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### *The impact of zinc on insulin fibrillation*

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Protein and peptide amyloid fibrillation is an increasingly significant field of research due to the growing prevalence and recognition of amyloid-related human diseases and in relation to therapeutic applications of peptide drugs where it constitutes a challenge during production and transportation. Insulin fibrillation represents a good model system for fibrillation studies and numerous pathways of insulin fibrillation have been suggested [1]. In general, partially unfolded insulin monomers (or dimers) are believed to be a vital prerequisite for prefibrillar association and eventually fibril formation (reviewed by Groenning in [1]). As fibrillation is commonly found to occur from the biologically active, monomeric form of insulin, zinc is considered to impede insulin fibril formation through stabilization of the physiological predominant hexameric forms. The question arises whether the assigned monomeric pathway at least to some degree could be a premise generated from the usual experimental procedure of inducing fibril formation; experiments that are conducted at acidic conditions with protonated histidine residues that cannot coordinate the Zn(II) ions, to induce the monomeric form believed to be the prerequisite of insulin fibrillation? However, in a more recent study [2], it was suggested that Zn(II) ions in contrast also inhibit fibrillation through differential stabilization of the insulin monomer. In the present work, we have investigated the presence and influence of zinc at well-defined stoichiometric levels at physiological pH, as well as the inner coordination sphere of Zn(II) during insulin fibril formation, using X-ray absorption spectroscopy (XAS). In addition, the results were validated with fiber diffraction studies, small-angle X-ray studies and ThT fluorescence studies.

[1] M. Groenning, S. Frokjaer, B. Vestergaard, *Formation, Curr. Protein Pept. Sci.*, 2009, 10, 5, 509-528., [2] A. Noormagi, J. Gavrilova, J. Smirnova, V. Tougu, P. Palumaa, *Biochem. J.*, 2010, 430, 511-518.

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