catalyzed by the non-ATPase (adenosine triphosphatase) chaperone p23 (*12*). Perhaps it is notable in this regard that we have not observed release of hormone in those reactions. We have not yet addressed whether the disassembly of intact complexes requires energy, but at least two components of molecular chaperone complexes, Hsp90 and Hsp70, are ATPases, and it is thought that Hsp90 and p23 can associate directly (*12*).

Purified hormone-IR complexes are stable, consistent with crystallographic studies revealing that the ligands are buried within the hydrophobic core of the ligand-binding domains, contacted by 15 to 20 amino acid side chains (*16*). In contrast, hormones are released from receptors in vivo with half-lives of a few minutes (*17*). Similarly, regulatory complexes commonly assemble cooperatively and stably in vitro (*1*, *18*), whereas they are exceptionally dynamic in vivo (*19*, *20*), turning over every few seconds (*21*). We propose that molecular chaperones resolve these apparent discrepancies by fully disassembling regulatory complexes in vivo, which may include release of the hormone when the complexes contain intracellular receptors. Notably, continuous disassembly of regulatory complexes would enable IRs and other regulators to sense and respond efficiently to fluctuations in hormone levels (*9*). This principle could extend similarly to other classes of signals that affect regulatory factor activity, stability, or localization.

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Regulation of the Different Chromatin States of Autosomes and X Chromosomes in the Germ Line of *C. elegans*

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The Maternal-Effect Sterile (MES) proteins are essential for germline viability in *Caenorhabditis elegans*. Here, we report that MES-4, a SET-domain protein, binds to the autosomes but not to the X chromosomes. MES-2, MES-3, and MES-6 are required to exclude MES-4 and markers of active chromatin from the X chromosomes. These findings strengthen the emerging view that in the *C. elegans* germ line, the X chromosomes differ in chromatin state from the autosomes and are generally silenced. We propose that all four MES proteins participate in X-chromosome silencing, and that the role of MES-4 is to exclude repressors from the autosomes, thus enabling efficient repression of the Xs.

The phenomenon of X-chromosome dosage compensation is fairly well understood in somatic cells (*1*). How the germ line modulates gene expression from the X chromosomes is less clear. Recent findings suggest that the X chromosomes in *C. elegans* are globally repressed during most of germline development (*2*, *3*). The four *C. elegans* MES proteins are prime candidates for regulating this repression. The *mes* genes display a maternal-effect sterile phenotype that is highly sensitive to X-chromosome dosage; among the progeny of *mes/mes* mothers, XX animals undergo germline degeneration and lack gametes, whereas XO animals are usually fertile (*4*, *5*). MES-2 and MES-6 are homologs of Enhancer of zeste and Extra sex combs, both members of the Polycomb group of transcriptional repressors (*6*, *7*). MES-3, which has no known homologs, forms a complex with MES-2 and MES-6 (*8*, *9*).

Cloning and sequencing the *mes-4* gene [fig. S1 (*10*)] revealed that it encodes a 3.2-kb transcript that is enriched in the germ line (*11*). The predicted MES-4 protein (898 amino acids in length) is similar in sequence and motif organization to the predicted *Drosophila* protein CG4976 (*12*), the mouse protein NSD1 (*13*), and the human protein MMSET (*14*) [fig. S2 (*10*)]. All three proteins share three plant homeodomain (PHD) fingers, which mediate protein-protein interactions (*15*), and a SET domain with flanking cysteine-rich regions. The SET domain, common to many chromatin-binding proteins, mediates protein-protein interactions (*16*) and in some cases [e.g., SUV39H1 (*17*)] methylates lysine residues of histone H3. MES-4 shows sequence similarity to SUV39H1 within the SET domain [fig. S2 (*10*)].

On the basis of immunofluorescence staining (*10*), MES-4 is localized to nuclei and associated with chromosomes. MES-4 is present in the distal, mitotic region of the germ line, barely detectable in the early- to mid-pachytene region, and up-regulated in later pachytene and in oocytes (Fig. 1A). In embryos, MES-4 is present in both somatic and germline nuclei until the 80- to 100-cell stage (Fig. 1, B to D). Subsequently, MES-4 staining diminishes in somatic cells but persists in the primordial germ cells Z2 and Z3 (Fig. 1, E and F), in accordance with the requirement for MES-4 to protect germline viability.

