twist protein in a cooperative way, thus creating a sharper boundary. The late sharpening of the twist boundary might interact to sharpen the twist boundary.

These data do not suggest any simple model to explain how the sim lines are made. In the absence of both twist and snail, sim is not expressed (Leptin and Grunewald 1990; Rushlow and Arora 1990), but the presence of either twist or snail alone allows the activation of sim. The ability of snail to activate sim expression (in twist mutants) seems to contradict its function as a repressor of sim in the mesoderm. Even in twist mutants, however, sim is off in the ventral-most band of cells and is only activated at the edge of the snail domain. Clearly, the precise position and width of the line is determined by twist and snail together.

Both twist and snail are initially activated in a narrow stripe. Assume that this expression is directly regulated by the maternal genes, because a zygotic gene required for the activation of twist and snail would have to be expressed (and its RNA translated into protein) before twist and snail. It is unlikely that such a gene exists, given the very early expression of twist and snail (only two nuclear cycles or 20 min after syncytial blastoderm formation, when dorsal protein becomes differentially distributed). Furthermore, no other zygotic genes with phenotypes similar to twist and snail are known. This suggests that there are no zygotic genes acting upstream of twist and snail and that any other gene that might act in parallel to twist and snail cannot be absolutely required for the formation of the mesoderm. Thus, twist and snail might be the only genes at the top of the hierarchy of zygotic genes involved in mesoderm development. In this case, they would be sufficient for zygotic mesoderm determination, a hypothesis that might be tested by expressing them ectopically.

Material and methods

Fly stocks

Unless mentioned otherwise, the twist allele used was Df(2R)S60 (Simpson 1983) and snail was Df(2L)TE116Gw11 (Ashburner et al. 1990). Both are complete null alleles, and no twist or snail RNA is produced, respectively. The twist snail double mutant was Df(2R)S60 snailD, provided by K. Arora. The twist alleles used in the experiment in Figure 5 were twiD, twii6, twiim3, and twiDps.

Antibody staining and in situ hybridization

Embryos from timed collections were dechorionated with bleach, fixed in 4% formaldehyde in PBS, and stained or hybridized (Tautz and Pfeifle 1989) as described previously (Leptin and Grunewald 1990). The snail antiserum (to be described in more detail elsewhere) was produced by immunizing rats with protein purified from bacteria expressing the full-length snail RNA (a gift from N. Brown) in the pET-3c expression vector. The serum was used at a dilution of 1:30.

In situ hybridizations on frozen sections

For hybridizations on frozen sections we used a protocol provided by Sommer and Tautz (1991), with slight modifications. Fixed and dechorionated embryos were oriented for transverse sectioning in OCT embedding medium, frozen, sectioned on a cryostat, and mounted on gelatin-coated microscope slides. The sections were fixed for 20 min in 4% formaldehyde in PBS, washed, in PBS and 0.1% Tween 20, digested for 10 min in a drop of proteinase K (50 μg/ml), washed, and fixed again for 20 min in 4% formaldehyde in PBS. They were hybridized overnight under a coverslip under the same conditions as for whole-mount embryos and were also washed and stained in the same way as whole-mount embryos.

Sections of stained embryos

Stained embryos were dehydrated thoroughly, transferred to araldite, prepared for sectioning, and sectioned on a microtome (10-μm sections) as described previously (Leptin and Grunewald 1990).

Acknowledgments

I thank B. Grunewald for technical help, R. Sommer and D. Tautz for helpful suggestions on hybridizing frozen sections with digoxigenin probes, H. Jäckle, S. Roth, A. Alberga, N. Brown, S. Crews, E. Knust, and M. Noll for reagents. G. Micklem made the in vitro snail protein for the production of antisera and many useful comments on the manuscript. I am also grateful to Jose Casal-Jimenez, Rolf Reuter, Siegfried Roth, Daniel St. Johnston, David Stott, Eric Weinberg, Rob White, and Michael Wilcox for suggestions and critical reading of the manuscript.

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Note added in proof

In contrast to the early mesodermal genes analyzed in this work, a recently described gene, zfh-1, requires snail for its mesodermal expression (Lai et al. 1991. Mech. Dev. 34: 123–134).

It will be interesting to see whether this is due to a direct positive regulatory effect of snail, or to repression of negative regulatory lateral genes, as discussed above.

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