Sex and Repression

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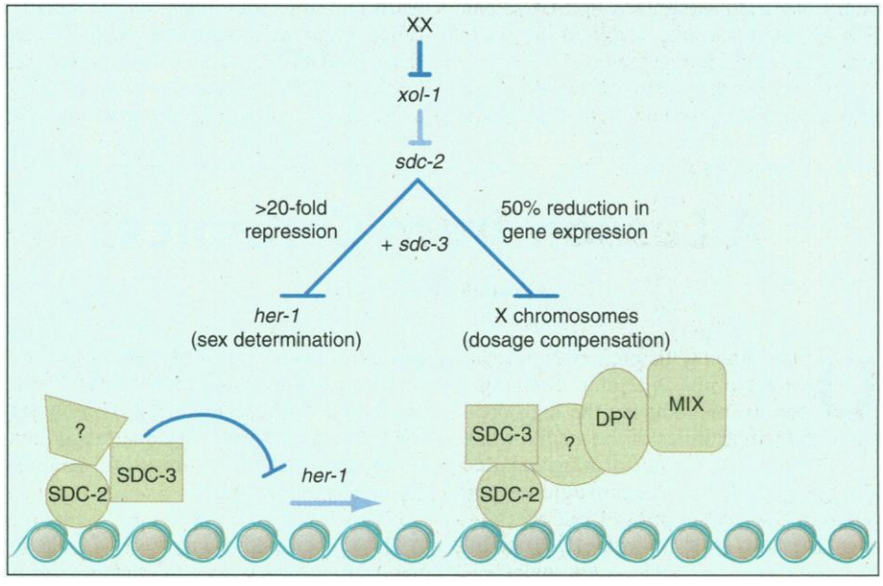
Remarkable progress has been made in identifying proteins that are involved in the behavior of whole chromosomes. Two of these areas of inquiry converged recently with the surprising discovery that subunits of a large protein complex required for dosage compensation in nematodes are related to, or actually shared with, the mitotic chromosome condensation and segregation machinery (the 13*S* condensin) originally identified in frogs and yeast (*1*–*4*). Dosage compensation in nematodes is a mechanism of partial transcriptional repression that occurs in hermaphrodites (XX genotype) to achieve a total level of X-linked gene expression that is equivalent to that in males (XO genotype) (*5*). Presumably, the common players in dosage compensation and chromosome condensation participate in a mechanistically similar function in their respective complexes, suggesting that dosage compensation may be mediated through organization of inhibitory chromosomal packaging. Although each of these chromosome-wide processes involve large protein complexes assembled on chromosomes, dosage compensation is remarkable in its exquisite specificity for the X chromosome. On page 1800, in this issue of *Science*, Dawes and colleagues (*6*) identify the SDC-2 protein in the nematode *Caenorhabditis elegans* as the critical targeting factor that assembles shared and dosage compensation–specific subunits on the hermaphrodite X chromosomes.

Not only does SDC-2 target X chromosomes for dosage compensation in hermaphrodites, but it also specifies hermaphrodite sexual development. Earlier genetic analysis demonstrated that SDC-2 controls a key regulatory branchpoint (see the figure) (*7*). Upstream is the *xol-1* gene, which perceives the sex of the individual by counting the number of X chromosomes per nucleus (*8*, *9*). Downstream are the two largely independent pathways of dosage compensation and sex determination. Now Dawes *et al.* show at the molecular level that the SDC-2 protein acts as a binary switch to coordinate these two pathways. SDC-2 is a large protein that triggers hermaphrodite differentiation through transcriptional repression of *her-1*, an autosomal gene required for male development. In contrast to the on-off regulation of *her-1*, SDC-2 recruits other dosage compensation regulators (the DPY-MIX proteins) to achieve a 50% reduction in expression of the hermaphrodite X chromosomes. Absence of SDC-2 allows male development and basal transcription of the X chromosome, whereas ectopic expression of SDC-2 in chromosomal males leads to hermaphrodite development and lethal down-regulation of X-chromosome gene expression. How does one protein control these two distinct types of gene repression?



