The role of structural disorder in protein degradation *in vitro* and *in vivo*

Peter Tompa[1,2]
[1]VIB-VUB Center for Structural Biology, Brussels, Belgium
[3]Institute of Enzymology, Budapest, Hungary

Abstract

Structurally disordered proteins (IDPs) are prevalent in the proteome and often function by partner recognition and induced folding. Structural disorder has a high incidence in chaperones, in which it plays specific mechanistic roles, such as “entropic exclusion” and “entropy transfer” [1, 2]. When disordered chaperone fail in mitigating defects of protein folding, structural disorder comes to the rescue in another guise. Regulated protein turnover is regulated by specific signals (degrons), which we suggest to have a “tripartite” nature [3, 4]. Tripartite degrons comprise: (1) a primary degron that specifies substrate recognition by cognate E3 ubiquitin ligases, (2) secondary site(s) comprising a single, or multiple neighboring, poly-ubiquitinated lysine(s), and (3) a segment that initiates substrate unfolding at the 26S proteasome. We formally demonstrate that all three elements are linked with local structural disorder, which is prevalent even in cases when protein degradation is signaled by unorthodox mono-ubiquitination [5]. Our recent studies focus on demonstrating that interaction of any of these degron elements with protein partners – degron masking – can inhibit the ubiquitination and degradation of the protein, thus it can serve as a primary mechanism for regulating protein turnover in the cell.

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