Staining in one-cell embryos revealed that one chromosome of each parental set of six lacks MES-4 (Fig. 2A). In four-cell embryos two chromosomes in each diploid nucleus lack MES-4 (Fig. 2B). The sensitivity of the Mes phenotype to X-chromosome dosage suggested that the unstained chromosome is the X. The following results verify this prediction: (i) a single unstained chromosome is observed in XO embryos (Fig. 2C); (ii) three unstained chromosomes are observed in XXX embryos (Fig. 2D); and (iii) the X portion of an X:autosome translocation is not stained (Fig. 2E).

MES-4 is also restricted to the autosomes in the adult hermaphrodite germ line. In the distal

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mitotic zone, MES-4 staining resembles staining for acetyl (Lys12) H4 (Fig. 3A) and methyl (Lys4) H3 (*11*) (Fig. 3F). These and other histone modifications correlated with active chromatin (*18*, *19*) mark the autosomes but not the Xs (*3*). After the near-disappearance and then reappearance of MES-4 during pachytene (Fig. 1A), it associates with five bivalents but is lacking from one, presumably the X (Fig. 3, A and F). Thus, MES-4 is off the Xs when X-linked oocyte genes become detectably expressed in late pachytene (*3*). MES-4 staining in male germ lines resembles that in hermaphrodites (*11*).

What feature of the autosomes and X chromosomes causes the differential binding of MES-4? Analysis of extrachromosomal arrays of exogenous DNA provide a clue. "Repetitive" arrays contain >100 copies of plasmid DNA (*20*, *21*), whereas "complex" arrays contain primarily high-complexity genomic DNA and few copies of plasmid DNA (*21*). Transgenes in repetitive arrays are generally silenced in the germ line, but transgenes in complex arrays can be expressed, suggesting that the germ line packages repetitive sequences into transcriptionally silenced chromatin (*21*). We observed that repetitive, germ line–silenced arrays do not display MES-4 staining (Fig. 2F), thus resembling X chromosomes. Complex, germ line–expressed arrays display MES-4 staining (Fig. 2G), thus resembling autosomes. Thus, MES-4 binding correlates with a chromatin organization that permits gene expression.

Molecular epistasis analysis revealed that the restriction of MES-4 to the autosomes is regulated by MES-2, MES-3, and MES-6, and that the MES system regulates histone modification patterns in a maternal-effect fashion. We initially examined homozygous *mes-2*, *mes-3*, and *mes-6* worms from heterozygous mothers; such M^+Z^- (M, maternal load; Z, zygotic synthesis) *mes* worms are fertile but produce 100% sterile progeny (*4*). In the mitotic zone of M^+Z^- *mes* hermaphrodites, MES-4 is excluded from the X chromosomes (Fig. 3, B and F), as in wild type. However, in oocyte nuclei, MES-4 is abnormally present on all chromosomes (Fig. 3, B and F). Thus, MES-2, MES-3, and MES-6

