pH-Dependent Dissociation of HdeA and HdeB Dimers

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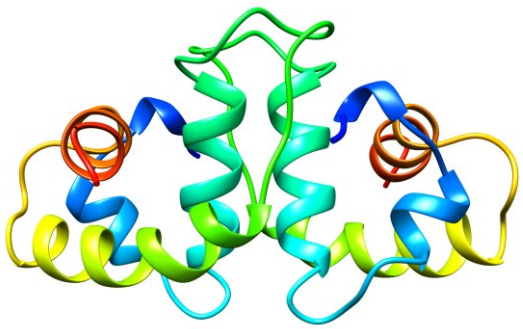
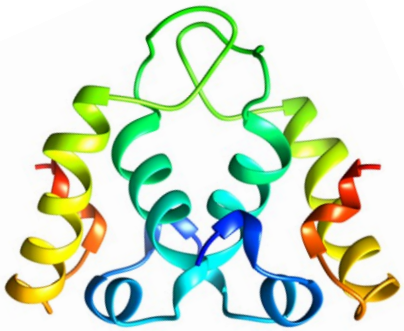
Enteric bacteria, like *Escherichia coli*, have to pass through the stomach before they can infect the intestinal mucosa. However, the lumen of the stomach is a very acidic environment with a pH usually between 1 and 3. To survive this acid trip, *E. coli* has evolved different systems to tolerate acid stress in the cytoplasm and periplasm, which is enveloped by an outer membrane permeable for protons. As consequence, the pH in the periplasm decreases rapidly to the same level as the environmental pH when *E. coli* enters the stomach and the proteins in the periplasm are vulnerable to acid-induced damage. In order to prevent denaturation and aggregation of periplasmic proteins, *E. coli* has two acid-activated chaperones, HdeA and HdeB, which support acid resistance in the periplasm. Their genes are encoded in the *hdeAB* operon in the genomic acid fitness island.

Despite their low sequence identity (< 20%), HdeA and HdeB monomers are structural homologues, which was proven by the crystal structures. However, the HdeA dimer (left picture) uses a different dimerization interface than the HdeB dimer (right picture). Both have in common that the well-folded dimers, which were mainly observed at neutral pH, are inactive. If the pH decreases, the dimers dissociate to partially disordered and chaperone-active monomers. These HdeA and HdeB monomers then bind to other proteins using a hydrophobic surface and prevent the aggregation of their substrates. After neutralization, HdeA monomers release these proteins and refold back into the inactive conformation.





In our study, we have investigated the behavior of the HdeA and HdeB dimers over a broad pH range. We developed, therefore, a new MD simulation protocol, which allows the imitation of pH titrating experiments resembling the entering of *E. coli* into the acidic stomach. For both proteins we were able to monitor their dissociation at low pH values and to characterize the titration properties of individual ionizable groups. The observed differences between HdeA and HdeB suggest a fine-tuning in the pH response of *E. coli*.

[1] W. Hong, Y. E. Wu, X. Fu, Z. Chang, *Trends Microbiol.*, **2012**, *20*, 328–335.
[2] A. K. Mates, A. K. Sayed, J. W. Foster, *J. Bacteriol.*, **2007**, *189*, 2759–2768.
[3] K. S. Gajiwala, S. K. Burley, *J. Mol. Biol.*, **2000**, *295*, 605–612.