Coordinate repression. Model for the pivotal role of SDC-2 in *C. elegans* sex determination and dosage compensation. SDS-2 acts with SDC-3 to strongly repress transcription of *her-1*, an autosomal gene required for male development. In parallel, SDC-2 recruits the other dosage compensation regulators (the DPY and the MIX proteins) to achieve a 50% reduction in transcription of the hermaphrodite X chromosomes.

One hypothesis is that SDC-2 recognizes DNA and assembles at distinct target sites on *her-1* and X, with different protein partners. Dawes *et al.* show that SDC-2 recruits the DPY proteins to the X chromosomes of hermaphrodites through its own association with the X. In a clever in vivo binding assay, the authors also show that SDC-2 binds to transgene arrays of the *her-1* regulatory region. SDC-2 is likely to be the targeting factor in each case because ectopic expression of SDC-2 is sufficient to initiate both hermaphrodite development and dosage compensation. All other pathway components must be available in XO males, so that regulation is switched to the hermaphrodite mode when only SDC-2 is ectopically expressed. This would be expected if SDC-2 is the key molecule missing from males.

SDC-2 has a close collaborator in both the sex determination and dosage compensation pathways. SDC-3 is required for *her-1* repression and for association of all the other dosage compensation proteins with the hermaphrodite X chromosomes (*10*, *11*). However, ectopic expression of only SDC-3 has no detectable effect on males that lack SDC-2 (*6*). Interestingly, the two roles of SDC-3 can be separated genetically, in support of the idea that the dosage compensation and sex determination target sites assemble biochemically distinct complexes. Dosage compensation–specific mutations in *sdc-3* eliminate a pair of zinc finger motifs, whereas sex determination–specific *sdc-3*(Tra) mutations alter a region with limited homology to the adenosine 5′-triphosphate–binding domain of myosin (*12*). That SDC-3 uses two functionally separate domains in its collaboration with SDC-2 suggests that hermaphrodites assemble two biochemically distinct SDC-2 complexes, one coating the X chromosomes and the other repressing *her-1*.

Whether or not the complexes on *her-1* and X differ in composition, their requirements for function clearly differ. So far, only three factors are implicated in the repression of *her-1*: SDC-1, SDC-2, and SDC-3. In contrast, a large group of proteins assemble on the X chromosomes of hermaphrodites to achieve dosage compen-

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sation, including SDC-2, SDC-3, DPY-26, DPY-27, MIX-1, and presumably DPY-28. These proteins colocalize over the X chromosomes, but it is not yet known if SDC-2 and SDC-3 directly contact the DPY-MIX protein complex. Antibodies to SDC-2 show that the protein remains associated with the X chromosomes even when other dosage compensation factors such as SDC-3 are defective (*6*). In contrast, SDC-2 binding to the *her-1* regulatory region is disrupted in the sex determination–specific *sdc-3*(Tra) mutants, which are defective in *her-1* repression. Therefore, the regulatory region of *her-1* might contain composite elements that can only stably bind SDC-2 and SDC-3 in concert. The density of regulatory elements recognized by SDC-2 and SDC-3 could also play a role in the stable arrangement of binding factors.

An exciting next phase of this work will undoubtedly address how SDC-2 mediates chromosome-wide recognition to assemble the dosage compensation machinery on the X. Although recognition of the *her-1* regulatory regions might be expected to occur by conventional DNA sequence-specific binding, it will be interesting to discover whether recognition of the X chromosome is less conventional. Dosage compensation in mammals, which occurs by X inactivation, is dependent on the cis-expression of a large noncoding RNA (Xist) rather than on DNA target sequences themselves, as inactivation can occur on autosomes that express multimers of Xist transgenes (*13*). Dosage compensation in *Drosophila* occurs by up-regulation of transcription in males and segments of the X retain dosage compensation when moved to autosomes, yet the identification of cis-acting sequences has been elusive (*5*). With SDC-2 and the complete sequence of the *C. elegans* genome in hand, one can envision a golden opportunity for understanding at least one way in which such a dramatic, chromosome-wide recognition mechanism has evolved.

