Rocks, clots, and fertility:
Fetuin family serum proteins play vital roles
in cellular remodeling and systemic clearance of debris

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Fetuin-A, fetuin-B, histidine-rich glycoprotein HRG, and kininogen (KNG) originated by gene duplication and exon shuffling within the cystatin superfamily of genes. The genes form a cluster of type III cystatin proteins (hepatic, constitutively secreted) in the mouse and human genome. We study the structure-function relationship of fetuin-A, fetuin-B and HRG by gene knockout in mice.

Fetuin-A is a serum protein with biological activities in cell metabolism, bone mineral turnover and innate immunity. Fetuin-A was shown to mediate apoptotic cell clearing and particle phagocytosis ex vivo. Using gene knockout technology we demonstrated that fetuin-A prevents soft tissue mineralization. Fetuin-A forms a colloidal complex with calcium phosphate called calciprotein particles, CPPs in analogy to the well established lipoprotein particles. Fetuin-A acts as a »mineral chaperone« stabilizing and clearing protein-mineral complexes. Combining fetuin-A deficiency (mineral clearing) with apolipoprotein E deficiency (lipid clearing) we created mice with calcifying atherosclerosis as a model of this major human disease. Fetuin-A deficient mice were also partially protected from *Plasmodium berghei* infection.

Fetuin-B deficient mice are female infertile suggesting a role of fetuin-B in oocyte maturation and fertilization. We demonstrated that fetuin-B inhibits with nM affinity the zona protease ovastacin thus preventing premature zona pellucida hardening.

Using knockout mice for HRG we showed that HRG regulates contact-initiated blood coagulation, effectively functioning as a soluble pH and Zn-dependent KNG antagonist. In addition to their functions in hemostasis, KNG and HRG serve as regulators of angiogenesis. HRG deficiency strongly modified antimicrobial yeast and bacterial defense reactions as well as cancer progression.

Thus fetuin family proteins modify mineral homeostasis, blood clotting, lipid metabolism, debris clearing and fertilization, linking carrier protein function with innate immunity and biological remodeling.

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Willi Jahnen-Dechent studied biology at Johannes-Gutenberg-University Mainz. He received his PhD from the University of Cologne in 1986 for doctoral work performed at the Max-Planck-Institute for Plant Breeding on plant-pathogen interactions (with Klaus Hahlbrock). He worked three years as a post-doctoral research fellow on plant cell recognition at University of Melbourne (with Adrienne Clarke), at the Ludwig Institute for Cancer Research Melbourne (with Richard Simpson), Australia and at Amherst University of Massachussetts, U.S.A. (with Robert Bernatzky). Upon returning to Germany in 1990 he switched from Plant Molecular Biology to Biomedical Research and became Assistant Professor at the Institute for Physiological Chemistry (with Werner Müller-Esterl) starting his work on the fetuin family of serum proteins. In 1999 he was appointed Professor of Cell and Molecular Biology at Interfaces at the Department of Biomedical Engineering, Medical Faculty of RWTH Aachen University.