H238N Mutant of Hsp47: Molecular Mechanism of Disrupted Collagen Binding

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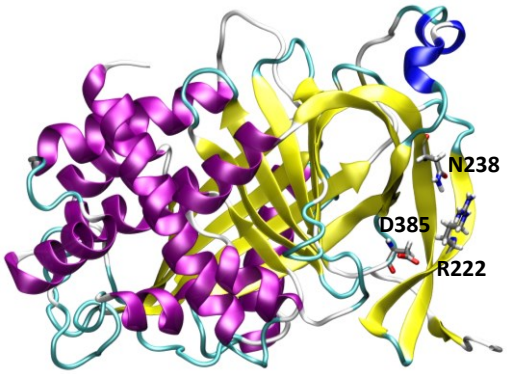
Heat shock protein 47 (Hsp47) is a molecular chaperone for collagen in humans. Although molecular chaperones typically recognize and bind nascent polypeptide chains and partially folded intermediates of proteins,[1] the Hsp47 molecule recognizes the folded conformation of collagen triple helices. Hsp47 can bind pH-sensitive to several types of collagen recognizing an arginine at the Yaa-position of a Xaa-Yaa-Gly triplet.

With the help of the crystal structure of Hsp47 in complex with trimeric collagen model peptides, it was shown that Hsp47 docks via a salt bridge to collagen.[2] This salt bridge is formed between the strictly conserved aspartate residue D385 of Hsp47 and the important arginine in the Xaa-Arg-Gly triplet. In addition to that salt bridge, the collagen interacts with the arginine residue R222 of Hsp47 via a hydrogen bond. Due to the fact that the collagen release from Hsp47 takes place in the *cis*-Golgi or ER-Golgi intermediate compartment and probably is accomplished by the lower pH in the Golgi compared with the ER, a pH-dependent substrate release mechanism based on a cluster of histidine residues was proposed.[2]



For the investigation of the pH-dependency of the collagen binding, the H238N mutant of Hsp47 was generated. However, the H238N mutant is not able to bind collagen. In order to investigate that unexpected experimental result, we performed constant pH MD simulations of the wild type and mutant form of Hsp47. The key finding is that the residues R222 and D385, which are involved in collagen binding in the wild type, are locked in an intramolecular salt bridge in the H238N mutant. This result offers a potential explanation for the behavior of the mutant on an atomic level.

References

[1] A. L. Fink, Physiol. Rev., **1999**, *79*, 425–449.
[2] C. Widmer, J. M. Gebauer, E. Brunstein, S. Rosenbaum, F. Zaucke, C. Drögemüller, T. Leeb, U. Baumann, Proc. Natl. Acad. Sci. U.S.A., **2012**, *109*, 13243–13247.