Proteins in the cell are regularly degraded and replaced with newly synthesized copies. This regular turnover minimizes the accumulation of toxic damage and ensures a functional proteome throughout the cell’s lifetime. An elegant balance between translation and degradation rates maintains protein concentration within a cell and assigns each protein a specific half-life.

Whether and how do the intrinsic structural features affect the lifetime of a protein? Our work extends the realm of this question by distinguishing topology of eukaryotic proteins and their potential to oligomerize into multicomponent complexes as two master regulators of protein half-life in the cell, apart from previously known ubiquitinoylation sites and the presence of intrinsically disordered regions amenable to proteasomal engagement. We exploit the experimental genome-scale half-life data of yeast and mouse proteins and relative degradation rate data of human proteins, along with wide-ranging information about their 3D geometry and extensive biochemical characterization of the complexes they assemble into, to develop a theory demonstrating how a wide spectrum of structural constraints regulates protein half-life in the cell. Native topology acts as a molecular marker of monomeric protein’s mechanical resistance and regulates their half-life on a genomic scale. Sequestration into multimeric complexes elongates oligomeric protein half-life in the cell, probably by burying ubiquitinoylation sites and disordered segments required for proteasomal engagement. Diversification of topology and sequestration into non-identical sets of complexes are further exploited to alter protein half-life during evolution. This work not only evaluates the independent and combined influence of different structural constraints on protein half-life, and places them into genomic context, but further deepens our understanding of the designing principles of biological macromolecules.

Reference: