LETTER

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_{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.*

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