

# Sex and death: from cell fate specification to dynamic control of X-chromosome structure and gene expression

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**ABSTRACT** Determining sex is a binary developmental decision that most metazoans must make. Like many organisms, *Caenorhabditis elegans* specifies sex (XO male or XX hermaphrodite) by tallying X-chromosome number. We dissected this precise counting mechanism to determine how tiny differences in concentrations of signals are translated into dramatically different developmental fates. Determining sex by counting chromosomes solved one problem but created another—an imbalance in X gene products. We found that nematodes compensate for the difference in X-chromosome dose between sexes by reducing transcription from both hermaphrodite X chromosomes. In a surprising feat of evolution, X-chromosome regulation is functionally related to a structural problem of all mitotic and meiotic chromosomes: achieving ordered compaction of chromosomes before segregation. We showed the dosage compensation complex is a condensin complex that imposes a specific three-dimensional architecture onto hermaphrodite X chromosomes. It also triggers enrichment of histone modification H4K20me1. We discovered the machinery and mechanism underlying H4K20me1 enrichment and demonstrated its pivotal role in regulating higher-order X-chromosome structure and gene expression.

## INTRODUCTION

I feel honored to receive the unexpected tribute of an E. B. Wilson Medal. I am extremely lucky to be a scientist during an explosive period of discovery in cell biology and to have carried out research with wonderfully talented and dedicated students, postdoctoral fellows, staff scientists, and collaborators at both the Massachusetts Institute of Technology and the University of California, Berkeley.

The work being honored began during my postdoctoral years when I joined the small cadre of scientists led by Sydney Brenner who saw the potential of the nematode *Caenorhabditis elegans* for understanding eukaryotic developmental mechanisms. I was drawn to the question of how the nematode specifies its sex. Determining

sex is a fundamental, binary developmental decision that most metazoans must make (Cline and Meyer, 1996).

I was stimulated to tackle this problem by my graduate work with Mark Ptashne, which demonstrated the power of a simple virus and a binary developmental decision to yield important lessons in gene regulation and development. My work was instrumental in elucidating the binary genetic switch by which bacteriophage lambda triggers one of two developmental fates: a quiescent lysogenic state or a replicating state (Meyer *et al.*, 1975, 1980; Meyer and Ptashne, 1980; Johnson *et al.*, 1978; Maurer *et al.*, 1980). The work revealed fundamentally new principles in gene regulation, including cooperativity in repressor binding to turn off gene expression (Johnson *et al.*, 1979).

Before I joined the nematode field, Victor Nigon and Robert Herman had shown that *C. elegans* determines sex with high fidelity by tallying X-chromosome number relative to the ploidy, the sets of autosomes (X:A signal; Figure 1A; Nigon, 1951; Madl and Herman, 1979). The process is finely tuned and executed with remarkable accuracy, allowing embryos with ratios of 1X:2A (0.5) and 2X:3A (0.67) to develop into fertile males and embryos with ratios of 3X:4A (0.75) and 2X:2A (1.0) to develop into self-fertile hermaphrodites

