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Evolution of the ubiquitin-activating enzyme Uba1 (E1)

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HIGHLIGHTS

- Ubiquitin tags thousands of proteins for destruction.
- Uba1 (E1) has evolved modestly from slime mold to humans.
- The kinetics of Uba1 (E1) are determined here by allometric interactions.
- Hydropathic pivot and hinge trends of Uba1 (E1) explain its evolution.

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ABSTRACT

Ubiquitin tags diseased proteins and initiates an enzyme conjugation cascade, which has three stages. The first-stage enzyme Uba1 (E1) has evolved only modestly from slime mold to humans, and is >14 times larger than Ub. Here we use critical point thermodynamic scaling theory to connect Uba1 (E1) evolution from yeast and slime mold to fruit flies and humans to subtle changes in its amino acid sequences.

1. Introduction

The ubiquitin-activating enzyme Uba1 (E1) constitutes the first step in the covalent cascade modification of target proteins with ubiquitin (Ub). Ubiquitin itself, discovered less than 50 years ago, tags thousands of diseased proteins for destruction [1,2]. It is small (only 76 amino acids), and is found unchanged in mammals, birds, fish and even worms. Because of its universality, Ub is a valuable proving ground for universal biophysical theories discussing protein amino acid sequences, structure and function [3]. Indeed key features of Ub functionality (hydropathic waves) were identified using critical point thermodynamic scaling theory [4]. The general biochemical logistics of Ub activation, conjugation and ligation are orchestrated sequentially by the Ub conjugation cascade of E1, E2 and E3 enzymes. Humans are known to harbor two E1, ∼30 E2 and ∼600 E3 enzymes in the Ub conjugation cascade [5]. While Ub is "perfect", Uba1 (E1) has evolved only modestly from slime mold to humans. The details of this evolution express several leading features of enzyme functionality. Uba1 (E1) is a large protein (>1000 amino acids), but it is readily treated by critical point thermodynamic scaling theory, with its firm foundations in statistical mechanics and its bioinformatically determined universal parameters [3]. It turns out that hydropathic waves are also useful for Uba1 (E1), which is >14 times larger than Ub.

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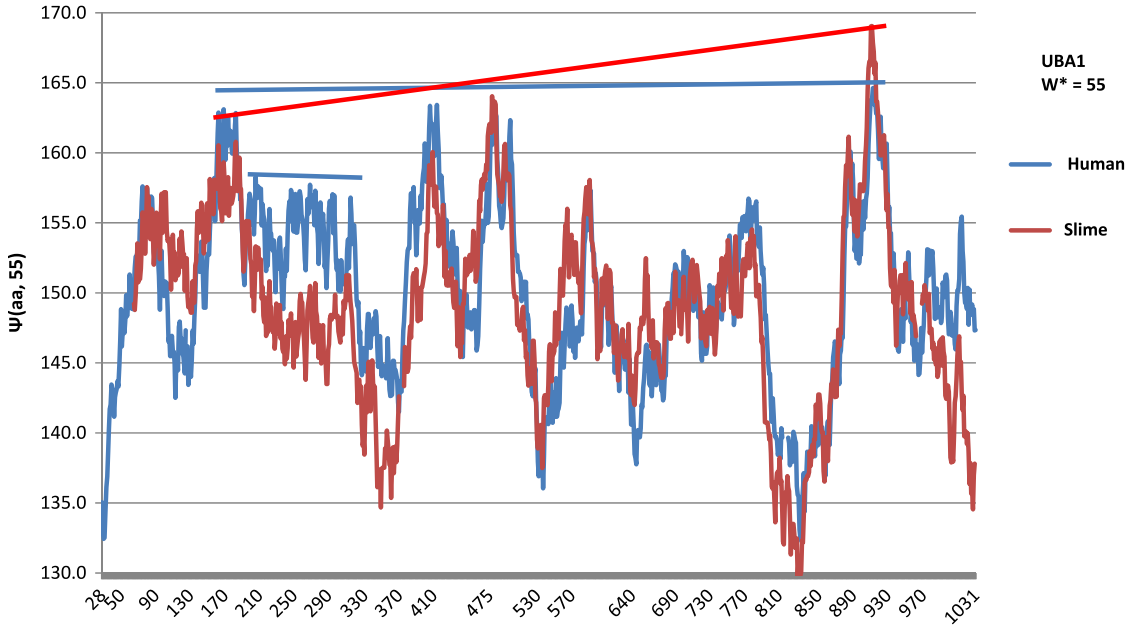

Fig. 1. The Ψ (aa, W^*) profiles for human and slime mold Uba1 (E1), using the modern MZ scale [7], which describes second-order (allosteric) evolutionary approaches to perfection (thermodynamic critical point [3]). A similarly successful value for W* using the standard KD classical (thermodynamically first-order) scale [6] was not found. Note the secondary leveling of the human profile between sites 200 and 330. The site numbering here is that of Uniprot P22314 (UBA_1HUMAN).

As before [3,4], all calculations are based on thermodynamically first- and second-order hydropathic Ψ (amino acid) scales [6,7], linearly scaled to a common center and a common range for each of the 20 amino acids. These are then converted to a triangular matrix Ψ (aa, W), where W is the length of a sliding window centered on each amino acid site. We have studied the range $1 \leq W \leq 75$, which is includes values of W much larger than the small value, fixed at $W \sim 5$, in most calculations using sliding windows [8]. Just as one focuses a microscope to optimize its image, one scans W to optimize its recognition of allometric regularities of hydropathic hot spots (hydrophobic extrema of Ψ (aa, W)) at special values of $W = W^*$.

2. Results

The hydrophobic extrema of neuroglobin form sophisticated patterns that are closely related to the evolution of specific species. For example, mouse and rabbit escape predators in different ways, and these differences are recognizable in their Ψ (aa, W^*) profiles [9]. There are several other examples already of proteins whose hydrophobic extrema form level sets. In Fig. 1 we plot the profiles of Uba1 (E1) for humans and slime mold. The choice $W^* = 55$ levels the human hydrophobic extrema, and simultaneously aligns the slime mold extrema linearly with a small tilt (about 15% of the overall range). Such excellent alignments (to within 1%) are unlikely and not accidental. For instance, the differences between the MZ and KD scales are small (85% correlation [10]), yet as Fig. 2 shows, the successful pivotal alignment with the MZ scale is lost with the KD scale.

Structural data are most complete for Uba1 (E1) yeast, and the human and yeast profiles are compared in Fig. 3. The differences are small, and are mentioned in the Fig. 3 caption. Before we compare the long-range ("allosteric") correlations of these figures, we show in Fig. 4 the results for fruit fly, which has a lifetime of days, not years. This implies that its Uba1 kinetics are $\sim 10^3$ faster than human Uba1 kinetics. It is plausible that the two hydrophilic minima discussed in Fig. 4, which are 3–6 lower values of Ψ (aa, W^*) (5%–10% of the full range) than in the human Ψ (aa, W^*), are good indicators of this kinetics acceleration.

3. Discussion

Before comparing our results with structural studies, we can turn to the Wiki on transition state theory (1935), which explains the reaction rates of elementary chemical reactions in terms of two parameters in one dimension. Structural studies contain information on the ground state, a minimum in configuration space, whereas rates are determined by the properties of transition states, technically also saddle points in configuration space. Both minima and saddle points are also thermodynamic critical points, where long-range attractive and short-range repulsive interactions are equal at the critical temperature, close to body temperature. Our conjecture here is that studying Ψ (aa, W^*) extrema, both the hydrophobic