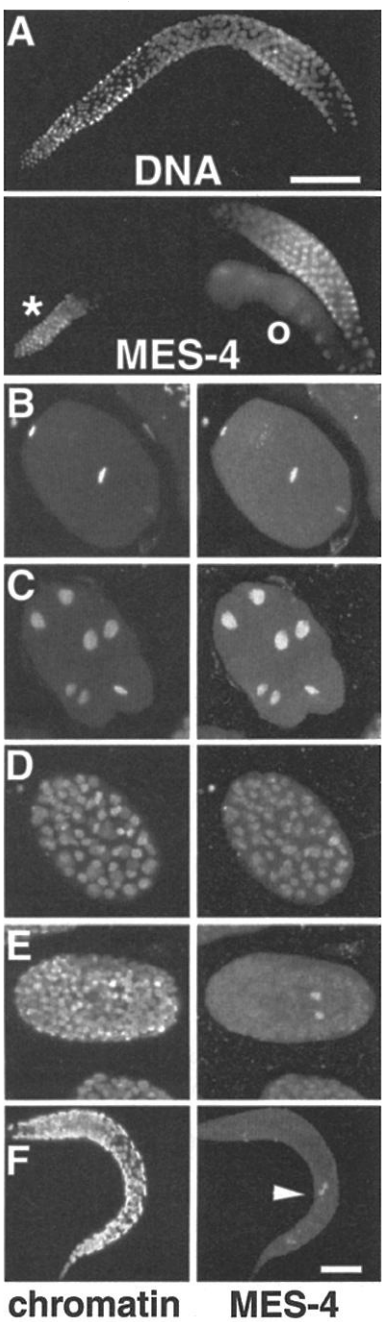

Fig. 1. MES-4 in the germ line and in embryos and larvae. Samples were stained with either DAPI (4′,6-diamidino-2-phenylindole) or antibodies to chromatin, and with anti–MES-4 (*10*). (**A**) Adult hermaphrodite gonad. (Upper panel) DAPI stain. (Lower panel) Anti–MES-4 stain. Asterisk marks the distal end, o marks oocytes. Bar, 50 μm. (**B**) One-cell embryo in metaphase. (**C**) Six-cell, (**D**) ~80-cell, and (**E**) ~180-cell embryo. (**F**) L1 larva. Arrowhead points to the germline cells Z2 and Z3. Bar, 10 μm (B) to (F).

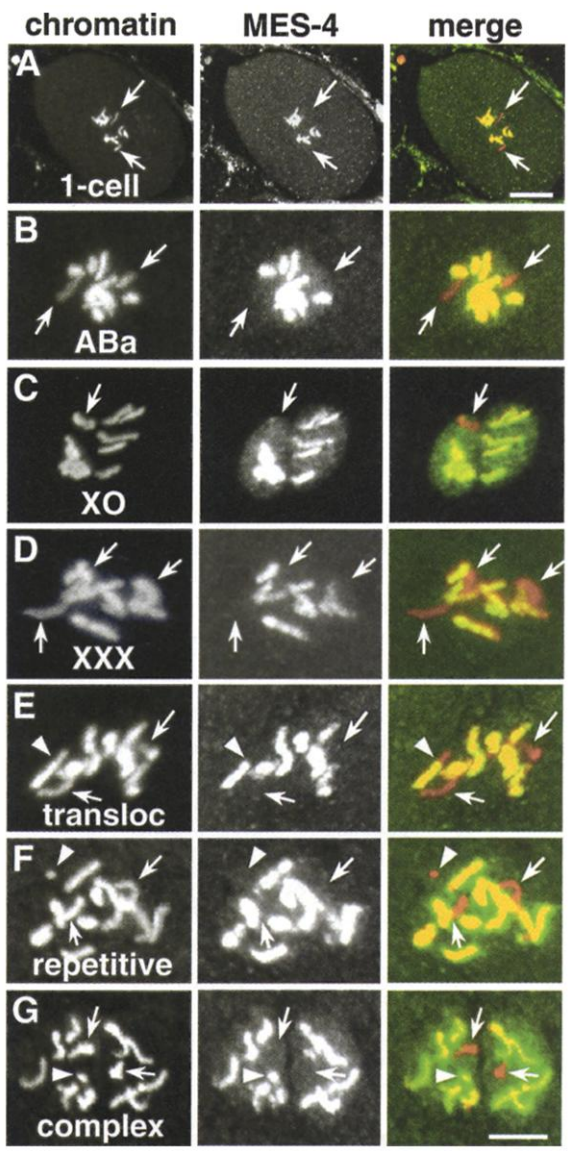

Fig. 2. MES-4 associates with autosomes and complex extrachromosomal arrays, but not with X chromosomes and repetitive arrays. Embryos were stained with either anti-chromatin (**A** to **E**) or ethidium bromide (**F** and **G**) (red in merge), and with anti–MES-4 (green) (*10*). Arrows point to chromatin lacking MES-4. (A) One-cell embryo at pronuclear meeting. Bar, 10 μm. (B) Nucleus in the ABa blastomere of a four-cell embryo. (C) Presumptive XO one-cell embryo generated by mating *fer-1* females with wild-type males. (D) Presumptive XXX one-cell embryo from a *him-8* hermaphrodite. (E) Embryo carrying *mnDp10*, a fusion of chromosome I and a duplicated portion of the X (*25*) (arrowhead marks the I:X boundary). The X-autosome translocation *mnT12* gave similar results (*11*). (F) Embryo carrying a repetitive extrachromosomal array (arrowhead) that contains many copies of GFP::*let-858* and *rol-6* (*21*). A repetitive GFP::*cam-1* array gave similar results (*11*). (G) Embryo carrying a complex extrachromosomal array (arrowhead) that contains genomic DNA and few copies of GFP::*let-858* and *rol-6* (*21*). A complex GFP::*tbg-1* array gave similar results (*11*). Bar, 5 μm (B) to (G).