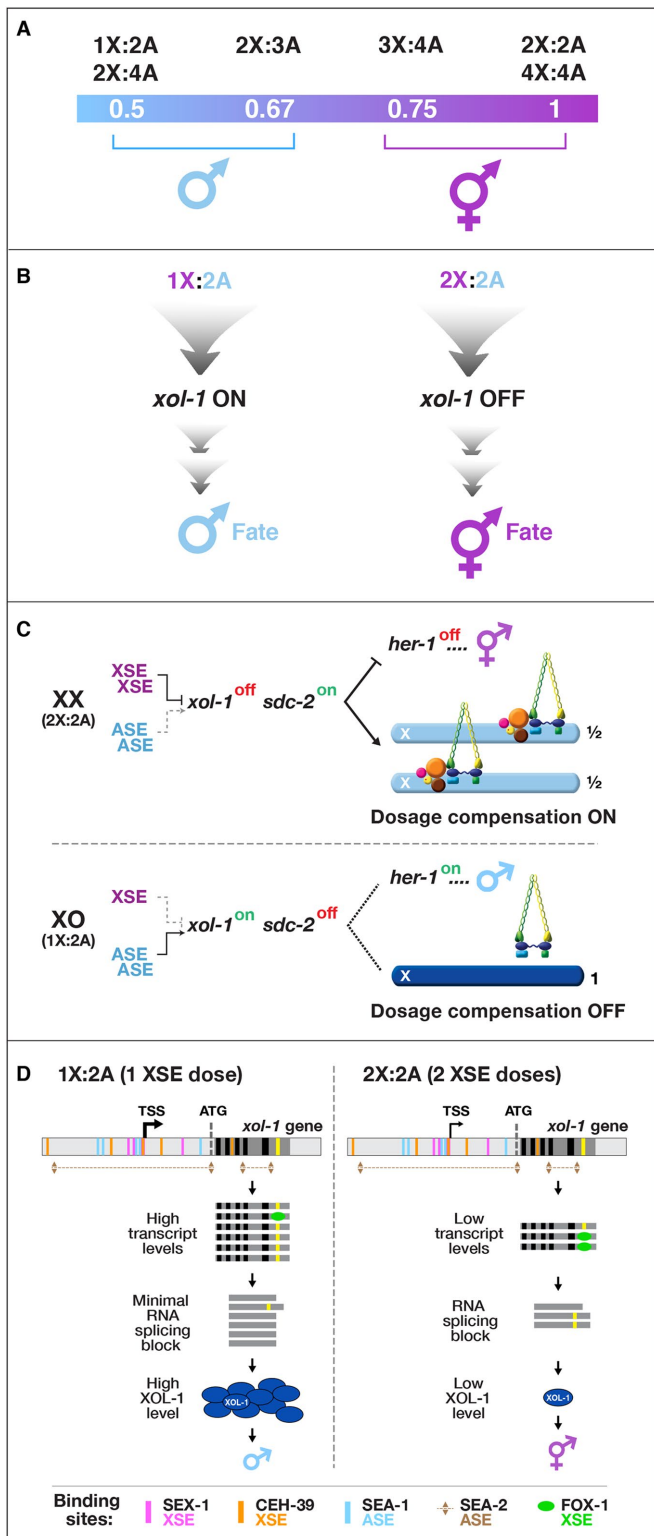
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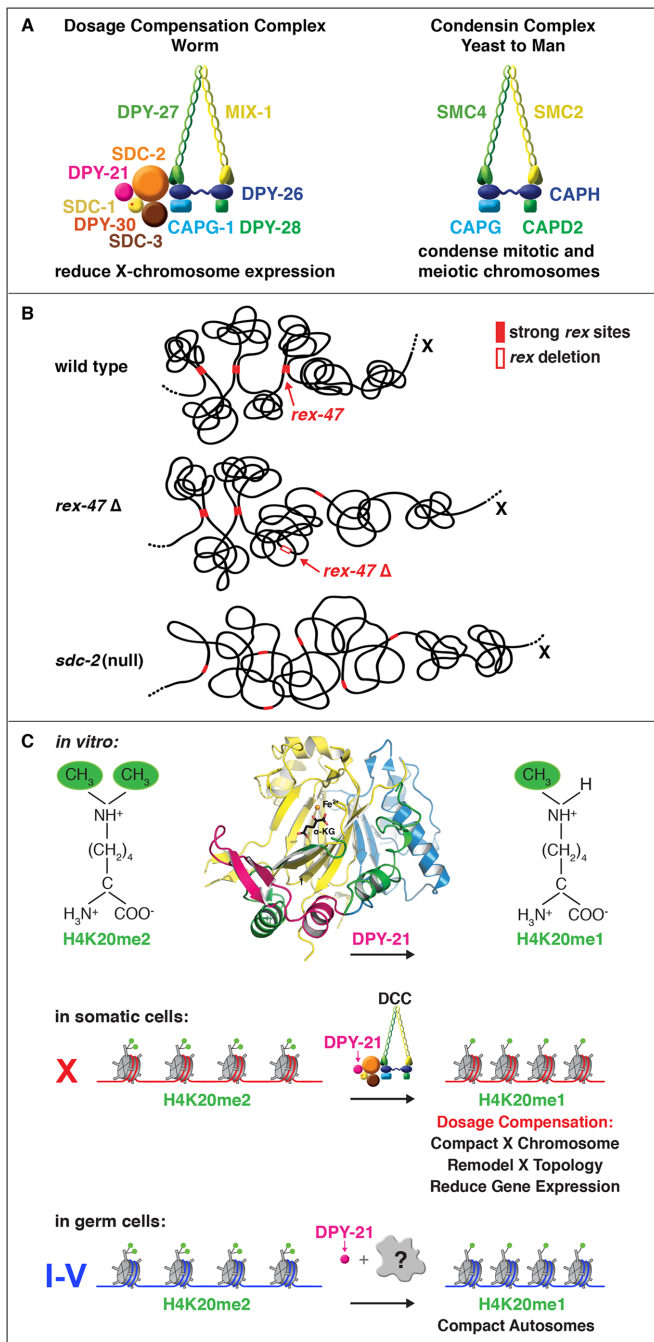
**FIGURE 1:** Chromosome-based sex determination. (A) The ratio of X chromosomes to sets of autosomes (X:A signal) determines nematode sex. (B) *xol-1* is the direct target of the X:A signal and the master sex-determination switch gene. It activates male fate when turned on and permits hermaphrodite fate when turned off. (C) Overview of the genetic hierarchy controlling both sex determination and dosage compensation in *C. elegans*. In diploid XX hermaphrodites, the dosage compensation complex (DCC) binds to both X chromosomes to reduce transcription by half, thereby equalizing it with that of the single male X. The hermaphrodite-specific gene *sdc-2* triggers

