Markku I. Tammi

Profile

Markku Tammi is a cell biologist who has worked on proteoglycans, lately on hyaluronan and its involvement in disease. He obtained M.D. in the University of Turku in 1975, followed by Ph.D. in 1979 with a thesis entitled "Arterial Glycosaminoglycans in Atherogenesis". After dissertation, until 1994, he worked with Prof. Heikki Helminen in the University of Kuopio on proteoglycans of articular cartilage, especially their response to joint loading. During 1984-1986 he made a postdoctoral fellowship in the University of California in Berkeley, studying yeast glycoproteins with Prof. Clinton Ballou. In 1994-1996 he joined, together with his wife Raija Tammi, M.D. Ph.D, Dr. Vincent Hascall's laboratory in Lerner Research Institute, Cleveland, to establish a new organotypic model for research on hyaluronan metabolism and functions in skin epidermis. After returning to Kuopio, the work was continued to show that hyaluronan as a major epidermal matrix molecule is strongly involved in keratinocyte migration, proliferation and differentiation, and epidermal wound healing. During the last 15 years, collaborating with local clinicians, they have also demonstrated that hyaluronan accumulates in certain cancers and forms a strong risk factor for unfavourable prognosis. Currently, his major interest is in the regulation of hyaluronan synthesis, both at transcriptional and posttranslational levels, and possibilities to use this information for diagnostic and therapeutic use. The work has resulted in a discovery of the key role of cellular UDP-GlcNAc concentration as a substrate for hyaluronan synthesis, and as a regulator of hyaluronan synthase transcription, and a modifier of HAS enzyme activity, the latter two via cytosolic protein O-GlcNAc modifications.

Regulation of hyaluronan synthesis and its importance for tissue remodeling and cancer

Markku I. Tammi, M.D., Ph.D.
Professor, Institute of Biomedicine,
School of Medicine, University of Eastern Finland, FINLAND

Hyaluronan is a multimillion molecular mass, linear, non-sulfated glycosaminoglycan with a repeating structure of [β1->3GlcNAc -β1->4GlcUA]. It is not attached to a core protein, but is synthesized as a free chain that runs out of the cell through a pore in plasma membrane, the pore formed by hyaluronan synthases (HAS1-3), the transferases that construct this polysaccharide using cytosolic UDP-sugars as substrates[1]. This unique way of secretion results in a cell surface glycocalyx, several micrometers thick[2)3)], and eventual release of hyaluronan into extracellular space where it organizes the matrix by aggregating with specific proteoglycans and forming transient cross-links with other matrix proteins.

Besides a lubricant and space filler between the cells and fibrous matrix components, hyaluronan has been recognized as an important signaling molecule, governing processes like cell migration, proliferation, inflammation, and malignant growth. In general, whenever tissues undergo remodeling, whether it be embyonic development, wound healing, or cancer, hyaluronan synthesis is activated. Expression of the three *Has* genes are subject to regulation by multiple stimuli, like growth factors, cytokines, prostaglandings, and hormones[1].

As the only *Has* with its deletion embryonically lethal, *Has2* regulation has received most interest. *Has2* promoter contains several response elements accounting for the influences of the inflammatory and growth promoting effectors mentioned above[1]. In addition, *Has2* expression is strongly modulated by the metabolic state of the cell, mediated by AMPK activity and cellular glucose supply, the latter through UDP-GlcNAc content and consequent *O*-GlcNAc-signaling (Figure 1)[4)5)].

Besides influencing *Has2* gene expression[5], UDP-GlcNAc content and *O*-GlcNAc-signaling have also more direct effects on HAS2 activity and hyaluronan synthesis. As a HAS substrate UDP-GlcNAc can either stimulate or inhibit hyaluronan synthesis, according to its cellular content[4]. In addition, HAS2 itself contains *O*-GlcNAc-moieties, which increase the stability or enzymatic activity of HAS protein (Fig.1). Furthermore, especially UDP-Glc secreted or leaked from cells stimulate *Has2* expression by activating a G-protein coupled UDP-sugar receptor. Thus, glucose and its UDP-sugar metabolites are strongly involved in the regulation of hyaluronan synthesis at multiple levels.
We have shown that hyaluronan accumulation in malignant tumors like breast, prostate, gastric, colon and ovarian cancers is an unfavourable prognostic factor for patient survival[6]. Immunohistochemical and real-time RT-PCR analyses of the HAS enzymes done in breast, ovarian and endometrial cancers have not revealed unequivocal correlation with hyaluronan content, suggesting that mechanisms other than gene expression are also involved. We are currently exploring the possibility that the aerobic glycolysis typical for cancer cells (Warburg effect), associated with high glucose uptake, contributes to the hyaluronan deposits via enhanced UDP-sugar supply. Hyaluronan and its synthesis are recognized as novel targets of therapy in cancer, but perhaps also in other chronic, low intensity inflammatory processes in which hyaluronan synthesis is increased, metabolic syndrome and arterial diseases as examples.