participate in excluding MES-4 from the X chromosomes. The distribution of acetyl (Lys12) H4 and methyl (Lys4) H3 in M^+Z^- *mes* worms resembles that in wild type throughout the germ line (*3*, *11*). Similarly, the distribution of an RNA polymerase II phospho-epitope, which correlates with active transcription, resembles that in wild type (*3*) (Fig. 3, D and F). The unaltered distribution of MES-4 in the distal germ line of M^+Z^- worms may result from epigenetic control of chromatin organization by maternally provided *mes-2*+, *mes-3*+, and *mes-6*+ products. Chromatin remodeling may occur during pachytene, e.g., to enable a short burst of expression of X-linked genes (*3*). Indeed, the level of MES-3, like MES-4, is markedly reduced during early- to mid-pachytene (*22*). In M^+Z^- worms, the absence of zygotically synthesized MES-2, MES-3, or MES-6 may allow MES-4, when it reappears in later pachytene, to aberrantly bind all chromosomes.

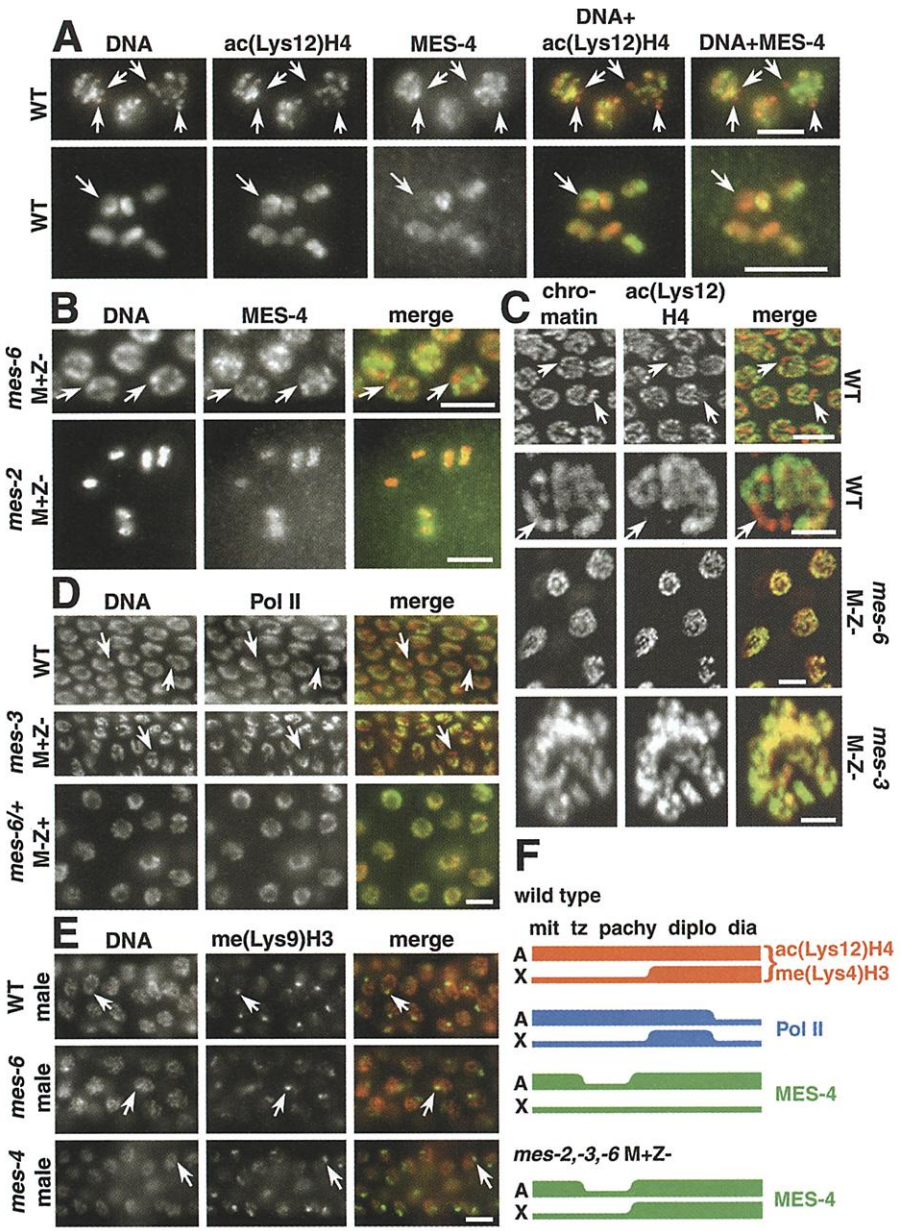

Fig. 3. MES-4, acetyl (Lys12) H4, methyl (Lys9) H3, and active RNA polymerase II in the germ lines of wild-type and *mes* mutant worms. Adult germ lines were stained with combinations of DAPI or anti-chromatin (red in merge), anti–MES-4 (green), anti-acetyl (Lys12) H4 (green), anti-dimethyl (Lys9) H3 (green), and the H5 antibody to phosphorylated RNA polymerase II (green) (*10*). Arrows point to the presumptive X chromosomes. (**A**) *mes*+ hermaphrodites. (Upper panels) Mitotic nuclei in a *glp-4* germ line, which contains few germ nuclei in prophase (*26*). (Lower panels) Oocyte chromosomes in wild type. (**B**) M^+Z^- *mes* hermaphrodites. (Upper panels) Distal mitotic nuclei in a *mes-6(bn64)* gonad. (Lower panels) *mes-2(bn11)* oocyte. (**C**) Pachytene nuclei in wild-type (upper two rows), M^-Z^- *mes-6(bn64)* (third row), and M^-Z^- *mes-3(bn88)* (bottom row) hermaphrodites. (**D**) Transition-zone nuclei in wild-type (upper panels), M^+Z^- *mes-3(bn35)* (middle panels), and M^-Z^+ *mes-6(bn64)/+* (bottom panels) hermaphrodites. (**E**) Pachytene nuclei in wild-type (upper panels), M^-Z^- *mes-6(bn66)him-8* (middle panels), and M^-Z^- *mes-4(bn67); him-8* (bottom panels) males. Bars [(C), rows 2 and 4], 2 μm. All other bars, 5 μm. (**F**) Schematic time line of marks on the autosomes (As) and Xs during germline development (mitotic, transition zone, pachytene, diplotene, diakinesis) in wild-type and M^+Z^- *mes* hermaphrodites. Derived from (*3*) and this paper.

