Heterodimers of proteoglycans and matrix metalloproteinase 9

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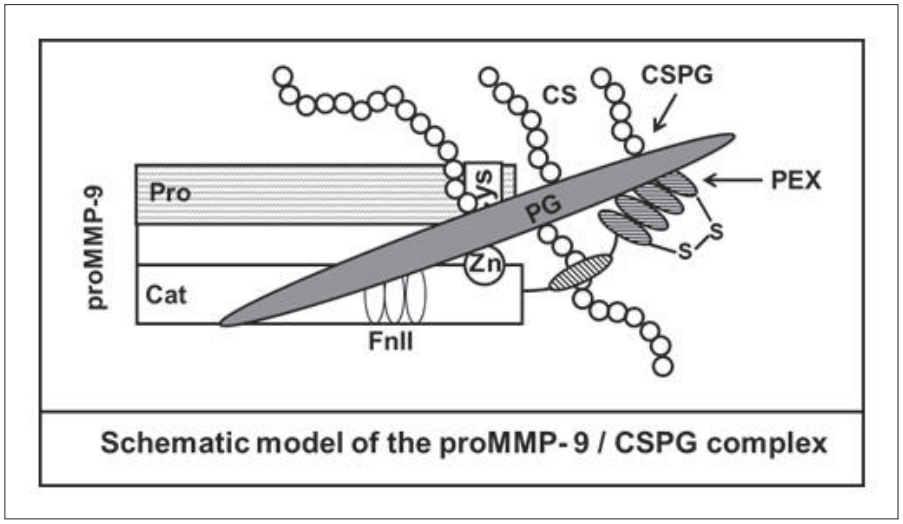
Lars Uhlin-Hansen was educated medical doctor from the University of Tromsø (UiT), Norway, in 1982. He started as a research fellow in 1985 and in 1987 he got a position as associated professor at Department of Biochemistry, UiT. In 1996 he started specialization in clinical pathology and since 2003 he has been a senior consultant pathologist at the University Hospital North Norway with the responsibility for diagnostic hematopathology. He also has the responsibility for the forensic pathology in Northern Norway and regularly works as an expert for the police and the court. In 2004 he was appointed professor, Head of Department of Pathology, UiT, and from 2009 Head of Tumor Biology Research Group. He has had several sabbaticals at foreign research institutions. From 1991-1992 he was a visiting fellow, Bone Research Branch, National Institute of Dental Research, National Institutes of Health, Bethesda. He was a visiting scientist at US Food and Drug Administration, Bethesda, from 1997-1998. He has also been a visiting pathologist, Hotel Dieu, Paris, and a visiting professor, Institute of forensic medicine, University of Copenhagen. The first years of his scientific career he studied proteoglycans in mononuclear phagocytes. Later the research has mainly focussed on matrix metalloproteinases and tumor biology.

Matrix metalloproteinases (MMPs) constitute a family of 23 proteins. They are zinc and calcium dependent, and together they can degrade most extracellular matrix (ECM) proteins. In addition, the MMPs can process a large number of non-ECM proteins such as growth factors, cytokines, chemokines and proteinase inhibitors. The MMPs are built up of various domains, modules and motifs. In addition to the pro- and catalytic domains, most MMPs contain a C-terminal hemopexin-like domain (PEX). The two gelatinases MMP-9 and MMP-2 also contain a unique module consisting of three fibronectin II-like (FnII) repeats in their catalytic region. This module is involved in the binding of some substrates and may facilitate the localization of the MMP to connective tissue matrices. The FNII repeats also act as exosites (noncatalytic sites) in the degradation of some substrates.

Interaction between MMPs and other matrix molecules may influence the enzyme activity by various mechanisms, including hiding existing exosites or exposure of new exosites. Several research groups have described interactions between MMPs and proteoglycans (PG)/glycosaminoglycans. Recently Kayoko Oguri and co-workers found that syndecan-2 acted as a suppressor for MMP-2 activation at the surface of lung carcinoma cells, and that this effect was mediated through the heparan sulfate (HS) side chains of syndecan-2. Further, their experiments indicated that the interaction between HS and MMP-2 reduced the metastatic potential of the cancer cells. The same research group found that MMP-9 bound to HS chains of glypican-like PGs on the surface of colon carcinoma cells. The MMP-9/PG complexes were concentrated on tips of cellular podia and played a role in motility of the cells. James B. McCarthy and coworkers found that both MT3-MMP and proMMP-2 bound to chondroi-



Schematic model of the proMMP-9 / CSPG complex

tin sulfate (CS) chains linked to PGs on the surface of melanoma cells. It was suggested that the binding to CS presented proMMP-2 to its membrane-bound activator. Both the catalytic and the hinge regions of MT3-MMP interacted with the CS chains, whereas proMMP-2 interacted through the HPX domain. The authors suggest that CS expressed at the surface of the tumor cells facilitate the activation of proMMP-2, thereby enhancing invasion and metastasis.

MMP-9 is produced as a monomer as well as various dimer forms. The homo-dimer, as well as several of the hetero-dimers are reduction sensitive and hence they are not dissociated in the presence of SDS. This suggests that the molecules are either covalently linked to each other through disulfide bonds or through a very strong reversible interaction where intramolecular disulfide bonds are essential. In the myeloid leukemic cell-line THP-1, we discovered a new type of reduction sensitive hetero-dimer, where pro MMP-9 is linked to the core protein of one or several CSPGs. We found that both the C-terminal PEX domain and the FnII module of the enzyme are involved in the linkage of MMP-9 to the CSPG core protein.

In vitro reconstitution of the pro MMP-9/CSPG complex has revealed the nature of the interactions between the two protein molecules. Further, the results show that the core protein of serglycin, which is a main CSPG synthesized by THP-1 cells, forms a complex with MMP-9. The binding of proMMP-9 to CSPG alters several biochemical properties of the enzyme, such as activation and binding to macromolecular substrates. The potential biological roles of the MMP-9·CSPG complexes will be also discussed.

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