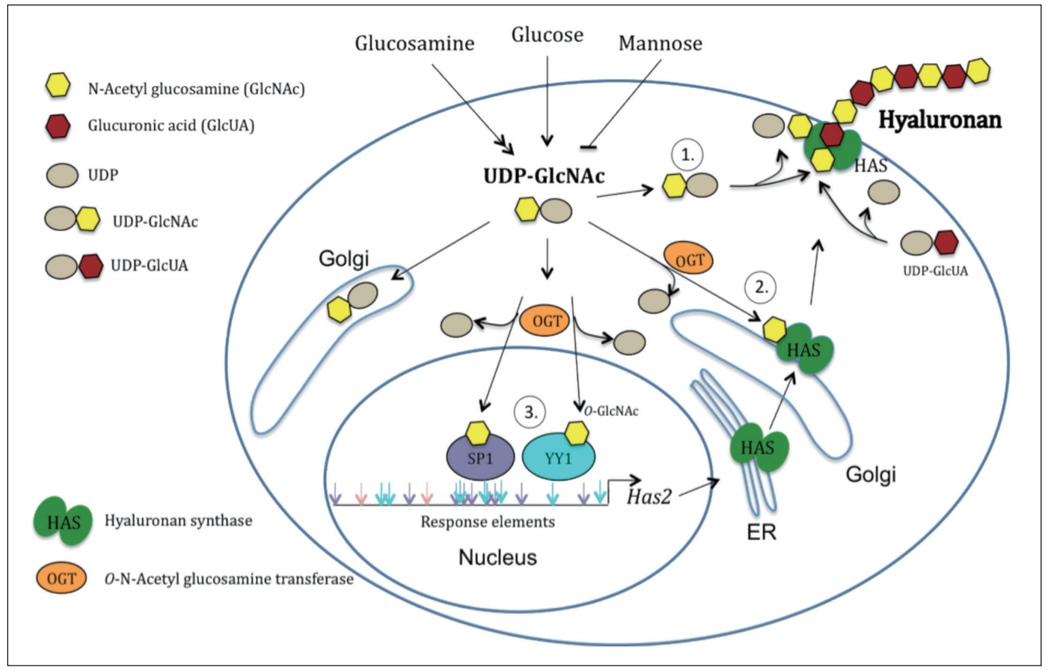

Figure 1. Multiple roles of UDP-GlcNAc in hyaluronan synthesis.
① As a substrate of HAS enzymes UDP-GlcNAc concentration has a direct influence on the rate of hyaluronan synthesis.
② With UDP-GlcNAc abundance, HAS serine/threonine residues are subject to modification by *O*-GlcNAc, mediated by OGT and resulting in enhanced enzymatic activity of HAS.
③ The cellular content of UDP-GlcNAc influences the level *O*-GlcNAc modifications in the transcription factors SP1 and YY1, which in turn control *Has2* gene expression. The cellular content of UDP-GlcNAc is increased by feeding cells with glucose or even more with glucosamine, and decreased by mannose. UDP-GlcNAc is synthesized in cytosol, where it is used for hyaluronan synthesis and *O*-GlcNAc modifications by OGT. Golgi membrane transporters are expected to maintain a high levels of UDP-sugars in this compartment despite concentration fluctuations in the cytosol.

Keywords: hyaluronan, glucose, UDP-GlcNAc, *O*-GlcNAc transferase, cancer

References

1) Tammi RH, Passi AG, Rilla K, Karousou E, Vigetti D, Makkonen K, Tammi MI. Transcriptional and posttranslational regulation of hyaluronan synthesis. *FEBS J.* (278): 1419-1428, 2011.
2) Kultti A, Rilla K, Tiihonen R, Spicer AP, Tammi RH, Tammi MI. Hyaluronan synthesis induces microvillus-like cell surface protrusions. *J Biol Chem* (281):15821-15828, 2006.
3) Rilla K, Kultti A, Tammi M, Tammi R. Pericellular hyaluronan coat visualized in live cells with a fluorescent probe is scaffolded by plasma membrane protrusions. *J Histochem Cytochem* (56): 901-910, 2008.
4) Jokela TA, Jauhiainen M, Auriola S, Kauhanen M, Tiihonen R, Tammi MI, Tammi RH. Mannose inhibits hyaluronan synthesis by downregulation of the cellular pool of UDP-N-Acetylhexosamines. *J. Biol. Chem.* (283):7666-7673, 2008.
5) Jokela TA, Makkonen KM, Oikari S, Kärnä R, Koli E, Hart GW, Tammi RH, Carlberg C, Tammi MI. Cellular content of UDP-N-Acetylhexosamines controls hyaluronan synthase 2 expression and correlates with *O*-GlcNAc modification of transcription factors YY1 and SP1. *J Biol Chem* (286): 33632-33640, 2011.
6) Tammi R, Kultti A, Kosma V-M, Pirinen R, Auvinen P, Tammi M. Hyaluronan in human tumors: Pathobiological and prognostic messages from cell-associated and stromal hyaluronan. *Semin Cancer Biol* (18): 288-295, 2008.