If MES-2, MES-3, and MES-6 participate in controlling histone modification patterns, they likely act maternally or in the early embryo: *mes* sterility is maternal-effect (*4*), and analysis of a temperature-sensitive allele of *mes-3* suggests that MES-3 function is required in the mother's germ line and during embryogenesis (*22*). Generally, M^-Z^- hermaphrodites have severely degenerated germ lines with poor chromosome morphology (*4*, *5*, *8*). However, some M^-Z^- and M^-Z^+ *mes-2*, *mes-3*, and *mes-6* worms contain some early meiotic nuclei with reasonable chromosome morphology (*10*). In these nuclei, acetyl (Lys12) H4, methyl (Lys4) H3, and active RNA polymerase are present on all chromosomes [Fig. 3, C and D (*11*)]. Thus, defective MES regulation in the maternal germ line allows the X chromosomes in the progeny's germ line to acquire histone and RNA polymerase modifications that are correlated with active chromatin. These results predict that the X chromosomes become desilenced in the germ lines of M^-Z^- *mes-2*, *mes-3*, and *mes-6* mutant hermaphrodites. The X-dosage effects observed in these mutants (*5*) support this prediction.

Is MES-4 a histone methyltransferase? MES-4 is not required for methylation on Lys4 of H3, because this activating mark is present on germline chromosomes in M^+Z^- and M^-Z^- *mes-4* mutants (*11*). MES-4 also is not required for the repressive methylation on Lys9 of H3 (*18*). In wild type, this mark is complex and dynamic in hermaphrodite germ lines; in male germ lines, it is notably localized to the single X chromosome in pachytene (*3*) (Fig. 3E). In the germ lines of M^-Z^- males from *mes-4*, *mes-2*, *mes-3*, or *mes-6* mothers, the distribution of methyl (Lys9) H3 appears normal [Fig. 3E (*11*)]. This suggests that silencing of the single X in males occurs independently of the MES system.

