Slippery Substrates Impair ATP-dependent Protease Function by Slowing Unfolding

Analysis of data in Fig. 8 of Too et al. (1) was flawed by our naïve error, now corrected by Kraut (2). In fitting the first order rate constant $k_{\text{proc}}$ for processive degradation by the complex between ClpXP and a stalled substrate, we ignored simultaneous decay by a second process, exit of substrate. Modeling by Kraut (2) now supplies accurate values of pertinent rate constants and reverses a conclusion of Too et al. (1). Slippery sequences predominantly change processive unfolding kinetics, not substrate dissociation. We here observe science advancing as it should: attentively interactive, self-correcting.

The first 7 figures in the article by Too et al. (1) consider the composition of substrates that cause an ATPase motor to slip and the topologic escape mode of intermediates. This lab previously showed that amino acid sequences (of viral origin) containing only glycine and alanine residues can cause stalling of proteasome degradation and processivity failure. Production of degradation intermediate end products is promoted by the joint action of a hard-to-unfold domain and a sequence that impairs delivering the translocation force that impels unfolding (3, 4). In Ref. 1 we asked whether the peculiar sequence elaborated by a viral human pathogen can also thwart a bacterial ATPase. It can. Systematic investigation of the composition of sequences that cause slippage revealed that side chains of simple shape and small size promote polypeptide slipping. This result contrasts markedly with an alternate view, e.g. in Ref. 5, that regions of “low sequences complexity” produce slipping. Persistent use of “sequence complexity” terminology in Ref. 2 to describe slippery sequences dismisses and fails to engage the major findings of Too et al.

Philip Coffino¹, Priscilla Hiu-Mei Too⁵, and Jenny Erales³
Department of Microbiology and Immunology, University of California, San Francisco, California 94143

1. Too, P. H., Erales, J., Simen, J. D., Marjanovic, A., and Coffino, P. (2013) Slippery substrates impair function of a bacterial protease ATPase by unbalancing translocation versus exit. J. Biol. Chem. 288, 13243–13257
2. Kraut, D. A. (2013) Slippery substrates impair ATP-dependent protease function by slowing unfolding. J. Biol. Chem. 288, 34729–34735
3. Hoyt, M. A., Zich, J., Takeuchi, J., Zhang, M., Govaerts, C., and Coffino, P. (2006) Glycine-alanine repeats impair proper substrate unfolding by the proteasome. EMBO J. 25, 1720–1729
4. Zhang, M., and Coffino, P. (2004) Repeat sequence of Epstein-Barr virus-encoded nuclear antigen 1 protein interrupts proteasome substrate processing. J. Biol. Chem. 279, 8635–8641
5. Kraut, D. A., Israel, E., Schrader, E. K., Patil, A., Nakai, K., Nanavati, D., Inobe, T., and Matouschek, A. (2012) Sequence- and species-dependence of proteasomal processivity. ACS Chem. Biol. 7, 1444–1453

DOI 10.1074/jbc.L113.532622
¹E-mail: philip.coffino@ucsf.edu
²Present address: 688 Minor Hall, University of California, Berkeley, CA 94702.
³Present address: Campus de Luminy, 163 Ave. de Luminy, 13288 Marseille CEDEX 09, France.
Letters:
Slippery Substrates Impair ATP-dependent Protease Function by Slowing Unfolding

Philip Coffino, Priscilla Hiu-Mei Too and Jenny Erales

J. Biol. Chem. 2014, 289:3826.
doi: 10.1074/jbc.L113.532622

Access the most updated version of this article at http://www.jbc.org/content/289/6/3826

Find articles, minireviews, Reflections and Classics on similar topics on the JBC Affinity Sites.

Alerts:
- When this article is cited
- When a correction for this article is posted

Click here to choose from all of JBC's e-mail alerts

This article cites 5 references, 4 of which can be accessed free at http://www.jbc.org/content/289/6/3826.full.html#ref-list-1