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PERSPECTIVES: MANTLE GEOCHEMISTRY

A Lesson from Ceramics

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Understanding the properties of mantle materials is a great challenge, because reproducing the high pressures and temperatures of the mantle while performing detailed measurements on model materials is extremely difficult. The lower mantle is believed to be dominated by $MgSiO_3$-rich minerals with a perovskite structure, a compact structure often adopted by oxides containing two different cations of moderately different sizes. Minor elements such as calcium, aluminum, iron, and hydrogen as part of water or hydroxyl groups, affect the stability and properties of these minerals (*1–7*). However, many of the physical properties of $MgSiO_3$ perovskites under mantle conditions, such as defect mobility, ionic transport, and flow properties, remain poorly understood, and this hampers our understanding of fundamental mantle processes.

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In contrast to the silicate perovskites, ceramic perovskites have been studied extensively for fuel cell applications (*8–11*). Physical measurements under rigorously controlled conditions on these ceramic materials have yielded data essential to gaining quantitative understanding of defect equilibria and transport. As I will show below, these materials, which are ionic conductors when dry and fast proton conductors when wet, are useful analogs for mantle perovskites.

The tetravalent B cations in the ceramic $A^{2+}B^{4+}O_3$ perovskites may be Ti, Zr, Ce, or Sn. At atmospheric pressure the divalent A cations are limited to Ca, Sr, and Ba, but at high pressures Mn, Fe, and Mg may also be incorporated (*12*). Trivalent rare earth elements (M = Y, Yb, Nd, Gd) may substitute tetravalent ions, resulting in a doped series $A^{2+}(B^{4+}_{1-x}M_x)O_{3-0.5x}$ in which the diminished positive charge is compensated by oxygen vacancies (*8*). At high temperatures, these ceramic perovskites are oxide ion conductors or mixed ionic-electronic conductors (*8*).

The rare-earth–doped ceramic perovskites readily absorb water (*8–11*). Hydroxyl groups fill oxygen vacancies, creating mobile protons. The hydrogen bonds are relatively weak (*9*), and the structure relaxes around the defects (*9, 13, 14*). At low temperature, hydrogen is the mobile species, but above 750 K the proton and hydrogen mobilities are similar (*8–11*). Crystallographic studies show only minor changes in atomic positions with rare earth element doping (*15, 16*).

In the ceramic perovskites, defect equilibria are dominated by the following substitutions:

$$2B^{4+}_B = 2M^{3+}_B + V_O \quad (1)$$

$$V_O + O^{2-}_O + H_2O = 2OH^-_O \quad (2)$$

where subscript B denotes sites occupied by tetravalent B atoms in the original structure and subscript O denotes oxygen sites. Equation 1 creates oxygen vacancies, V_O, and Eq. 2 fills them. Equation 1 is most favored, and the trivalent ion solubility greatest, for the smallest size difference between the rare earth and tetravalent ion. The very strong relaxation of the neighboring oxygen atoms around each defect appears to compensate electrostatic and size mismatch locally and prevent long-range order. Hydration according to Eq. 2 is strongly exothermic by 100 to 170 kJ per mole of water, becoming more exothermic with increasing B-cation size for a given divalent cation. Proton mobility is favored by dense structures and short oxygen-oxygen distances.

These insights into the defect chemistry of ceramic perovskites can now be used to develop conceptual models for the behavior of $MgSiO_3$ under mantle conditions. Incorporation of trivalent species such as aluminum or ferric iron into $MgSiO_3$ perovskite can follow two competing mechanisms (*17*): vacancy formation according to Eq. 1 or coupled substitution of two trivalent ions for silicon and magnesium according to

$$Mg^{2+}_A + Si^{4+}_B = M^{3+}_A + M^{3+}_B \quad (3)$$

Atomistic simulations suggest that, at low pressure, oxygen vacancy formation (Eq. 1) is favorable for Al, whereas coupled substitution on B and A sites (Eq. 3) is favorable for Fe^{3+} (*4*). The latter is supported by experiment (*3*). The calculations sug-

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