Supernova 1987A, which showed that radioactive nickel was moving at unexpectedly high velocities in Supernova 1987A. This observation suggested that large-scale flows had carried matter from near the neutron star to the outer shells of the exploding star. Multidimensional simulations indeed revealed the development of violent overturn motions between the newly formed neutron star and the supernova shock where neutrino heating creates a convectively highly unstable layer. While ongoing accretion maintains large neutrino fluxes from the neutron star, rising hot matter helps to push the shock farther out. Both effects seem to be crucial for the success of the delayed explosion mechanism described above (*6–9*).

Most recently, the first three-dimensional computations of this sort have been performed (*10*), marking another milestone for the growing sophistication of supernova modeling. The results essentially confirmed those of previous two-dimensional models (*9*). Mushroom-shaped structures (see the figure) develop and grow to large scales. Creating seed perturbations, this neutrino-driven postshock convection can explain the anisotropic distribution of nucleosynthesis products in many supernovae (*11*). In combination with rotation, it might also produce global asymmetries (*12*) and the large recoil velocities measured for young pulsars (*13*).

However, no simulation to date is sufficiently accurate to provide conclusive evidence for the viability of the neutrino-heating mechanism. In the best two- and three-dimensional models, the neutrino physics is still grossly simplified. The stars explode fairly rapidly, leaving behind small neutron stars and ejecting large amounts of strontium, yttrium, and zirconium, in disagreement with the abundances of these elements in our Galaxy. Neutrinos dominate the supernova energetics and determine the conditions for nucleosynthesis. Describing their transport and interactions accurately is therefore essential for resolving these problems.

A new level of refinement has been achieved by integrating the Boltzmann equation for the neutrino transport in Newtonian (*14*, *15*) and general relativistic (*16*) hydrodynamical models. But no explosions could be obtained in spherically symmetric (one-dimensional) models.

The next step must be two- and three-dimensional simulations with such an accurate treatment of the neutrinos (*17*). Improved descriptions of neutrino interactions in dense matter should ultimately be included (*18*). Increasing interest in studying the properties of hot neutron star matter is also highly desirable. The role of magnetic fields in the explosion is still poorly understood and deserves further exploration. Only an adequate inclusion of all these aspects of the problem will bring us closer to a standard model for the explosion of massive stars.

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PERSPECTIVES: DEVELOPMENT

Doublesex in the Middle

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The morphology of male and female organisms is often strikingly different. From the time of Aristotle (*1*), biologists have attempted to elucidate the mechanistic basis of this sexual dimorphism. Mutants that display aberrant sexual phenotypes, most notably those of the fly *Drosophila* and the worm *Caenorhabditis elegans*, have allowed the definition of elaborate genetic hierarchies that control sex determination and somatic sexual differentiation (*2, 3*). However, a crucial question is: What are the target genes and biological processes controlled by these genetic hierarchies during the creation of sexually dimorphic animals? Biologists addressing this question in *Drosophila* have focused their efforts on a regulatory gene called *doublesex* (*dsx*) at the "bottom" of the sex determination hierarchy (*4–7*). Yet, as Ahmad and Baker illustrate in a recent issue of *Cell* (*8*), *dsx* is not at the bottom of a cascade of regulatory genes but instead sits right in the middle of a complex web of regulation. Their results, together with findings from other studies (*4–7*), lead us to consider *dsx* from a new angle as the linchpin that imposes sexual identity on developmental events in many tissues through its complex interactions with other regulatory hierarchies.

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In the fly, the sex determination hierarchy of regulatory genes begins with a counting mechanism based on X chromosome control elements (*9*). These elements regulate expression of the Sex lethal protein (Sx1), a splicing factor required for expression of the transformer protein (Tra) in female flies. Tra, in its turn, regulates expression of the female isoform of the Doublesex protein (DsxF). In males, the X chromosome signal does not activate Sxl expression, Tra is not produced, and *dsx* mRNA is spliced by default to encode the male isoform, DsxM. Both Dsx proteins are transcription factors that bind to DNA through a unique zinc-binding domain (see the figure) (*10, 11*). In the only confirmed direct molecular interaction of Dsx with a target gene, Dsx binds to an enhancer that regulates the expression of two yolk protein genes, resulting in either repression (DsxM) or stimulation (DsxF) of the transcription of these genes (*12*). Because the yolk proteins do not regulate other genes, *dsx* is commonly described as the last regulatory gene in the sex determination hierarchy. Reality, however, is far more complex.

