Destruction of long-range interactions by a single mutation in lysozyme

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Abstract

- We propose a mechanism, based on a 10-μs molecular dynamics simulation, for the surprising misfolding of hen egg-white lysozyme caused by a single mutation (W62G). Our simulations of the wild-type and mutant lysozymes in 8 M urea solution at biological temperature (with both pH 2 and 7) reveal that the mutant structure is much less stable than that of the wild type, with the mutant showing larger fluctuations and less native-like contacts. Analysis of local contacts reveals that the Trp-62 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. Thus, a native-like cluster or nucleation site can form near these residues in the wild type but not in the mutant. The time evolution of the secondary structure also exhibits a quicker loss of the -sheets in the mutant than in the wild type, whereas some of the -helices persist during the entire simulation in both the wild type and the mutant in 8 M urea (even though the tertiary structures are basically all gone). These findings, while supporting the general conclusions of a recent experimental study by Dobson and coworkers [Klein-Seetharam J, Oikama M, Grimshaw SB, Wirmer J, Duchardt E, Ueda T, Imoto T, Smith LJ, Dobson CM, Schwalbe H (2002) *Science* 295:1719–1722], provide a detailed but different molecular picture of the misfolding mechanism.

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