(Figure 1A). I wanted to determine the molecular mechanisms by which *C. elegans* counts its X chromosomes to determine how small changes in the concentrations of molecular signals can be translated into dramatically different developmental fates. Jonathan Hodgkin had found that mutations in individual genes caused diploid XX animals to develop into males or XO animals into hermaphrodites, showing the problem might be genetically tractable (Hodgkin and Brenner, 1977; Hodgkin, 1980).

I was also mindful of a possible complication. Many organisms that use sex chromosomes to determine sexual fate evolved the essential, chromosome-wide regulatory process called dosage compensation to balance X-chromosome gene expression between the sexes (Muller, 1932; Lyon, 1962). The failure to do so is lethal (Cline, 1978; Cline and Meyer, 1996). We had no knowledge of whether the worm had a dosage compensation mechanism and whether its regulation might be genetically linked to the sex determination decision. If so, the phenotype caused by disrupting the X:A signal might be sex-specific lethality due to improper X gene expression, thus masking any reversal of sexual fate. While I considered how to approach this problem, Thomas Cline showed that a single developmental switch gene coordinately controls both sex determination and dosage compensation in *Drosophila melanogaster*, which also uses an X:A signal to determine sex (Bridges, 1921; Cline, 1978, 1979). Null mutations in the switch gene caused the masculinization and death of 2X:2A animals, but 1X:2A mutants were wild type. The path to take became clear.

Early work as a postdoc and professor demonstrated that nematodes compensate for the difference in X-chromosome dosage between sexes by repressing X transcript levels in hermaphrodites and revealed, via extensive genetic screens, the identity of numerous genes that implement dosage compensation (Meyer and Casson, 1986; Miller et al., 1988; Plenefisch et al., 1989). We found that dosage compensation and sex determination were linked by genes that coordinately controlled both processes, a finding that allowed us to discover the master sex-determination switch gene *xol-1* (XO lethal) and the molecular basis of the X:A signal, which controls *xol-1* directly (Figure 1B; Villeneuve and Meyer, 1987; Miller et al., 1988; Nusbaum and Meyer, 1989; DeLong et al., 1993; Klein and Meyer, 1993; Rhind et al., 1995; Davis and Meyer, 1997; Carmi et al., 1998; Dawes et al., 1999).