A remarkable example of this complexity is revealed by Ahmad and Baker (*8*), who show that Dsx controls the differentiation of specific male genital tissues (the paragonia and vas deferens) by regulating the expression of the *Drosophila* fibroblast growth factor (FGF) gene. The fly FGF signaling pathway is known to direct development of the trachea (*13*), but its new role in sexual differentiation is unexpected. In males, the paragonia and vas deferens are derived from a group of mesodermal cells that migrate over the epithelia of the genital imaginal disc late in larval development and come to rest in two invaginations on the surface of the disc. Ahmad and Baker demonstrate that this unprecedented (in *Drosophila*) incorporation of mesodermal cells into the epithelia of the genital disc is dependent on expression of Branchless/FGF (the ligand for the FGF receptor) in the target regions of the disc. They also show that in female flies DsxF represses *branchless* expres-

sion. By inhibiting transcription of the *branchless* gene, DsxF blocks the ability of mesodermal cells expressing Breathless to migrate to the appropriate location in the genital disc, thus preventing development of the male genital structures derived from these cells.

Dsx plays an even more complex part in regulating another aspect of genital disc development: the sex-specific control of cellular proliferation (*5, 6*). *Drosophila*'s genital disc comprises cells from multiple adjacent embryonic segments that give rise to the female genitalia, the male genitalia, and anal structures. In female genital discs, cells derived from the eighth abdominal segment (A8) undergo extensive cell division and give rise to the majority of the female genital tissues; proliferation of A9 cells is inhibited. In males the situation is reversed. An elegant series of experiments has shown that Dsx directs the proliferation of a narrow band of organizer cells at the boundary between the anterior and posterior compartments of each segment. In females, DsxF blocks Hedgehog-induced expression of the DPP/transforming growth factor β morphogen in the organizer of the nondividing A9-derived region of the disc. In males, DsxM blocks the activity of another Hedgehog-induced morphogen, Wingless, in the organizer of the nondividing A8 region. Loss of either of these morphogenetic signals inhibits cellular proliferation.

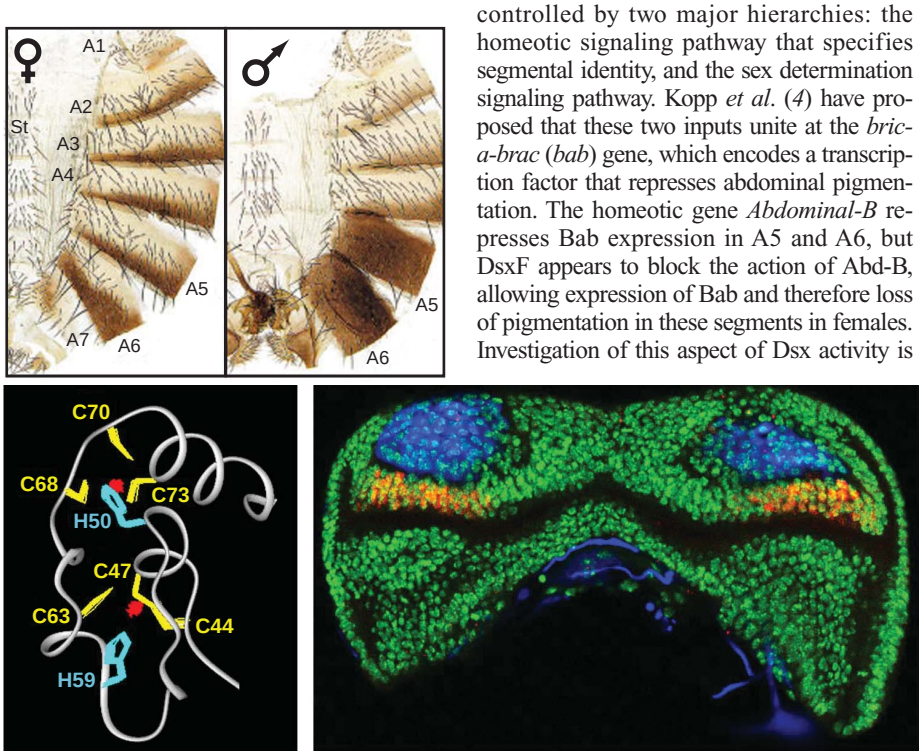
In the preceding example, Dsx acts upstream of the *wingless* and *dpp* signaling pathways to regulate their activity. Surprisingly, Dsx also acts downstream of *wingless* and *dpp* to modulate the response of another target gene, *Dachshund* (*dac*), to these signals (*6, 7*). In the developing primordia of male and female genital discs, Wingless and Dpp are expressed in both male and female genital discs. In females, Dac is expressed in cells that express Wingless and repressed in cells that express Dpp. Remarkably, in males, the opposite occurs: Dac is expressed in Dpp-positive cells and repressed in Wingless-positive cells. These differences depend on the expression of either DsxF or DsxM in the genital disc cells, with each isoform having both positive and negative effects on Dac expression. Thus, Dsx acts in concert with other regulatory signals to impose sex specificity on cellular differentiation.