The *C. elegans* germ line uses a type of chromatin regulation not described previously, involving a Polycomb-group repressive complex and an autosome-specific protein. We propose that the primary function of the MES system is to keep the X chromosomes repressed during most of germline development (*2*, *3*). The MES-2/MES-3/MES-6 com-

plex may participate directly in this repression. Intriguingly, EED, the mammalian homolog of ESC and MES-6, is involved in maintaining X-chromosome inactivation in extraembryonic tissues of female mouse embryos (*23*). How might MES-4 participate in X-chromosome repression? MES-4 on the autosomes may protect them from the binding, spreading, or action of repressors, such as the MES-2/MES-3/MES-6 complex or histone-modifying enzymes. This would serve to focus repression on the X chromosomes, which lack MES-4 protection. This model for MES-4 action is consistent with several observations, including the following: (i) *mes-4* mutants display the same sensitivity to X-chromosome dosage as *mes-2*, *mes-3*, and *mes-6* mutants; and (ii) MES-4, like MES-2, MES-3, and MES-6, is required for repression of germline expression of transgenes present in repetitive arrays (*24*). The activation of transgenes in *mes-4* mutants may be due to titration of limited levels of repressor by autosomal chromatin that in wild type does not bind the repressor. This scenario predicts that the X chromosomes are desilenced in *mes-4* mutants, as we predicted occurs in *mes-2*, *mes-3*, and *mes-6* mutants.

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Sp1 and TAFII130 Transcriptional Activity Disrupted in Early Huntington's Disease

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Huntington's disease (HD) is an inherited neurodegenerative disease caused by expansion of a polyglutamine tract in the huntingtin protein. Transcriptional dysregulation has been implicated in HD pathogenesis. Here, we report that huntingtin interacts with the transcriptional activator Sp1 and coactivator TAFII130. Coexpression of Sp1 and TAFII130 in cultured striatal cells from wild-type and HD transgenic mice reverses the transcriptional inhibition of the dopamine D2 receptor gene caused by mutant huntingtin, as well as protects neurons from huntingtin-induced cellular toxicity. Furthermore, soluble mutant huntingtin inhibits Sp1 binding to DNA in postmortem brain tissues of both presymptomatic and affected HD patients. Understanding these early molecular events in HD may provide an opportunity to interfere with the effects of mutant huntingtin before the development of disease symptoms.

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder manifested by psychiatric, cognitive, and motor symptoms typically starting in midlife and progressing toward death. HD is caused by expansion of a polyglutamine tract in the huntingtin protein. The number of diseases caused by polyglutamine expansions continues to grow, and a common mechanism could underlie these disorders. One hypothesis suggests that expanded polyglutamines result in aberrant interactions with nuclear proteins and thereby lead to transcriptional dysregulation (*1–7*). If huntingtin is involved in regulating gene transcription, it is important to determine which genes may be affected by normal and/or mutant huntingtin. Some obvious candidates are genes whose expression is altered in HD patients or in animal models of HD. Neurotransmitter receptor alterations have been described in early-stage human HD autopsy material, and many of these changes have been confirmed in transgenic mouse models of HD (*8*, *9*). Gene expression assays on DNA microarrays have shown that the scope of mRNA changes in transgenic HD mice involves several groups of genes, including neurotransmitter receptors and intracellular signaling systems (*10*). The known regulatory sequences of these genes contain binding sites for the transcription factor Sp1, suggesting that huntingtin may interfere with Sp1-mediated transcription. Sp1 is a ubiquitous transcriptional activator whose major function is recruitment of the general transcription factor TFIID to DNA (*11*). TFIID is a multisubunit complex made up of the TATA box–binding protein (TBP) and multiple TBP-associated factors (TAFs) (*12*). Involvement of one of the human TAFs, TAFII130, in activator-TAF interactions has been examined in detail (*13*, *14*). TAFII130 interacts with various cellular activators, including Sp1 and CREB, suggesting that TAFII130 may be critical for the transcriptional activation function of these factors by bridging them to the basal machinery.

Using the yeast two-hybrid system (*15*), we found that both Sp1 and TAFII130 interact with full-length huntingtin (Fig. 1).[5] The interactions between Sp1 and huntingtin are stronger in the presence of an expanded polyglutamine repeat (HttQ75) as compared to the nonexpanded repeat length (HttQ17) (Fig. 1A), whereas the interactions between TAFII130 and huntingtin are not significantly influenced by the polyglutamine tract length (Fig. 1B). Although the glutamine-rich regions of Sp1 (Sp1AB) and TAFII130 (TAFII130-M) are sufficient for their interaction with huntingtin, the presence of the COOH-terminal DNA binding domain of Sp1

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