assembly of the DCC onto X and activates the hermaphrodite sexual fate by repressing the male-determining gene *her-1*, which is the first gene in the sex-determination branch of the genetic hierarchy. In diploid XO males, *xol-1* represses *sdc-2*, thereby preventing the DCC from binding to the male X and preventing *sdc-2* from repressing *her-1*. (D) Model for X:A signal assessment. XSEs and ASEs bind directly to numerous sites in *xol-1* regulatory regions to antagonize each other and thereby control *xol-1* transcription. Molecular rivalry at the *xol-1* promoter between XSE transcriptional repressors (nuclear receptor SEX-1, magenta binding sites; homeodomain protein CEH-39, orange binding sites) and ASE transcriptional activators (T-box transcription factor SEA-1, blue binding sites; zinc-finger protein SEA-2, numerous brown binding sites) causes high *xol-1* transcript levels in 1X:2A animals with one dose of XSEs and low levels in 2X:2A embryos, with two doses of XSEs. The RNA binding protein FOX-1, an XSE, then enhances the fidelity of X counting by binding to an alternatively spliced *xol-1* intron (yellow), thereby blocking proper splicing and causing mRNA splice variants with in-frame stop codons. High XOL-1 protein levels induce male fate and low XOL-1 levels permit hermaphrodite fate. Black rectangles, *xol-1* exons; dark-gray rectangles, *xol-1* introns; light-gray rectangles, 5' and 3' *xol-1* regulatory regions.



**FIGURE 2:** Overview of dosage compensation in *C. elegans*. (A) The DCC is compared with condensin I of other eukaryotes. The DCC condensin subunits (MIX-1, DPY-27, DPY-26, DPY-28, and CAPG-1) are color matched to their condensin I homologues. All DCC condensin subunits except DPY-27 also act in other distinct condensins that function in *C. elegans* mitosis and meiosis. The DPY-27 paralogue SMC-4 (Hagstrom *et al.*, 2002) replaces DPY-27 in mitotic and meiotic condensins. The DCC likely arose by duplicating and modifying the gene encoding SMC-4 to create DPY-27 for a specific role in gene expression. The DCC also includes the XX-specific protein SDC-2 that triggers DCC assembly onto X. Two DCC subunits aid SDC-2 in recruiting the complex to X: SDC-3 (a zinc-finger protein) and DPY-30 (a subunit of the MLL/COMPASS H3K4me3 methyltransferase complex). Two subunits, SDC-1 (a zinc-finger protein) and DPY-21 (Jumonji C H4K20me2 demethylase), are required for DCC activity but not DCC assembly. (B) Cartoon model of TAD formation on a segment of X. Top, the DCC remodels the topology of X into a

## COUNTING CHROMOSOMES TO DETERMINE SEX

We discovered that a set of X-linked genes called X-signal elements (XSEs) communicates X-chromosome dose by repressing *xol-1* in a cumulative, dose-dependent manner (Figure 1C; Akerib and Meyer, 1994; Nicoll *et al.*, 1997; Carmi *et al.*, 1998; Gladden *et al.*, 2007; Gladden and Meyer, 2007; Farboud *et al.*, 2013). In addition, a set of genes encoded on autosomes called autosomal signal elements (ASEs) communicates the ploidy by stimulating *xol-1* activity in a cumulative, dose-dependent manner to counter XSEs (Figure 1C; Powell *et al.*, 2005; Farboud *et al.*, 2013). XOL-1, a GHMP kinase, is activated in 1X:2A embryos to set the male fate but repressed in 2X:2A embryos to promote the hermaphrodite fate, including the activation of dosage compensation (Rhind *et al.*, 1995; Luz *et al.*, 2003). Both XSEs (nuclear receptors and homeodomain proteins) and ASEs (T-box and zinc-finger proteins) bind directly to multiple, distinct sites in *xol-1* regulatory DNA in vitro to counteract each other's activities and regulate *xol-1* transcription (Figure 1D; Farboud *et al.*, 2013). Disrupting ASE and XSE binding sites in vivo recapitulated the misregulation of *xol-1* transcription caused by disrupting the cognate signal element genes. The X:A signal is thus transmitted in part through multiple antagonistic molecular interactions carried out on a single promoter (Farboud *et al.*, 2013). Fidelity of X:A counting is then enhanced by a second tier of repression, via an XSE that binds a *xol-1* intron to prevent proper RNA splicing (Figure 1D; Hodgkin *et al.*, 1994; Nicoll *et al.*, 1997; Skipper *et al.*, 1999). The concept of a sex signal using competing XSEs and ASEs arose as a theory for *D. melanogaster* one century ago (Bridges, 1921). Recent work showed the fruit fly signal does not fit this simple paradigm, but our work showed the worm signal does (Erickson and Quintero, 2007; Farboud *et al.*, 2013).