The most readily apparent sexually dimorphic feature of *Drosophila*—familiar to all students who have sexed flies in a genetics lab course—is the dark black pigmentation on the dorsal aspect of the A5 and A6 abdominal segments of males. This phenotype is controlled by two major hierarchies: the homeotic signaling pathway that specifies segmental identity, and the sex determination signaling pathway. Kopp *et al*. (*4*) have proposed that these two inputs unite at the *bric-a-brac* (*bab*) gene, which encodes a transcription factor that represses abdominal pigmentation. The homeotic gene *Abdominal-B* represses Bab expression in A5 and A6, but DsxF appears to block the action of Abd-B, allowing expression of Bab and therefore loss of pigmentation in these segments in females. Investigation of this aspect of Dsx activity is particularly exciting because dimorphic pigmentation has evolved only recently in a subgroup of *Drosophila* that includes *D. melanogaster*. Thus, *D. melanogaster* presents biologists with an excellent opportunity to investigate the molecular events leading to the acquisition of sexually dimorphic traits.

The *dsx* gene does not sit at the bottom of the regulatory hierarchy controlling differentiation of sexually dimorphic structures. Rather, this gene resides at the junction of a complex network of regulatory interactions that include homeotic genes, ligand-based signal transduction cascades, and other transcriptional regulators. As we move from genomics to systems biology, so the study of development will shift from the characterization of discrete genetic hierarchies to understanding the integration of multiple regulatory signals and the target genes they control.

With the exception of the yolk protein genes, there is as yet no proof of direct interaction of the Dsx proteins with any of the targets discussed. In addition to identifying more targets for Dsx, we anticipate biochemical studies to confirm the direct nature of proposed interactions, as well as in vivo experiments to dissect the cis-acting sequences through which the target genes integrate sex-specific signals from Dsx with other regulatory inputs.

Given that Dsx is the only sex determination protein showing sequence conservation across phyla, its importance reaches far beyond flies. Sequences related to the unusual DNA binding domain (DM) of Dsx have been identified in proteins regulating aspects of sexual differentiation in worms, chickens, turtles, mice, humans, and several species of fish (*14*). Initial evidence implicates DM proteins in diverse aspects of the sexual development of different species. Understanding what DM proteins do in different species is likely to reveal more examples of doublesex in the middle.



The differences between males and females. Regulation of sexual differentiation by Doublesex. The male and female Dsx proteins of *Drosophila* are transcription factors that share a unique DNA binding motif, the DM domain (**lower left**). This module contains intertwined CCHC and HCCC Zn^{2+}-binding sites and is conserved across several phyla in proteins involved in sex determination. In the fly, Dsx imposes sex specificity on a complex array of developmental events, including differential pigmentation of the abdominal segments (**upper left**). In addition, Dsx is important for development of the paragonia and vas deferens of male flies, which depends on migration of FGF receptor–positive mesodermal cells (blue) into the vicinity of epithelial cells (red) expressing FGF in the male genital disc (**lower right**).

CREDIT: LOWER LEFT FROM (*11*); UPPER LEFT FROM (*4*); LOWER RIGHT COURTESY OF BRUCE BAKER.

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