Proteasomes on the chromosome

Cell Research (2017) 27:602–603. doi:10.1038/cr.2017.28; published online 7 March 2017

Targeted proteolysis plays an important role in the execution and regulation of many cellular events. Two recent papers in *Science* identify novel roles for proteasome-mediated proteolysis in homologous chromosome pairing, recombination, and segregation during meiosis.

Protein degradation by the 26S proteasome drives a variety of processes central to the cell cycle, growth, and differentiation. Proteins are targeted to the proteasome by covalently ligated chains of ubiquitin, a small (8.5 kDa) protein. The protein ligases that catalyze ubiquitin addition recognize targets by direct interaction or by binding to sites of post-translational modification (PTM). One such PTM is SUMOylation. SUMO (small ubiquitin-like moiety) ligation can disrupt protein-protein interactions or, conversely, drive protein complex assembly via interactions between SUMOylated proteins and proteins that contain SUMO interaction modules (SIMs) [1]. One such type of interaction involves the recognition of SUMOylated proteins by SUMO targeted ubiquitin ligases (STUBLs), which catalyze polyubiquitylation and thus effect proteasome-mediated degradation [2].

While PTM-dependent proteasome-mediated degradation has been extensively documented for the mitotic cell cycle, considerably less is known about roles of this process during meiosis. Meiosis involves the division of the diploid genome into haploid gametes, and thus requires separation of homologous chromosomes of different parental origin (hereafter called homologs) at the first of two nuclear divisions (meiosis I). Homologous recombination is critical to

this process, both in mediating homolog association and in providing crossovers that tether homologs and ensure their accurate segregation. Meiotic recombination is initiated by DNA double-strand breaks (DSBs) at many sites along chromosomes, and the multiple interhomolog interactions formed by DSB repair drive homolog association, culminating in the end-to-end homolog synapsis by a protein structure called the synaptonemal complex (SC) [3]. SC-associated focal protein complexes, here called recombination nodules (RNs), form around and stabilize interhomolog recombination intermediates and thus facilitate homolog pairing. Later, most RNs are removed, and associated recombination intermediates are disassembled as noncrossover recombinants. A smaller number of RNs are preserved and the recombination intermediates that they contain are resolved as crossovers. While normally promoting interhomolog pairing and crossover formation, SC can also form between stably paired nonhomologous chromosomes that are fortuitously juxtaposed. Unless this nonhomologous synapsis is removed, it can interfere with homologous chromosome pairing, recombination, and ultimately proper chromosome segregation.

What roles do SUMO, ubiquitin, and the 26S proteasome play in the chromosome pairing and segregation events of meiosis? Two recent papers, published in *Science*, address this question. Previous work, primarily in budding yeast, has implicated SUMO as playing important roles in SC assembly [4], and studies in mice have identified RNF212 and HEI10, putative SUMO and ubiquitin

ligases, respectively, as RN components that impact crossover formation [5, 6]. In the first of the two papers, Ahuja *et al.* [7] report that budding yeast *pre9Δ* mutants, which lack a nonessential proteasome subunit, display defects in meiotic DSB repair, in chromosome pairing and synapsis, and in crossover formation. Similar defects are seen, but to a lesser extent, in cells treated with the proteasome inhibitor MG132. These defects all can be ascribed to a failure to remove nonhomologous synapsis. In budding yeast, centromeres are clustered early in meiosis, and SC recruited to these clustered centromeres pairs them without regard to homology [8]. Thus, most initial SC formation occurs between nonhomologous chromosomes. Ahuja *et al.* show that, in *pre9Δ* mutants, this early SC is never taken apart, and homologs never properly associate or synapse. This results in decreased interhomolog recombination, unrepaired DSBs, and a general reduction in crossovers. Thus, it appears that full proteasome function is needed to remodel or remove SC proteins from sites of nonhomologous pairing (Figure 1A). Patterns of proteasome recruitment to meiotic chromosomes in early meiosis are consistent with this suggestion; other proteasome localization data suggest a role in the disassembly of the SC at the end of meiosis I prophase.

