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Session 6 "Hyaluronan and Cell Interaction"

Metabolic fate of orally administered hyaluronan

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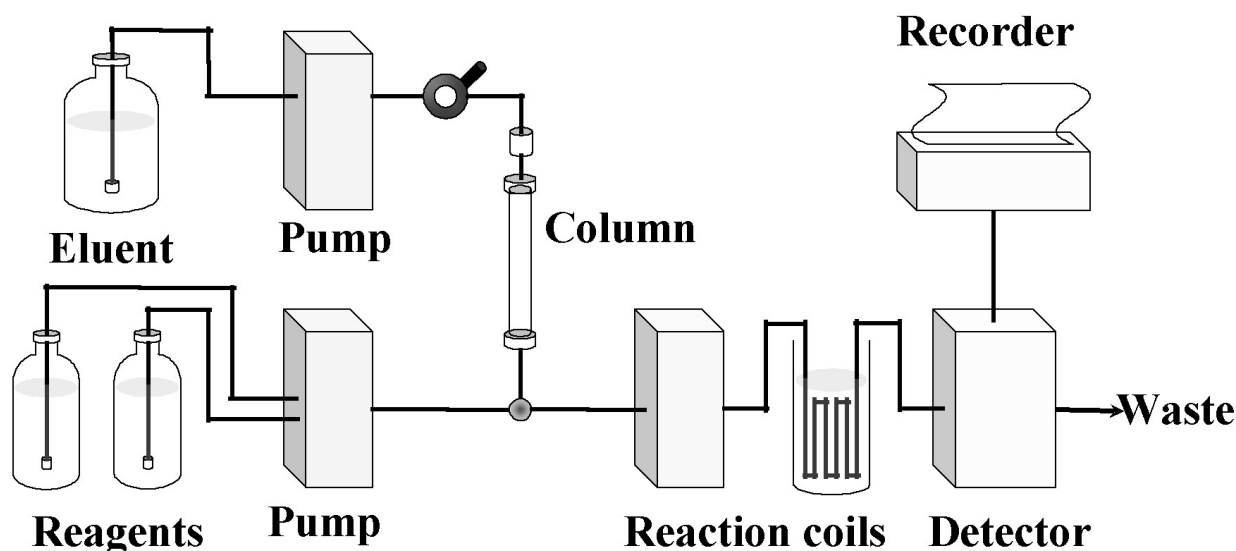


Toshihiko Toida graduated in Analytical Pharmaceutical Chemistry in 1978 at Chiba University, Faculty of Pharmaceutical Sciences, and obtained his Ph.D. in Bio-analytical Chemistry in 1983 at the same University. From 1983 to 1989, he was Research Associate/Lecturer in the Department of Biochemistry in Teikyo University, College of Medicine directed by Professor Ineo Ishizuka, and he was focusing on the structure and function of acidic glycosphingolipids. From 1989 to 2003,

he was Associate Professor in Chiba University, Faculty of Pharmaceutical Sciences, directed by Professor Toshio Imanari, and he has been working on the structure and function of glycosaminoglycans/proteoglycans. He has spent a sabbatical year at Professor Robert Linhardt's laboratory in the University of Iowa, College of Pharmacy in 1996. In 2003, he was promoted to Professor at Chiba University. His main research interests are now focusing on the structures and physiological functions of sulfated polysaccharides from the natural products, especially the effects of orally administered polysaccharides on immune system

The postcolumn HPLC system for determination of hyaluronan using 2-cyanoacetamide and NaOH as fluorogenic reagents.

(A. Mada, H. Toyoda and T. Imanari: "Utility of a carbon column for high-performance liquid chromatographic separation of unsaturated disaccharides produced from glycosaminoglycans." *Anal. Sci.* (1992), 8, 793-797.)



Chondroitin sulfate (CS) and hyaluronan (HA) are glycosaminoglycans widely distributed in animal tissues, which have anti-inflammatory and chondroprotective properties. Oral administration of CS and/or HA are widely used for treatment of osteoarthritis, but are highly controversial because their mode of action is unclear and clinical trials have provided contradictory results. For example, the researchers involved in the NIH GAIT (Glucosamine/chondroitin Arthritis Intervention Trial; <http://nccam.nih.gov/research/results/gait/>) project recently reported that CS combined with glucosamine provided statistically significant pain relief compared to placebo, *i.e.*, about 79 percent had a 20 percent or greater reduction in pain versus about 54 percent for placebo for a subset of participants with moderate-to-severe pain by osteoarthritis. According to the researchers, however, because of the small size of this subgroup these findings should be considered preliminary and need to be confirmed in further studies. Consequently, the effect of CS for treatment of osteoarthritis is still unclear. We also found that few amount of orally administered CS (MW_{avg}, 15,000, from bovine tracheal cartilage) to mice could be detected in blood plasma. On the other hand, we reported previously that chondroitin 4-sulfate (CS-A) up-regulates the antigen-specific Th1 immune response of murine splenocytes sensitized with ovalbumin *in vitro*, and that CS suppresses the antigen-specific IgE

responses (*Immunol. Lett.* (2002) 84, 211-216). We also demonstrated that a specific sulfation pattern of the CS polysaccharide was required for the Th1-promoted activity, as other polysaccharides such as dextran and dextran sulfate did not significantly induce this activity. While the presence of some *O*-sulfo groups appeared to be essential for activity, CS-A and synthetically prepared partially *O*-sulfonated CS induced higher Th1-promoted activity than synthetically prepared, fully *O*-sulfonated CS (*Biochem. J.* (2004) 382, 269-278). On the contrary, HA did not show any activities on immune systems of mice (unpublished data).

Despite its structural simplicity, HA exhibits a broad spectrum of biological activities by interacting with a large body of hyaluronan-binding proteins and proteoglycans. The Serum-derived Hyaluronan-Associated Protein (SHAP) is covalently bound to HA, and the SHAP-HA complex represents the only case with covalent HA-protein crosslinking. Especially, Professor Koji Kimata and co-workers have published many interesting and important papers on biological functions of SHAP-HA complex. Based on these previous observations, we orally administered HA to mice and found that HA has increased SHAP-HA level in blood plasma. In this short presentation, a part of metabolic fate of orally administered HA (MW_{avg}, 20,000, from *Streptococcus zooepidemicus*) will be shown based on analytical approach.

Keywords: hyaluronan, metabolic fate, oral administration, SHAP-HA complex