Genetic control of *Drosophila* telomere stability

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We have undertaken a systematic study of the genes required to prevent telomeric fusions in *Drosophila melanogaster*. We have found that mutants in the *UbcD1* and *pendolino* (*peo*) genes display frequent telomere-telomere associations (TAs), most of which are resolved during anaphase. Both *UbcD1* (Cenci et al., Genes Dev., 11:863-875, 1997) and *peo* (our unpublished results) encode ubiquitin conjugating (E2) enzymes, suggesting that the targets of these genes are telomeric proteins that are removed from chromosome ends via ubiquitin-mediated proteolysis, to prevent telomere stickiness.

We have recently obtained additional insight into the role of UbcD1 at chromosome ends. First, we have found that terminally-deleted X chromosomes, devoid of Het-A and TART sequences, are involved in *UbcD1*-induced telomere attachments with the same frequency as normal X chromosomes. Second, we have determined that the frequency of X-ray-induced chromosome aberrations in *UbcD1* mutants is lower than that observed in wild type controls. Third, we have found that *UbcD1* interacts with *mus309*, a gene orthologous to the human Bloom syndrome gene. *mus309* honmozygous mutants do not exhibit telomeric attachments and show a low frequency (6%) of spontaneous chromosome breakage. However, in *mus309 UbcD1* double mutants, the frequency of telomeric attachments is 10-fold lower than in *UbcD1* single mutants. One interpretation of these results is that the *mus309* gene encodes the protein that fails to be degraded in *UbcD1* mutants, causing telomere stickiness. This protein would redistribute after X-ray irradiation, facilitating repair of chromosomal damage.

We have identified 17 new mutants (at 10 loci) that exhibit elevated frequencies of TAs. In some of these mutants TAs are resolved during anaphase, as occurs in *UbcD1* and *peo*, while in others TAs result in anaphase bridges and cause extensive chromosome breakage. The latter cytological phenotype is very similar to that elicited by mutations in *Su(var)2-5* (Fanti et al., Mol. Cell, 2:527-538, 1998), a well known dominant suppressor of position effect variegation (PEV) that encodes HP1. We have thus analyzed (i) whether the chromosomal distribution of HP1 is disrupted in our mutants and (ii) whether they have the ability of modifying PEV. Results obtained to date along these two levels of observations will be presented.