In the second of the two papers, Rao *et al.* [9] examine roles for SUMO, ubiquitin, and the proteasome in RN dynamics and crossover designation during mouse spermatogenesis. They used immunocytology to examine meiotic chromosome spreads in mutants lacking RNF212 or HEI10, and upon chemical

Figure 1 (A) The budding yeast 26S proteasome (red) disassembles synaptonemal complex at sites of nonhomologous synapsis between centromeres, freeing up homologs to pair and synapse. The proteasome may also remove synaptonemal complex from other sites of nonhomologous synapsis. (B) Recombination nodule (RN) dynamics in male mouse meiosis. RNF212 (blue)-catalyzed SUMOylation stabilizes RNs and recombination intermediates, promoting homolog pairing, but also recruits HEI10 (purple). HEI10 ubiquitylates yet-to-be determined targets in RNs to recruit the 26S proteasome, destabilizing most RNs; at a subset of RNs, RNF212 activity dominates. These RNs perdure and the recombination intermediates that they contain are resolved as crossovers.

inhibition of SUMOylation, ubiquitin activation, or proteasome-mediated proteolysis. They find that SUMOylation, ubiquitylation, and proteasome activity are all required for efficient homolog synapsis, normal homologous recombination, and normal RN dynamics. Based on this and previous work [6], Rao and coworkers propose a model (Figure 1B) in which crossover/noncrossover decision is implemented by an unstable circular feedback loop (referred to by the authors as a “SUMO-ubiquitin relay”) with two stable outcomes. Initially, RNF212-catalyzed SUMOylation promotes RN assembly, thus stabilizing recombination intermediates to promote synapsis. At the same time, RNF212-deposited SUMO recruits the HEI10

STUBL, which ubiquitylates RN proteins and targets them for degradation by the proteasome, thus destabilizing RNs and causing the disassembly of underlying recombination intermediates as noncrossovers. At a few RNs, RNF212 activity predominates over HEI10-mediated destabilization. These RNs and the underlying recombination intermediates perdure, and ultimately are resolved as crossovers at the end of meiosis I prophase. The factors that determine whether HEI10 or RNF212 activity will predominate at a given RN remain unknown, but they must involve signaling over considerable distances, since most organisms display non-random spacing between stable RNs and resulting crossovers [10].

Taken together, these two papers document, for the first time, a role for SUMO- and ubiquitin-mediated proteasome targeting in normal meiotic chromosome transactions and recombination. In particular, by showing that the proteasome is recruited to its “sites of action” on meiotic chromosomes, they suggest that the proteasome is an active participant in the orderly disassembly of chromosome structures, rather than simply degrading proteins removed by other processes. The two papers open the door for further investigation, including identification of the relevant targets of SUMOylation, ubiquitylation and proteolytic degradation, as well as the regulatory mechanisms by which these events are controlled.

Michael Lichten¹

¹Laboratory of Biochemistry and Molecular Biology, Center for Cancer Research, National Cancer Institute, Bethesda, MA 20892-4260, USA

Correspondence: Michael Lichten

E-mail: michael.lichten@nih.gov

References

- 1 Jentsch S, Psakhye I. *Annu Rev Genet* 2013; **47**:167-186.
- 2 Nie M, Boddy MN. *Biomolecules* 2016; **6**:14.
- 3 Cahoon CK, Hawley RS. *Nat Struct Mol Biol* 2016; **23**:369-377.
- 4 Watts FZ, Hoffmann E. *Bioessays* 2011; **33**:529-537.
- 5 Reynolds A, Qiao H, Yang Y, et al. *Nat Genet* 2013; **45**:269-278.
- 6 Qiao H, Prasada Rao HB, Yang Y, et al. *Nat Genet* 2014; **46**:194-199.
- 7 Ahuja JS, Sandhu R, Mainpal R, et al. *Science* 2017; **355**:408-411.
- 8 Tsubouchi T, Roeder GS. *Science* 2005; **308**:870-873.
- 9 Rao HB, Qiao H, Bhatt SK, et al. *Science* 2017; **355**:403-407.
- 10 Zickler D, Kleckner N. *Semin Cell Dev Biol* 2016; **54**:135-148.