

FIGURE 3.1 Aggregation competes with productive protein folding. Aggregation of nonnative protein chains as a side reaction of productive folding in the crowded environment of the cell. Enhancement of aggregation and chain compaction by macromolecular crowding and effects of chaperones are indicated. U, unfolded protein chain released from ribosome; I, partially folded intermediate; N, native, folded protein. Crowding is also predicted to enhance the formation of amyloid fibrils. (Adapted from [6], with permission of Science AAAS.)

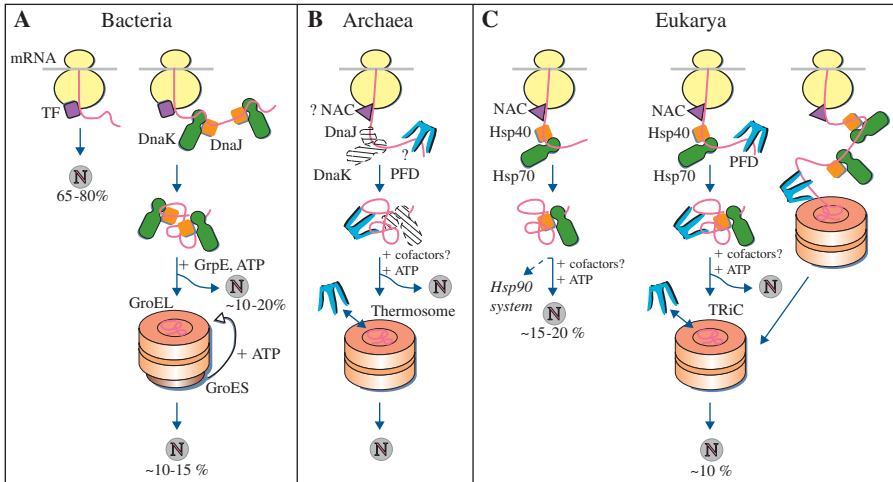


FIGURE 3.2 Chaperone pathways of protein folding in the cytosol. Models for the chaperone-assisted folding of newly synthesized polypeptides in the cytosol. (A) Bacteria. TF, trigger factor; N, native protein. Nascent chains probably interact generally with TF, and most small proteins (65 to 80% of total) may fold rapidly upon synthesis without further assistance. Longer chains (10 to 20% of total) interact subsequently with DnaK and DnaJ and fold upon one or several cycles of ATP-dependent binding and release. About 10 to 15% of chains transit the chaperonin system (GroEL and GroES) for folding. GroEL does not bind to nascent chains and is thus likely to receive a substantial fraction of its substrates after their interaction with DnaK. (B) Archaea. PFD, prefoldin; NAC, nascent chain-associated complex. Only some archaeal species contain DnaK/DnaJ. (C) Eukarya (the example of the mammalian cytosol). Like TF, NAC probably interacts generally with nascent chains. The majority of small chains may fold upon ribosome release without further assistance. About 15 to 20% of chains reach their native states in a reaction assisted by Hsp70 and Hsp40, and a fraction of these must be transferred to Hsp90 for folding. About 10% of chains are co- or posttranslationally passed on to the chaperonin TRiC in a reaction mediated by Hsp70 and PFD. (Adapted from [6], with permission of Science AAAS).

