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News from *Arabidopsis* on the Meiotic Roles of Blap75/Rmi1 and Top3α

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Two articles published in this issue of *PLoS Genetics* present novel data concerning the members of a key regulator of genetic crossing-over. Working with the plant *Arabidopsis thaliana*, the authors of the two reports provide exciting new data and further understanding of the meiotic anti-crossing-over function of the Topoisomerase 3α (Top3α) and Blap75/Rmi1 proteins, and thus presumably that of the protein complex that contains these proteins and the RecQ-like helicase BLM.

The highly conserved RecQ-like helicase BLM, which is mutated in patients with Bloom syndrome, acts in a protein complex that can dissociate homologous recombination intermediates in vitro and in vivo (reviewed in [1–3]). The importance of this anti-recombination role is clearly shown by the elevated levels of genetic instability, mitotic recombination, and sister-chromatid exchanges in the somatic tissues of the cancer-prone Bloom syndrome patients. This complex, known as BTB in mammals and RTR in yeast, involves BLM and at least two other proteins: Top3α and Blap75/Rmi1. BLAP75/RM11 is a highly conserved protein in eukaryotes originally identified through its interactions with the BLM [4,5] and independently as Rmi1/Nce4 in yeast through its genetic interactions with BLM homolog Sgs1 [1,6]. A fourth protein component of this complex, Rmi2, has recently been identified [7,8], and it is likely that others will follow (discussed by [9]). It is proposed that the principal anti-recombinational role of this complex involves BLM helicase-driven migration of double Holliday junctions (dHJs) to form a hemi-catenane intermediate. The resolution of this structure by a topoisomerase (Top3α) does not lead to the exchange of flanking DNA sequences, and thus BLM acts to avoid crossing-over [3,10–12]. BLM also has affinity for DNA structures other than dHJs and clearly also plays other anti-recombination roles [13–15]. To add to these, a very recent report shows a pro-recombination role for Sgs1/BLM in resection of 5′-ended strands at DNA double-strand breaks [16].

What about *A. thaliana*, the subject of the two reports discussed here? *Arabidopsis* has a total of seven identified RecQ-like proteins, with RecQ4α being the strongest candidate for the *Arabidopsis* BLM/Sgs1 ortholog [17–19]. The accompanying papers report the identification of the *Arabidopsis* orthologs of BLAP75/RMI1 [20,21] and Topo3α [21], as well as the characterization of the mitotic and meiotic phenotypes of the corresponding mutant plants. *top3α* mutant plants have severe developmental defects, are methyl methanesulfonate (MMS)-sensitive, and show elevated levels of mitotic recombination and mitotic chromosome abnormalities. Similar mitotic phenotypes are observed in *recQ4α* and *blap75/rmi1* mutants, suggesting a functional interaction between RecQ4α and Top3α. This is further supported by the partial suppression of *top3α* developmental defects in double *recQ4α/top3α* mutants.

In most (studied) eukaryotes, homologous recombination that occurs during the first meiotic prophase ensures the proper segregation of homologous chromosomes (homologs) at the first meiotic division. These events are initiated by programmed double-strand breaks that generate broken DNA ends that invade homologous sequences on the homolog, a subset of which are processed to form dHJs. These must be resolved to permit the separation of homologs at the first meiotic anaphase, and the mode of this resolution determines whether or not the recombination is accompanied by physical exchange of chromosome arms of the homologs (crossing-over). The potential of crossing-over to cause genome reorganization (insertions, deletions, inversions, translocations) has led to the evolution of multiple controls of recombination.

It has long been recognized that the numbers and distribution of meiotic crossovers are strictly regulated. In the last decade, the existence of cross-over and non-cross-over recombination pathways has been established, and many details of molecular mechanisms elucidated [22–28]. In this context lies the importance of the characterization of the essential meiotic anti-crossing-over role of the BTB/RTR complex in *Arabidopsis* by the Grelon and Puchta groups, reported in this issue of *PLoS Genetics* [20,21].

These reports show that *Arabidopsis* *blap75/rmi1* and *top3α* mutants are capable of full chromosome synopsis, resulting in normal pachytene figures. The structure of the synaptonemal complex at pachytene was verified by staining of *blap75* mutant meioseos with antisera against Asyl and Zyp1, two synaptonemal complex proteins, and proper chromosome pairing was shown by fluorescence in situ hybridization (FISH) [20]. Staining with antiserum against Dmc1, a marker for early meiotic recombination intermediates, also shows normal numbers and timing of foci. Although these immunological and FISH analyses haven’t been carried out for *top3α* mutants, the DAPI-stained pachytene figures of *top3α* present the same (normal) aspect as those of the *blap75* mutants. Epistasis analyses confirm that *Blap75/Rmi1* acts downstream of *Spo11* (DNA cleavage/recombination initiation), *Rad51*, and *Mnd1* (homolog invasion). It thus appears that early steps of meiosis, up to homolog pairing and synaptonemal complex formation, occur normally in the absence of *Blap75/Rmi1* and *Top3α* in *Arabidopsis*. However, aberrant diakinesis and interlocked metaphase I figures follow, and chromosomes fragment at anaphase I. The interlocked bivalents observed at


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The phenotype contrasts strikingly with that seen in either study, implying meiotic arrest breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely. Interestingly, no evidence of unrepaired chromatid breaks, are equally likely.


