

the proteasome interior? And to what extent are alternative approaches to accessing the activities of the proteasome exploited *in vivo*? The proteasome is a remarkable machine, and there is still much to learn.

References

- Hershko, A. and Ciechanover, A. (1998) The ubiquitin system. *Annu. Rev. Biochem.* 67, 425–479
- Coux, O. *et al.* (1996) Structure and functions of the 20S and 26S proteasomes. *Annu. Rev. Biochem.* 65, 801–847
- Rechsteiner, M. (1998) The 26 S proteasome. In *Ubiquitin and the Biology of the Cell* (Peters, J.-M. *et al.*, eds), pp. 147–189, Plenum Press
- Bochtler, M. *et al.* (1999) The proteasome. *Annu. Rev. Biophys. Struct.* 28, 295–317
- Wenzel, T. and Baumeister, W. (1995) Conformational constraints in protein degradation by the 20S proteasome. *Nat. Struct. Biol.* 2, 199–204
- Löwe, J. *et al.* (1995) Crystal structure of the 20S proteasome from the archaeon *Tacidophilum* at 3.4 Å resolution. *Science* 268, 533–539
- Groll, M. *et al.* (1997) Structure of 20S proteasome from yeast at 2.4 Å resolution. *Nature* 386, 463–471
- Unno, M. *et al.* (2002) The structure of the mammalian 20S proteasome at 2.75 Å resolution. *Structure* 10, 609–618
- Hershko, A. *et al.* (2000) The ubiquitin system. *Nat. Med.* 6, 1073–1081
- Pickart, C.M. (2001) Mechanisms underlying ubiquitination. *Annu. Rev. Biochem.* 70, 503–533
- VanDemark, A.P. and Hill, C.P. (2002) Structural basis of ubiquitylation. *Curr. Opin. Struct. Biol.* 12, 822–830
- Liu, C.W. *et al.* (2003) Endoproteolytic activity of the proteasome. *Science* 299, 408–411
- Lee, C. *et al.* (2001) ATP-dependent proteases degrade their substrates by processively unraveling them from the degradation signal. *Mol. Cell* 7, 627–637
- Navon, A. and Goldberg, A.L. (2001) Proteins are unfolded on the surface of the ATPase ring before transport into the proteasome. *Mol. Cell* 8, 1339–1349
- Rape, M. and Jentsch, S. (2002) Taking a bite: proteasomal protein processing. *Nat. Cell Biol.* 4, E113–E116
- Lee, C. *et al.* (2002) Concurrent translocation of multiple polypeptide chains through the proteasomal degradation channel. *J. Biol. Chem.* 277, 34760–34765
- Groll, M. *et al.* (2000) A gated channel into the proteasome core particle. *Nat. Struct. Biol.* 7, 1062–1067
- Whitby, F.G. *et al.* (2000) Structural basis for the activation of 20S proteasomes by 11S regulators. *Nature* 408, 115–120
- Förster, A. *et al.* The pore of activated 20S proteasomes has an ordered 7-fold symmetric conformation. *EMBO J.* 22, 4356–4364
- Chu-Ping, M. *et al.* (1994) Identification, purification, and characterization of a high molecular weight, ATP-dependent activator (PA700) of the 20 S proteasome. *J. Biol. Chem.* 269, 3539–3547
- Kisselev, A.F. *et al.* (1999) The sizes of peptides generated from protein by mammalian 26 and 20S proteasomes. Implications for understanding the degradative mechanism and antigen presentation. *J. Biol. Chem.* 274, 3363–3371
- Zwickl, P. *et al.* (1999) An archaeobacterial ATPase, homologous to ATPases in the eukaryotic 26S proteasome, activates protein breakdown by 20S proteasomes. *J. Biol. Chem.* 274, 26008–26014
- Schmidtke, G. *et al.* (2000) Evidence for the existence of a non-catalytic modifier site of peptide hydrolysis by the 20S proteasome. *J. Biol. Chem.* 275, 22056–22063
- Kisselev, A.F. *et al.* (2002) Binding of hydrophobic peptides to several non-catalytic sites promotes peptide hydrolysis by all active sites of 20S proteasomes. Evidence for peptide-induced channel opening in the alpha-rings. *J. Biol. Chem.* 277, 22260–22270
- Touitou, R. *et al.* (2001) A degradation signal located in the C-terminus of p21WAF1/CIP1 is a binding site for the C8-subunit of the 20S proteasome. *EMBO J.* 20, 2367–2375
- Snyder, H. *et al.* (2003) Aggregated and monomeric alpha-synuclein bind to the S6' proteasomal protein and inhibit proteasomal function. *J. Biol. Chem.* 278, 11753–11759
- Coffino, P. (2001) Regulation of cellular polyamines by antizyme. *Nat. Rev. Mol. Cell Biol.* 2, 188–194
- Glickman, M.H. *et al.* (1998) A subcomplex of the proteasome regulatory particle required for ubiquitin-conjugate degradation and related to the COP9-signalosome end eIF3. *Cell* 94, 615–623
- DeLano, W.L. (2002) The PyMOL Molecular Graphics System. DeLano Scientific, San Carlos, CA, USA

0962-8924/\$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tcb.2003.09.001

Ran in the spindle checkpoint: a new function for a versatile GTPase

Hoi-Yeung Li^{1,*}, Kan Cao^{1,2,*} and Yixian Zheng^{1,2}

¹Department of Embryology, Carnegie Institution of Washington and Howard Hughes Medical Institute, Johns Hopkins University, 115 West University Parkway, Baltimore, MD 21210, USA

²Department of Biology, Johns Hopkins University, 115 West University Parkway, Baltimore, MD 21210, USA

The small GTPase Ran has a well-established role in nucleocytoplasmic trafficking. In recent years, the repertoire of Ran has expanded to include regulation of spindle assembly, formation of the nuclear envelope and DNA replication. Now, new studies further extend the role of Ran to regulating the spindle checkpoint during mitosis.

Extensive studies in nuclear trafficking have shown that Ran acts as a molecular switch to regulate the assembly and disassembly of nuclear transport receptor–cargo complexes, depending on the guanine-nucleotide-bound state of Ran [1,2]. The nucleotide exchange factor RCC1 catalyzes formation of RanGTP, whereas the hydrolysis of RanGTP is stimulated by RanGAP1 and RanBP1. Because RCC1 is chromatin-bound whereas RanGAP1 and RanBP1 are cytoplasmic, the concentration of RanGTP is high in the nucleus. This distribution of RanGTP ensures the directionality of nuclear import and export during interphase (Figure 1).

* These authors contributed equally to this work.
Corresponding author: Yixian Zheng (zheng@ciwemb.edu).