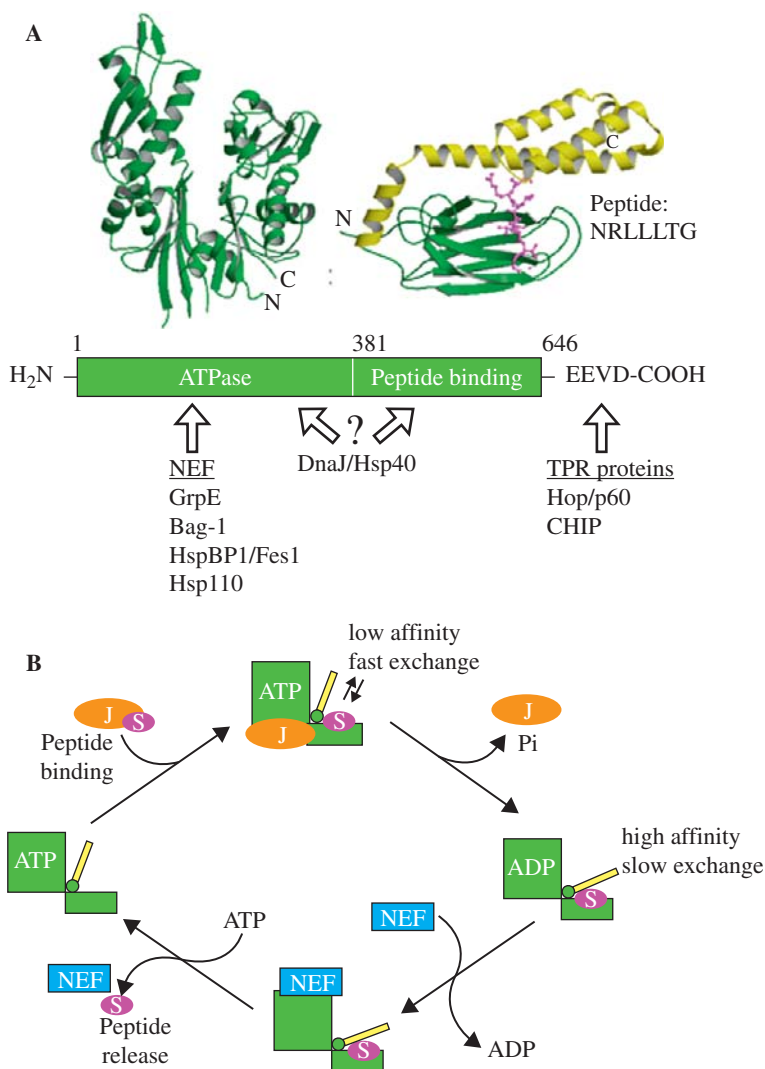


FIGURE 3.3 Structure and reaction cycle of the Hsp70 chaperone system. (A) (Top) Structures of the ATPase domain [58] and the peptide-binding domain [53] of Hsp70 shown representatively for *E. coli* DnaK. The α -helical latch of the peptide-binding domain is shown in yellow and a ball-and-stick model of the extended peptide substrate in pink. ATP indicates the position of the nucleotide binding site. The amino acid sequence of the peptide is indicated in single-letter code. (Bottom) The interaction of prokaryotic and eukaryotic cofactors with Hsp70 is shown schematically. Residue numbers refer to human Hsp70. NEF, nucleotide exchange factors (GrpE in case of *E. coli* DnaK; Bag, HspBP1, and Hsp110 in case of eukaryotic cytosolic Hsp70). TPR, tetratricopeptide repeat domain; Hop, Hsp organizing protein; CHIP, C-terminus of Hsp70 interacting protein. Only the Hsp70 proteins of the eukaryotic cytosol have the COOH-terminal sequence EEVD that is involved in binding of TPR cofactors [142]. (B) Hsp70 reaction cycle with Hsp70 colored as in (A). J, DnaJ; NEF, nucleotide exchange factor; S, substrate peptide. (Adapted from [6], with permission of Science AAAS.)

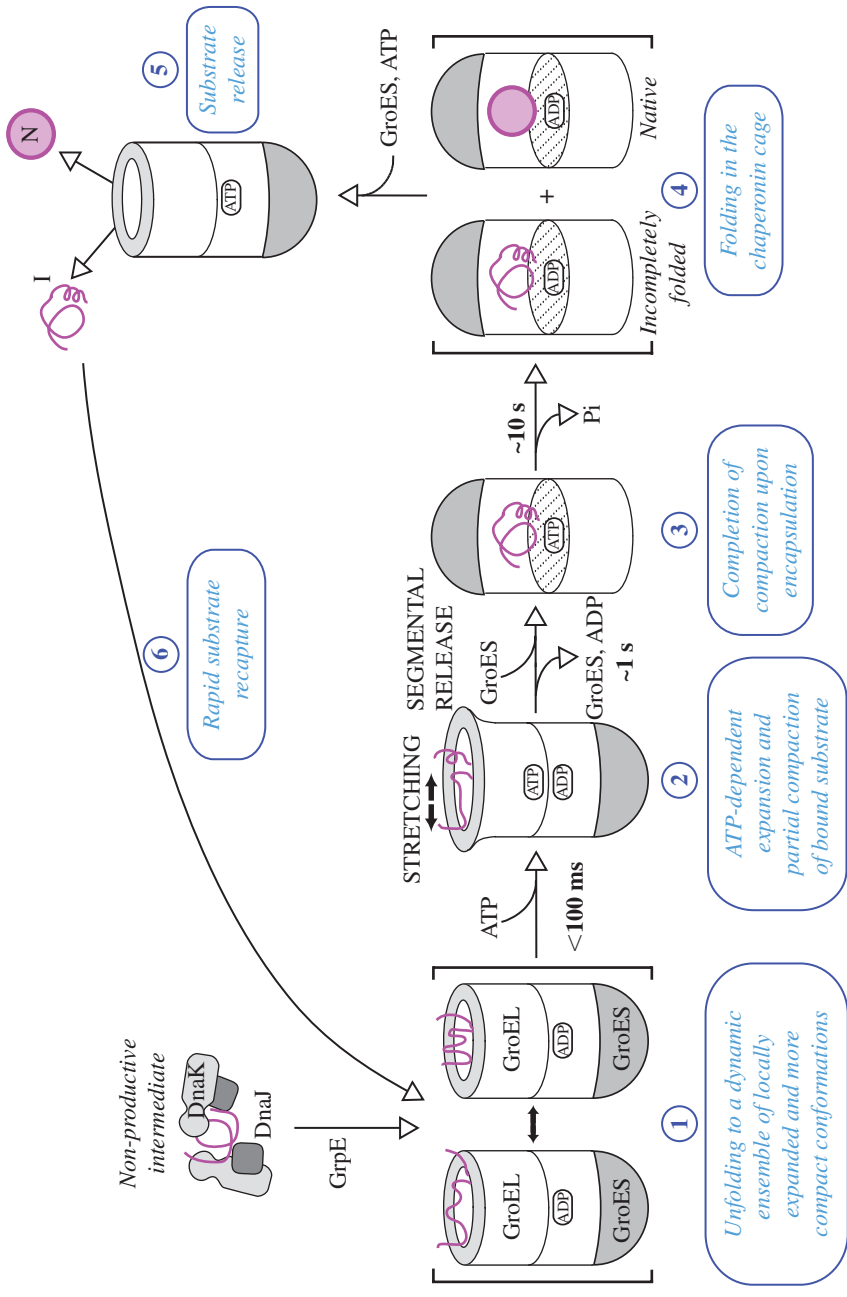


FIGURE 3.4 Protein folding with the GroEL–GroES chaperonin system. Working model summarizing the conformational changes in a substrate protein upon transfer from DnaK–DnaJ (Hsp70 system) to GroEL and during GroEL–GroES-mediated folding. Note that binding of a second substrate molecule to the open ring of GroEL in steps 4 and 5 is omitted for simplicity. N, native state; I, folding intermediate. (From [81], with permission of Elsevier).