congression seen in Kif18A-depleted cells. For example, tubulin mutations that suppress microtubule dynamics, and thus presumably reduce the rate of chromosome movement during mitosis, do not prevent proper chromosome positioning in yeast [14]. This raises a question about whether Kif18A might have additional functions during chromosome congression?

The measured effects of Kif18A on kinetochore microtubule dynamics correspond well with its ability to depolymerize stabilized microtubules *in vitro*, but they differ from the effects of *kip3* deletion on cytoplasmic microtubules in budding yeast, and uncovering the reasons for these differences will likely lead to a better understanding of kinesin-8 function. In a recent study, Gupta *et al.* [11] made detailed measurements of microtubule dynamic parameters in yeast cells lacking *kip3* (*kip3Δ* cells). They found that microtubules in *kip3Δ* cells spent less time in an attenuated state and more time growing or shrinking, indicating that microtubules are more dynamic in the absence of Kip3p (Figure 1B). In addition, the rate of microtubule depolymerization was significantly increased in the absence of Kip3p, suggesting that the motor might be needed to govern the velocity of depolymerization.

When considering the results of these two studies [2,11], it appears that the yeast kinesin-8 suppresses microtubule dynamics and reduces shortening velocity, while the human motor promotes dynamics and increases shortening velocity. The similar biochemical activities measured for Kif18A and Kip3p suggest that these differences are not likely due to intrinsic differences between the two motors. Are the differences an indication of motor regulation or indirect effects on other regulatory factors? Obviously, these questions warrant further investigation.

Mayr *et al.*'s [2] interesting study functionally dissects a novel component of the machinery for chromosome congression [2]. The complexity of the problem illuminated by their work and recent studies of Kip3p function [11,12,15] suggest that unraveling the molecular mechanisms that kinesin-8 family motors utilize to regulate dynamic microtubules will remain quite a fascinating problem for a number of years to come.

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Sex Determination: Controlling the Master

Sex is determined in *Drosophila* by the activity of the Sex-lethal master regulator. Activity of Sex-lethal is initiated early in females by chromosome-counting transcription factors, then reinforced by signaling through the Janus kinase pathway.

Douglas A. Harrison

Drosophila Sex-lethal (Sxl) is the prototype developmental 'master regulator', a term used to describe proteins whose activities are sufficient to initiate an entire developmental program. Sxl is the binary switch that determines whether a fly will develop as a male or a female [1]. But even the master is controlled. It has been known for some time that the on/off state of *Sxl* is decided by a set of early embryonic transcription factors, plus the Janus kinase (JAK) signaling pathway. But a recent *Current Biology* paper by Avila and

Erickson [2] demonstrates that the transcription factor input to *Sxl* expression can be separated from the JAK signaling input. The former initiates early transcription of *Sxl*, but JAK signaling reinforces expression, helping to promote a positive autoregulatory loop.

Like mammals, normal flies with two X chromosomes and two copies of each autosome develop as females, while flies with only one X develop as males. Unlike mammals, sex determination in flies is accomplished on a cell-by-cell basis. Each cell must independently assess chromosome complement and initiate the proper developmental program. Early transcriptional activation of *Sxl* in females stimulates the female sexual developmental program, while the failure to initiate early transcription of *Sxl* results in default male development. In addition to sexual differentiation, Sxl also controls dosage compensation, the process through which the dose of X chromosome genes is equalized by differential levels of transcription in females versus males. Lack of *Sxl* activity in mutant females causes twice as much transcription from every gene on the X chromosome, the fatal flaw for which *Sxl* is named.

Sxl is an RNA-binding protein that promotes alternative splicing of specific target genes (Figure 1). The major downstream target of Sxl is the *transformer* (*tra*) gene [3]. Sxl protein promotes the splicing of *tra* pre-mRNA to make active Tra protein in females, while the default transcript of *tra* found in males encodes an inactive truncated protein. Active female Tra is itself a splicing factor and acts together with Transformer2 to generate female-specific forms of *doublesex* (*dsx*). Dsx is a transcriptional regulator with male and female isoforms which promote alternative sexual developmental plans by differentially regulating sets of target genes that lead to male or female differentiation.

In addition to its downstream action on *tra* RNA, active Sxl protein splices its own mRNA, which is critical to the stable establishment of the active *Sxl* state [4,5] (Figure 1). Initiation of

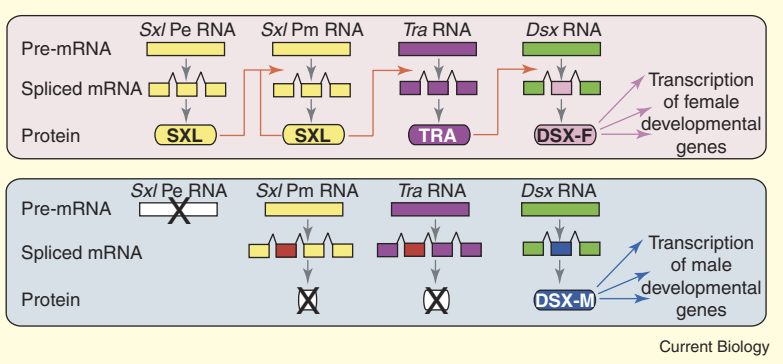

Figure 1. An alternative RNA splicing cascade regulates *Drosophila* sex determination.

The activities of Sxl and downstream components are illustrated for females (pink box) and males (blue box). Active products of each gene are shown as colored boxes and inactive or absent products are marked by X. Exons encoding translational stop codons leading to inactive proteins are red. Protein regulation of alternative splicing is indicated by orange arrows and regulation of transcription is indicated by pink or blue arrows.

