Misbehaving Proteins

Protein (Mis)Folding, Aggregation, and Stability

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Protein Folding, Misfolding, Stability, and Aggregation

An Overview

Regina M. Murphy[1,3] and Amos M. Tsai[2]

Protein misfolding and aggregation problems arise in diverse arenas. In the manufacture of commercial protein products, correctly folded proteins in stable formulations are critical for safety and efficacy. In the clinic, there is increasing awareness that protein aggregation is an underlying cause of several severe and chronic diseases. This chapter provides a brief background on the nature of folded and misfolded proteins and on the forces that drive protein folding, misfolding, and aggregation. We then give an overview describing the organization and contents of the remainder of this volume.

1. IMPORTANCE OF PROTEIN MISFOLDING AND AGGREGATION

1.1. Manufacture of Protein Products

In a typical biopharmaceutical production process there are many points at which protein aggregation can occur. A protein expressed in *Escherichia coli* often aggregates shortly after it is synthesized. With varying degrees of success, correctly folded active protein can be recovered by solubilization and refolding. When a recombinant protein is made in mammalian cells, the cellular machinery can process the protein such that solubility is often maintained at the time of harvest. However, successful synthesis in the bioreactor is far from a guarantee of a soluble final drug substance. Unwanted aggregation is a common by-product of rigorous purification processes. For instance, monoclonal

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