Poster Presentation

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Structure-Function Relationships of the Collagen-Specific Chaperone Hsp47

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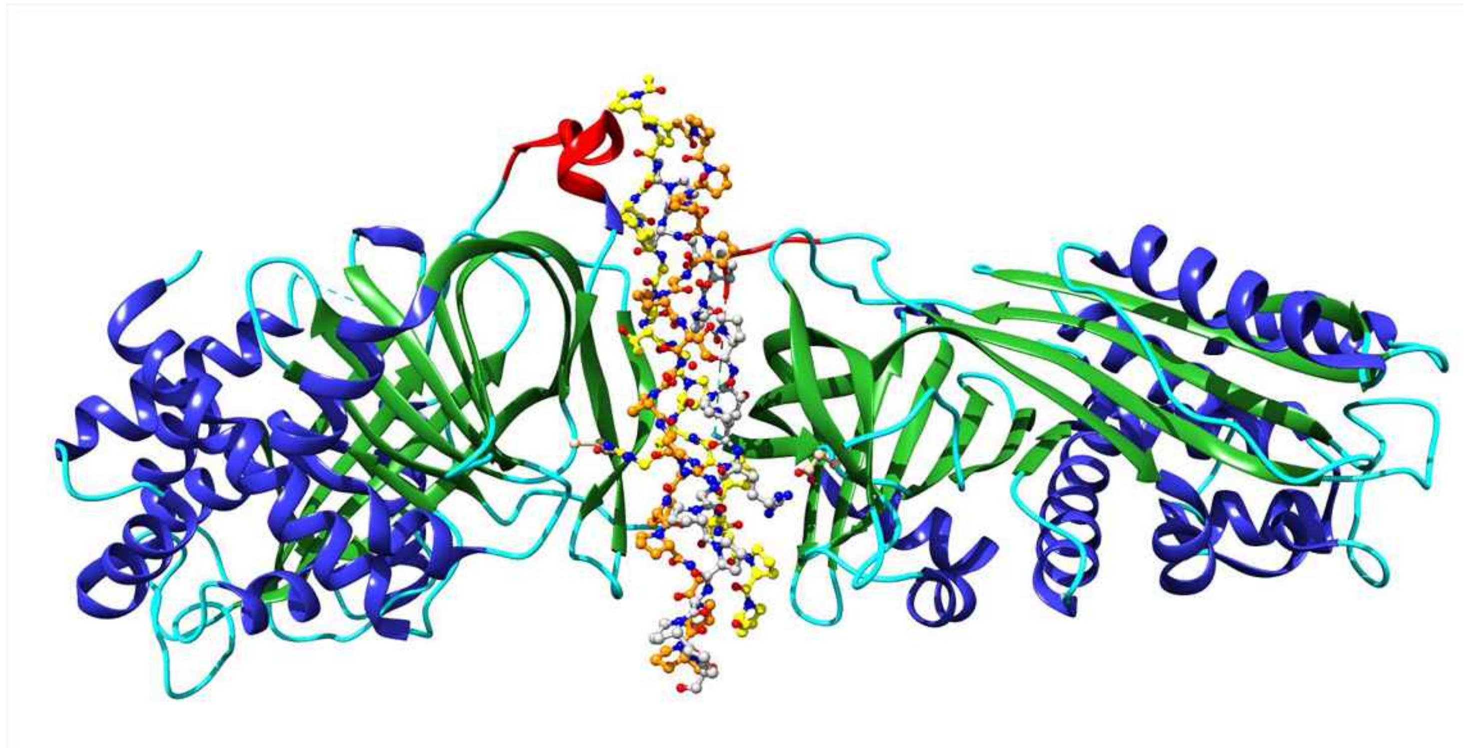
Hsp47 is an essential collagen specific chaperone that is crucial for proper formation of the collagen triple helix. KO-mice die at an early emybronic state and missense mutations are linked to severe forms of osteogenesis imperfecta (Ishida & Nagata, 2011). On the other hand, Hsp47 is strongly upregulated in fibrotic pathogenies and has in proof-of-principle studies been successfully targeted . It is a very unusual chaperone as it specifically recognises the folded conformation and releases ist client upon changes in pH and not in an ATP-cycle dependent manner. We have deterined the crystal structure of Hsp47 alone and in complex with homotrimeric collagen model peptides (Widmer et al., 2012), revealing a 2:1 stoichiometry Hsp47:collagen-trimer. The specific recognition of an arginine at the Y-position of the triple helix is explained by a saltbridge to an aspartic acid of Hsp47. Based on these structures we have undergone further investigation in order to shed light on the pH-triggered client release and to gain further insight into client recognition. We have undergone a systematic site-directed mutagenesis study of histidine residues in the binding interface. Interestingly, only few side-chains are predicted to change significantly their protonation state by a pH change from 7 to 6. We have furthermore investigated the influence of the reactive center loop, which is disordered in most crystal structures. An open question is how many binding sites for Hsp47 exist in procollagen. EM studies reveal a large number of specific binding sites, explaining how Hsp47 clamps and stabilises the triple helix and prevents lateral aggregation.

[1] *C. Widmer, J. Gebauer, E. Brunstein et al., Proceed Nat Academ Sci U.S.A., 2012, 109, 13243-7.,* ***[2]*** *Y. Ishida, K. Nagata, Methods Enzymol. 2011, 499, 167-82.*



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