Mineralization Regulators: The role of fetuin – A in health and disease

Microcalcification is frequent in tissue remodelling. Ectopic calcification results when mineral deposition exceeds clearance. This is common in many metabolic and degenerative diseases. We showed that $\alpha_2$-HS glycoprotein/fetuin-A (genetic symbol AHSG) is an important regulator of ectopic calcification. Fetuin-A acts as a »mineral chaperone« on the systemic level stabilizing and clearing protein-mineral complexes. Fetuin-A deficient mice developed severe calcification of soft tissues especially when maintained on the genetic background DBA/2 or when challenged metabolically or surgically. Calcification severely impaired heart, lung and kidney function as well as reproduction. Fetuin-A deficiency in humans was associated with all-cause as well as cardiovascular mortality. Fetuin-A is a major non-collagen protein in bone. The bone phenotype of fetuin-A deficient mice indicated altered cell differentiation and structural changes in the mineralized bone matrix. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations. In the presence of fetuin-A this vesicle-mediated calcification process was greatly retarded suggesting that fetuin-A was cytoprotective and that fetuin-A deficiency triggered apoptosis with ensuing dystrophic calcification. The calcification phenotype in mice was not associated with apparent changes in calcium and phosphate homeostasis, but with a decreased inhibitory activity of the fetuin-A deficient extracellular fluid on mineral formation. The inhibition was mediated by the formation of a soluble colloidal complex of fetuin-A, calcium and phosphate, termed »calciprotein particles, CPP« in analogy to lipoprotein particles (LDL, HDL, etc.). Thus fetuin-A belongs to a novel class of protective plasma proteins with an important role in mineral metabolism »mineral chaperones«. I will present an update of our most recent Fetuin-A related research explaining the severe calcification phenotype of DBA/2, fetuin-A deficient mice as well as the foreshortened bone phenotype of C57BL/6, fetuin-A deficient mice.


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