Chaperones of the Cell: Functions in Health and Disease

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Proteins – polymer chains of the 20 amino acid building blocks – are responsible for practically all cellular functions. In order to become biologically active, most proteins must fold into a defined three-dimensional conformation. Protein folding was originally thought to occur spontaneously, but the past decades have witnessed a paradigm shift in our understanding of this fundamental process. While the final fold of a protein is determined by its genetically encoded amino acid sequence, we now know that in the crowded environment of cells, newly-synthesized proteins depend on molecular chaperones (themselves proteins) to reach their folded states efficiently and at a biologically relevant time scale. Assistance of protein folding is provided by a network of chaperones which act to prevent misfolding and the formation of potentially toxic protein aggregates, often in an ATP-regulated mechanism. Molecular chaperones act by different mechanisms, with the so-called chaperonins serving as a particularly fascinating example. These large cylindrical complexes transiently encapsulate a single molecule of unfolded protein in a cage-like structure for folding to occur unimpaired by aggregation. Once folded, many proteins continue to require chaperone surveillance to retain their functional states, especially under conditions of cell stress. Failure of the chaperone machinery to maintain protein homeostasis, i.e. the conformational integrity and balance of the cellular proteome, facilitates the manifestation of diseases in which misfolded proteins form toxic aggregates. These disorders prominently include Alzheimer's and Parkinson's disease, as well as a range of other neurodegenerative pathologies. Seeking ways to activate chaperone machineries offers new therapeutic strategies for these currently incurable diseases.