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Chemical Chaperones: Mechanisms of Action and Potential Use

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Abstract An increasing number of studies indicate that low-molecular-weight compounds can help correct conformational diseases by inhibiting the aggregation or enable the mutant proteins to escape the quality control systems, and thus their function can be rescued. The small molecules were named chemical chaperones and it is thought that they nonselectively stabilize the mutant proteins and facilitate their folding. Chemical chaperones are usually osmotically active, such as DMSO, glycerol, or deuterated water, but other compounds, such as 4-phenylbutiric acid, are also members of the chemical chaperone group. More recently, compounds such as receptor ligands or enzyme inhibitors, which selectively recognize the mutant proteins, were also found to rescue conformational mutants and were termed pharmacological chaperones. An increasing amount of evidence suggests that the action of pharmacological chaperones could be generalized to a large number of misfolded proteins, representing new therapeutic possibilities for the treatment of conformational diseases. A new and exciting strategy has recently been developed, leading to the new chemical group called folding agonist. These small molecules are designed to bind proteins and thus restore their native conformation.

Keywords Chemical chaperones · Pharmacological chaperones · Conformational diseases · Protein misfolding · Quality control machinery

1 Chemical Chaperones

Chemical chaperones are small molecules with a common feature mimicking the chaperone function of molecular chaperones. Many osmolytes as well as compounds with the ability to bind to hydrophobic surfaces can rescue mutant proteins from aggregation or can help them to escape from quality