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Single Mutation Effect on Lysozyme Stability and Misfolding RUHONG ZHOU, IBM Thomas J. Watson Research Center — We propose a mechanism, based on an unprecedended 10+ microsecond molecular dynamics simulation, for the surprising misfolding of hen lysozyme caused by a single mutation (W62G). Our simulations of the wild-type and the mutant lysozyme in 8M urea solution at biological temperature (with both pH = 2 and pH = 7) reveal that the mutant structure is much less stable than the wild-type, with the mutant showing larger fluctuations and less native-like contacts. Analysis of local contacts reveals that the Trp62 residue is the key to a cooperative long-range interaction within the wild-type where it acts like a bridge between two neighboring basic residues. A native-like cluster or nucleation site can thus form near these residues in the wild-type, but not in the mutant. These findings, while supporting the general conclusions of a recent experimental study by Dobson and coworkers, provide a detailed but different molecular picture of the misfolding mechanism.

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