MOLECULAR BIOLOGY

Promiscuous Chromosomal Proteins: Complexes About Sex

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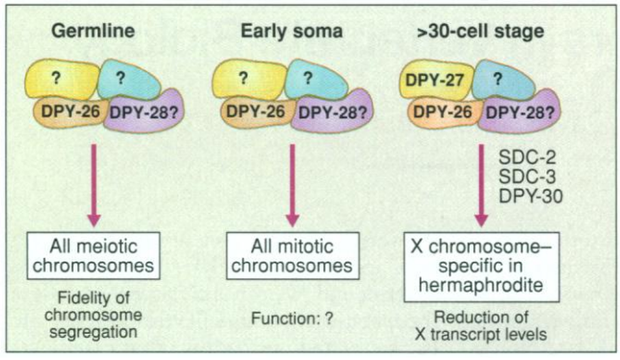
Chromosomes undergo dynamic structural changes as they progress through the cell cycle. During mitosis, chromosomes are highly condensed, presumably to facilitate movement and ensure proper segregation. At other stages of the cell cycle, chromosomes are decondensed to varying extents, permitting replication, repair, and gene expression to occur. Two reports in this issue of *Science* (*1*, *2*) reveal a mechanistic link between chromosome segregation and chromosome-specific gene regulation, thus providing insight into how global features of chromosome structure contribute to function. Meyer and co-workers now provide evidence that in nematodes, subunits of a protein complex critical for X chromosome dosage compensation are shared with the machinery required for chromosome segregation in meiosis, suggesting that both processes are accomplished by the regulated condensation of chromosomes.

How does the structural composition of chromosomes control the ability of their diverse resident genes to be expressed at appropriate levels? For most genes, this function is accomplished through gene-specific regulatory sequences that establish a local domain of expression. However, in many species, X-linked genes experience an additional level of control in which expression of the entire X chromosome is adjusted to be equivalent between two sexes (in general, between XX female and XY male; in nematodes, between XX hermaphrodite and XO male) (*3*). This process of dosage compensation occurs in mammals by X inactivation, in which one X chromosome in each female cell forms a transcriptionally repressed structure termed the Barr body (*4*). In nematodes, however, both hermaphrodite X chromosomes are transcriptionally active, but partially repressed relative to the single male X chromosome (*5*). This repression is remarkable, because it provides a very subtle level of control (twofold) that must be superimposed on the diverse gene-specific controls of the many X-linked genes. Although subtle, this level of regulation is critical for the development and viability of the nematode because mutations that disrupt the ability to regulate or implement dosage compensation result in sex-specific lethality. Failure to turn on dosage compensation is lethal to hermaphrodites, whereas a failure to repress the process is lethal to males (*3*).

The work of Meyer and colleagues has led to the emergence of a model in which regulated chromosome condensation forms the basis for the twofold repression of X-linked transcription in hermaphrodites. At least two of the genes required for dosage compensation in nematodes encode proteins that are specifically associated with the hermaphrodite X chromosomes. In previous work, Chuang *et al.* (*6*) showed that the DPY-27 dosage compensation protein is a member of the SMC (structural maintenance of chromosomes) family of proteins. This family includes proteins that participate in chromosome segregation and condensation in budding yeast (*7*) and fission yeast (*8*), chromosome condensation in *Xenopus* extracts (*9*), and the mitotic chromosome scaffold in chicken (*10*). Genetic and immunolocalization data indicate that DPY-27 is distinct among the SMC family members so far described in that it does not function on all chromosomes but is specialized for the hermaphrodite X chromosomes (*6*).

The link between chromatin structure and dosage compensation can now be expanded to include DPY-26 and likely DPY-28. Both proteins are required in meiosis for proper chromosome segregation in addition to their function in dosage compensation (*11*). Lieb *et al.* (*2*) show that in the germline, DPY-26 protein is associated with all meiotic chromosomes. Subsequently, DPY-26 is bound to all mitotic chromosomes early in embryogenesis, but this more general localization resolves into an X chromosome–specific colocalization with DPY-27, as dosage compensation is initiated in the hermaphrodite (see figure). Further, Chuang *et al.* (*1*) show that DPY-26, DPY-27, and at least two other subunits are physically associated in a protein complex at this stage. The authors suggest a model in which DPY-27 acts as a specificity factor to direct DPY-26 and probably other chromatin components to the X chromosome in somatic cells at the 30-cell stage of embryogenesis. In the germline, DPY-27 is not expressed, and thus DPY-26 can interact with all chromosomes to promote segregation. The similarity of the meiotic and dosage compensation phenotypes of *dpy-26* and *dpy-28* mutants (*11*) and the apparent instability of DPY-26 and DPY-27 in *dpy-28* mutants (*1*, *2*) suggest that the DPY-28 protein will behave as does DPY-26: associating with all chromosomes in meiosis and early embryogenesis, then subsequently being redirected to the X chromosome in a DPY-27–dependent protein complex.



DPY-26 functions in distinct chromosomal processes. In meiosis, where DPY-26 promotes chromosome segregation, DPY-26 protein is associated with all meiotic chromosomes and is proposed to function as part of a complex that may also include DPY-28 and one or more members of the SMC family of chromosome condensation proteins. DPY-26 is also associated with all mitotic chromosomes during the first few embryonic mitoses, but the functional significance of this association is not known. At the 30-cell stage of embryogenesis, DPY-26 is sequestered in a protein complex that includes DPY-27, an SMC protein that functions exclusively in X chromosome dosage compensation. This DPY-27–dependent protein complex is directed specifically to the X chromosome in hermaphrodites by the action of SDC-2, SDC-3, and DPY-30, a set of regulatory proteins required for the activation of dosage compensation in XX individuals. Binding of the DPY-27–dependent protein complex to the hermaphrodite X chromosomes results in a 50% reduction of X transcript levels.