## X-CHROMOSOME DOSAGE COMPENSATION: REPRESSING X CHROMOSOMES VIA MOLECULAR MACHINES

Strategies for dosage compensation differ from worms to mammals, but invariably a regulatory complex is targeted to X chromosomes of one sex to modulate transcription along the entire chromosome (Meyer, 2010; Kuroda *et al.*, 2016; da Rocha and Heard, 2017; Samata and Akhtar, 2018). This heritable regulation of X-chromosome expression during development is exemplary for dissecting the coordinate regulation of gene expression over large chromosome

hermaphrodite-specific conformation by forming topologically associating domains (TADs). DCC-dependent looping interactions are found between high-affinity *rex* sites (filled red rectangles) located at TAD boundaries. Middle, deletion of the high-affinity DCC binding site *rex-47* (open red rectangle) located at a DCC-dependent TAD boundary eliminates boundary formation. Bottom, severe disruption of DCC binding by an *sdc-2* mutation eliminates formation of all DCC-dependent TADs on X. (C) The DPY-21 H4K20me2 histone demethylase regulates three-dimensional chromosome structure and gene expression by modulating enrichment of H4K20me1. The 1.8 Å crystal structure and biochemical activity of DPY-21 revealed a novel, highly conserved H4K20me2 JmjC demethylase subfamily that converts H4K20me2 to H4K20me1 in vitro in an Fe<sup>2+</sup>-dependent and α-ketoglutarate-dependent manner. In somatic cells, DPY-21 binds to X chromosomes via the DCC and enriches H4K20me1 to repress gene expression. The H4K20me1 enrichment controls the higher-order structure of X chromosomes by facilitating compaction and TAD formation. In germ cells, DPY-21 enriches H4K20me1 on autosomes in a DCC-independent manner to promote chromosome compaction.

territories and the role of chromosome structure and chromatin modification in regulating gene expression.

We discovered the *C. elegans* dosage compensation complex (DCC) and showed its homology to condensin, a complex that mediates the compaction, resolution, and segregation of mitotic and meiotic chromosomes from yeast to humans (Figure 2A; Chuang *et al.*, 1994, 1996; Hsu *et al.*, 1995; Lieb *et al.*, 1996, 1998; Davis and Meyer, 1997; Dawes *et al.*, 1999; Tsai *et al.*, 2008; Csankovszki *et al.*, 2009; Mets and Meyer, 2009; Pferdehirt *et al.*, 2011; Hirano, 2016). We found the DCC binds to both hermaphrodite X chromosomes to reduce transcription by half, thus equalizing X expression between the sexes (Figure 1C; Chuang *et al.*, 1996; Jans *et al.*, 2009; Kruesi *et al.*, 2013). Failure to do so causes elevated X expression and hermaphrodite-specific lethality. Ectopic binding of the DCC to the single male X chromosome in *xol-1* mutants causes male-specific lethality.

Most DCC condensin subunits also control the structure and function of mitotic and meiotic chromosomes by participating in two other distinct condensin complexes, whose roles in recombination and chromosome segregation were dissected (Hagstrom *et al.*, 2002; Chan *et al.*, 2004; Tsai *et al.*, 2008; Csankovszki *et al.*, 2009; Mets and Meyer, 2009; Meyer, 2010). The promiscuous DCC condensin subunits are initially recruited to hermaphrodite X chromosomes by a large (350 kDa) hermaphrodite-specific DCC subunit called SDC-2 (sex determination and dosage compensation) that triggers binding to *cis*-acting elements on X called *rex* (recruitment elements on X) sites (Dawes *et al.*, 1999; Csankovszki *et al.*, 2004; McDonel *et al.*, 2006). These *rex* sites recruit the DCC in an autonomous, sequence-dependent manner using DNA motifs enriched on X (Jans *et al.*, 2009; Pferdehirt *et al.*, 2011).

