Mammalian sex-determining factors with homology to DNA binding proteins are required for splicing, according to a study by Paolo Sassone-Corsi and coworkers at the Université Louis Pasteur (Strasbourg, France). Examination of high mobility group (HMG) domain containing SRY and Sox proteins demonstrated a surprising but clear association with splicing complexes.

SRY, the testis-determining factor found on the Y-chromosome in mice and humans, is one of several Sox family members involved in sexual development. It is known to bind DNA, in support of the proposal that HMG domain proteins act as architectural facilitators for building transcription complexes.

Sassone-Corsi’s group thus expected to find Sox proteins colocalized in the nucleus with transcription factors. Instead, SRY and SOX6 proteins associated with splicing factors in nuclear speckle domains. Depletion of SOX6 in HeLa cell extracts blocked splicing of multiple substrates, and expression of the HMG domain only of either SOX6, SOX9, or SRY restored splicing in the extracts, indicating functional overlap of the proteins.

The group’s results provide the first association between splicing and sex determination in mammals. The Drosophila genes transformer and sex-lethal encode mRNA splicing factors required for sex determination in flies, indicating that regulated splicing of sex-determining factors may be evolutionarily conserved. According to Sassone-Corsi, to complete the connection “the next step is to identify natural physiological substrates of the Sox and SRY proteins.” He thinks the Sox proteins may control regulated splicing by determining which spliceosomal complexes are formed in different cell types, analogous to the way transcription factors can regulate the basal transcription machinery.

Reference: Obe, K., et al. 2002. Proc. Natl. Acad. Sci. USA. 99:1146–1151.

# Keeping the cord in place

The structure of a nerve cord must be actively maintained, according to a new study by Oliver Hobert (Columbia University, New York, NY) and colleagues. The findings are the first indication that maintenance of neuronal circuitries demands a dedicated mechanism of its own, beyond those involved in its initial patterning.

Hobert and colleagues deduced this by studying the ventral nerve cord (VNC) in Caenorhabditis elegans. Development of the VNC is initiated by outgrowth of the VPT interneuron, which then secretes signals that direct growth of other VNC neurons. In the last decade, says Hobert, it was assumed that the important patterning factors were all made during embryonic development.

But in the new work, Hobert and colleagues have shown that ablation of the PVT in the first larval stage causes aberrant placement of axons across the ventral midline, even though growth of the axons was completed before ablation. Deletion of zig-4, which encodes an adhesion protein produced by the PVT, had similar effects. Fewer axons were affected than after ablation, however, suggesting that other zig family members may be important.

The maintenance mechanism may counteract stresses caused by mechanical forces. Loss of this maintenance mechanism could potentially be a factor in human neurodegenerative disease, as humans have proteins with a topology similar to that of the zig family proteins.

Reference: Aurelio, O., et al. 2002. Science. 295:686–690.

# Structural Mad-ness

The spindle checkpoint is turned on when unattached kinetochores generate a signal that inhibits the anaphase-promoting complex (APC) preventing premature chromosome separation. Now, Hongtao Yu and colleagues (University of Texas Southwestern Medical Center, Dallas, TX) have shown that conformational changes in the protein Mad2 are important in triggering this checkpoint pathway.

Monomeric Mad2 is recruited to the kinetochore when it forms a complex with Mad1. Mad2 can also associate with Cdc20, an APC activator, thereby inhibiting Cdc20 and the APC.

Mad2 is constitutively present in the cell, but does not always inhibit Cdc20. Yu set out to determine the basis of inhibition by analyzing the structure of bound and unbound Mad2. NMR structures of free Mad2 and Mad2 bound to a Mad2-binding peptide (MBP1) revealed a striking shift in the conformation of the protein upon peptide binding. A single β strand and the COOH terminus of the protein translocated from one end of the main β sheet to the other.

Binding of either Mad1 or Cdc20 caused similar conformational shifts in Mad2. According to Yu, the results suggest that Mad1 binding to Mad2 might help convert the protein to a form more compatible for binding to Cdc20, and that protein complexes containing Mad2 and Cdc20 may spread through the cell, dispersing the checkpoint signal. Yu would now like to identify how Mad2 changes its binding partner from Mad1 to Cdc20, especially given the fact that the two bind Mad2 with similar affinities.

Reference: Luo, X., et al. 2002. Mol. Cell. 9:59–71.