What determines the X specificity of this protein complex containing subunits that otherwise might operate on all chromosomes? Although DPY-27 may provide tissue specificity by sequestering DPY-26 in a

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soma-specific complex, DPY-27 alone is clearly not sufficient to direct binding of the complex to the X chromosome because both proteins are present but not associated with the X chromosome in XO males (*2*, *6*). The chromosomal specificity is likely to derive from the elaborate regulatory hierarchy responsible for ensuring that the X chromosome dosage compensation machinery is activated only in the hermaphrodite (see figure) (*3*). Among the regulatory components is SDC-3, a zinc finger protein (*12*) that together with SDC-2 and DPY-30 is required for DPY-26 and DPY-27 localization (*1*, *2*). An as-yet-undefined interaction of SDC proteins with the DPY-27 complex or a change in X chromatin accessibility induced by the SDC proteins could result in the capture and stabilization of the dual-function proteins DPY-26 and DPY-28 on the X chromosomes during embryogenesis in XX hermaphrodites.

What are the implications for chromosome condensation? DPY-26 is a novel protein, but on the basis of immunolocalization data it is likely a structural component of the condensed chromosome. Studies in other species suggest that SMC family members are likely to play a role in general chromosome condensation in nematodes, so we may expect new members to be found as the germline partners of DPY-26. Interestingly, the structure of SMC proteins suggests a possible energy-dependent motor function that could be used for chromatin reorganization (*6*, *13*). Will distinct protein partners specify the extent of chromosome compaction achieved? Under this scenario, specialized partners for DPY-26 may have evolved to provide both X chromosome recognition and the ability to modulate condensation to achieve the fine level of gene repression critical for dosage compensation in the nematode.

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DEVELOPMENT

A Fin-de-Siècle Achievement: Charting New Waters in Vertebrate Biology

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In an accomplishment of historic proportions, reported as a group of 36 papers in the December issue of *Development*, scientists at the Max-Planck-Institut für Entwicklungsbiologie in Tübingen and Massachusetts General Hospital in Boston have initiated a systematic genetic analysis of how the vertebrate embryo is formed (*1*). Led by Christiane Nüsslein-Volhard and Wolfgang Driever, the groups have amassed and begun to analyze a collection of more than 1800 developmental mutants representing defects in about 500 different genes that contribute to the form and function of the zebrafish embryo. The seminal insights garnered from a similar analysis of *Drosophila* embryogenesis (*2*) were recognized last year by the Nobel committee, and we can expect that the current assault on the zebrafish embryo, which is unprecedented in its scale and method of approach in vertebrates, will have an equal impact on future research. The timing of the effort is superb, given the relatively recent appreciation of the degree to which both the molecules and the logic underpinning embryonic development are conserved throughout the vertebrates (*3*). As a result, the benefits to be accrued from analyses of these mutants are profound. We can anticipate that study of the zebrafish mutants will yield insights into the genes and mechanisms that coordinate normal vertebrate embryogenesis and that, when altered, result in a variety of inherited disorders in humans.

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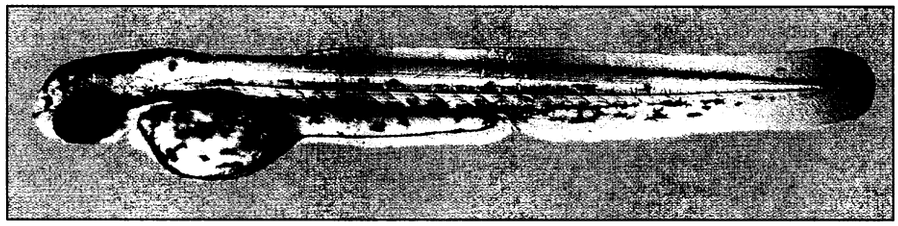

The subject. A 48-hour zebrafish embryo.

The zebrafish mutant collection identifies genes that participate in a wide variety of processes. Some mutations affect general cellular behaviors such as cell division and nuclear replication. Some mutations affect early processes critical for formation of the body pattern. A great many of the mutants were identified because they are defective in the formation of specific tissues or organs, including the notochord, somitic muscle, the ear, regions of the brain, the neural crest, the heart, and blood. In addition, two groups of mutations were recovered because they are likely to disrupt neural circuitry in specific ways. One class affects the control and coordination of locomotion behavior, and the other, recognized in Friedrich Bonhoeffer's laboratory in Tübingen, affects the neural connections formed between the retina and the optic tectum. Although the researchers point out that they have not identified all of the genes that might be mutated to a form that disrupts any of these processes, it is likely that a significant sample of such genes is represented in the mutants.

The zebrafish was chosen as a focus for the studies for several persuasive reasons. First, the external development and transparency of the zebrafish embryo mean that aberrant patterns of development can be recognized as they arise, giving the investigator a clue as to the time and place that the wild-type gene might normally function. Previous work, largely developed by the cadre of zebrafish laboratories in Oregon, had set the stage for an appreciation of mutant embryonic phenotypes by providing a detailed description of normal embryonic development in the zebrafish (*4*) and by analyzing in detail a few, particularly informative embryonic mutants (*5*), which alerted the zebrafish research community to the potential significance of