## CONDENSIN-DRIVEN REMODELING OF X-CHROMOSOME TOPOLOGY DURING DOSAGE COMPENSATION

Involvement of condensin subunits in dosage compensation suggested the DCC might alter the topology of X to regulate gene expression. Furthermore, other observations promoted the view that the DCC acts globally through a chromosome-wide mechanism to repress transcription rather than locally on a gene-by-gene basis. For example, a nearby DCC binding site is neither necessary nor sufficient to compensate an endogenous X-linked gene, and all transgenes integrated randomly on X, whether near or far from a DCC binding site, become dosage compensated (Jans *et al.*, 2009; Wheeler *et al.*, 2016). We found the DCC remodels hermaphrodite X chromosomes into a unique, sex-specific spatial conformation, distinct from autosomes, using its highest-affinity *rex* sites (Figure 2B; Crane *et al.*, 2015). Dosage-compensated X chromosomes have self-interacting domains (~1 Mb) resembling mammalian topologically associating domains (TADs; Crane *et al.*, 2015; Galupa and Heard, 2017). TADs on X have stronger boundaries and more regular spacing than those on autosomes. Most TAD boundaries on X coincide with the highest-affinity *rex* sites. Those boundaries are lost in DCC mutants, causing X structure to resemble that of autosomes (Figure 2B; Crane *et al.*, 2015). Deleting a single endogenous *rex* site at a DCC-dependent boundary disrupted the boundary, indicating the DCC forms TADs using its strongest binding sites (Figure 2B; Crane *et al.*, 2015). Our study was the first to identify the machinery and DNA sites that create chromosome-wide TAD structure and to use specific mutations to disrupt it. The structure of dosage-compensated X's offers fertile ground to decipher the mechanistic relationship between higher-order chromosome structure and gene expression.

## DYNAMIC CONTROL OF X-CHROMOSOME CONFORMATION AND REPRESSION BY A HISTONE H4K20 DEMETHYLASE

The role of chromatin modification in establishing higher-order chromosome structure during gene regulation has been elusive. Dosage-compensated X chromosomes of *C. elegans* are enriched in H4K20me1 (Liu *et al.*, 2011; Vielle *et al.*, 2012; Wells *et al.*, 2012; Kramer *et al.*, 2015). We dissected the mechanism underlying H4K20me1 enrichment on X during dosage compensation and discovered a key role for H4K20me1 in regulating X-chromosome topology and chromosome-wide gene expression (Bian *et al.*, 2017; Brejc *et al.*, 2017). Structural and functional analysis of DCC subunit DPY-21 revealed a novel Jumonji C demethylase subfamily that converts H4K20me2 to H4K20me1 in worms and mammals via an Fe<sup>2+</sup>-dependent and  $\alpha$ -ketoglutarate-dependent mechanism (Figure 2C; Brejc *et al.*, 2017). H4K20me1 is also enriched on the inactive X chromosome of female mice, relating our studies to mammalian development (Kohlmaier *et al.*, 2004). Inactivation of demethylase activity in *C. elegans* eliminated H4K20me1 enrichment on X in nematode somatic cells, increased X-linked gene expression, reduced X compaction, and disrupted X conformation by diminishing TAD formation (Figure 2C; Bian *et al.*, 2017; Brejc *et al.*, 2017). DPY-21 demethylase binding to X is both DCC-dependent and cell-cycle-dependent, enriching H4K20me1 on X during interphase, but not mitosis. Thus, the DCC recruits an "eraser" of a histone modification, enriching H4K20me1 by activating an H4K20me2 demethylase.

DPY-21 also binds to autosomes (but not X) of germ cells in a DCC-independent manner to enrich H4K20me1 and compact chromosomes (Figure 2C; Brejc *et al.*, 2017). Thus, DPY-21 is an adaptable chromatin regulator. Its demethylase activity can be harnessed during development for distinct biological functions by targeting it to diverse genomic locations. In both somatic and germ cells, H4K20me1 modulates three-dimensional topology, showing a direct link between chromatin modification and higher-order chromosome structure.

## THE NEXT STEPS

Deeper mechanistic insights into sex determination and dosage compensation await future experiments with single-cell and single-molecule resolution as well as continued structural analysis of the DCC.

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