Sxl activity in females requires transcription from two distinct promoters, initially from an early establishment promoter (Sxl_{Pe}) that is active before dosage compensation begins and later from a maintenance promoter (Sxl_{Pm}) that is required for production of *Sxl* during sexual differentiation [6] (Figure 2). The key to flipping the sex determination switch is that transcription from the early promoter is preferentially established in females, while transcription from the late promoter occurs in both sexes. The mRNA product transcribed from the Sxl_{Pe} is spliced, by default, to make active Sxl protein. By contrast, the pre-mRNA from the late *Sxl* promoter requires pre-existing Sxl protein to be spliced properly to encode active Sxl.

The Sxl_{Pe} is activated by a set of four known proteins encoded on the X chromosome [7–10]. These

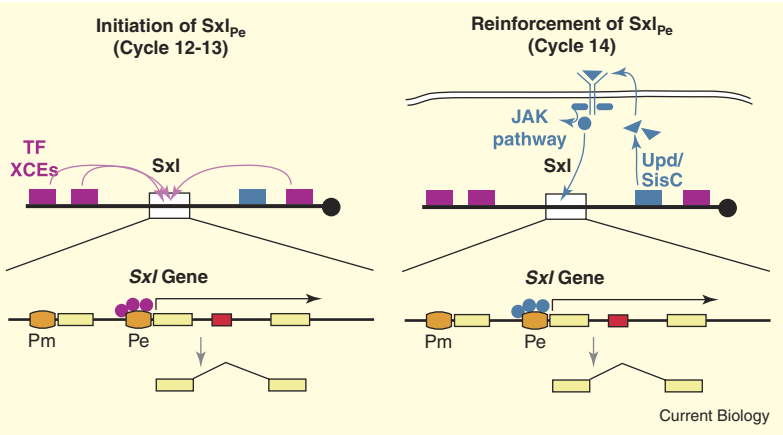

Figure 2. Biphasic regulation of *Sxl* establishment promoter in females.

The two temporal phases of Sxl_{Pe} (Pe, orange) transcriptional regulation in females are indicated. Initiation of transcription from Sxl_{Pe} in nuclear cycles 12–13 results from additive actions of the three transcription factor products (purple circles) encoded by the Transcription Factor X Chromosome Counting Elements (TFXCEs; purple boxes). In the reinforcement phase, Upd/SisC activates the JAK signaling pathway [11] (components in blue) which ultimately results in activation of the STAT transcription factor (blue circles) that binds directly to Sxl_{Pe} to continue transcription. *Sxl* mRNA (yellow boxes) produced in both phases is spliced, by default, to produce active Sxl protein. Later expression of *Sxl* through the maintenance promoter (Pm, orange) requires active Sxl protein to remove an exon encoding a translational terminator (red box), thus producing more active Sxl protein.

X chromosome counting elements (XCEs) are expressed early in development, prior to dosage compensation, so that the gene products are twice as abundant in females as in males. The level of activity of these counting proteins in females is sufficient to establish stable expression from the Sxl_{Pe}, while that from males is not. Three essential XCEs encode transcription factors that bind directly to the Sxl_{Pe}. The fourth XCE, *sisterless-C* (*sisC*), has a weaker influence on sex determination. The *sisC* locus was found to map to *unpaired* (*upd*) [9,10], which encodes a ligand for the JAK signaling pathway, an evolutionarily conserved pleiotropic developmental cell signaling cascade [11,12]. The effect of Upd/SisC as an XCE is mediated by JAK signal transduction, as mutations in other JAK pathway signaling components, such as the kinase signal transducer (JAK) and the transcription factor target (STAT), also reduce *Sxl* activation.

Avila and Erickson [2] demonstrated that the role of JAK signaling is distinct from that of the transcription factor XCEs in Sxl_{Pe} establishment. The loss of Upd or other JAK pathway proteins in mutant females does not affect the onset of expression from Sxl_{Pe}, but later results in the failure of Sxl_{Pe} expression to be maintained [2]. They further showed that the effects of JAK signaling on *Sxl* expression are mediated through sequences in the establishment promoter that match the consensus for STAT binding sites, suggesting that Sxl_{Pe} is regulated directly by the canonical JAK pathway. The authors conclude that the regulation of Sxl_{Pe} is accomplished in two phases: initiation of transcription, regulated by the transcription factor XCEs, and maintenance of transcription, mediated by Upd/SisC and the JAK pathway signaling.

Two phase regulation of Sxl_{Pe} is surprising, because the entire window of both phases of expression from that promoter lasts less than one hour. Yet, the role of JAK signaling only in the later reinforcement step of Sxl_{Pe} activity may explain why *upd*/*sisC* has a weaker role in sex determination than the other X chromosome counting elements. Loss of Sxl_{Pe} reinforcement does not affect early initiation and, in many cases, female embryos defective in JAK signaling will ultimately establish stable Sxl activity and turn on the female switch. This raises a question of how the sex determination machinery is often able to recover from failure of the reinforcement step. The phenomenon suggests that there is some redundancy in the mechanisms that establish and stabilize the binary Sxl switch. Though we do not yet understand how this works, building such a robust system makes good sense, given the importance of this decision to the organism.

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Evolutionary Robotics: Emergence of Communication

The emergence of communication is considered one of the major transitions in evolution. Recent work using robot-based simulation shows that communication arises spontaneously. While deceptive communication arises in a purely competitive setting, cooperative communication arises only subject to group or kin selection.

Hod Lipson

Communication plays a critical role in evolution: Back in the early days of the primordial soup, horizontal gene transfer between unrelated individuals was likely to be prevalent, leading to the rapid invention and sharing of new genes [1]. When speciation began, some individuals leaped ahead by segregating themselves into non-interbreeding species, but after some two billion years communication returned again in the form of multi-cellular colonies with complex signaling patterns [2]. Today, some argue, communication is even more