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Session 6 "Hyaluronan and Cell Interaction"

Applied research on an inhibitor of hyaluronan synthesis

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Keiichi Takagaki obtained his MS degree from the Faculty of Science, Hirosaki University, Japan in 1980. He started his professional career as a Research Associate in the Department of Biochemistry, Hirosaki

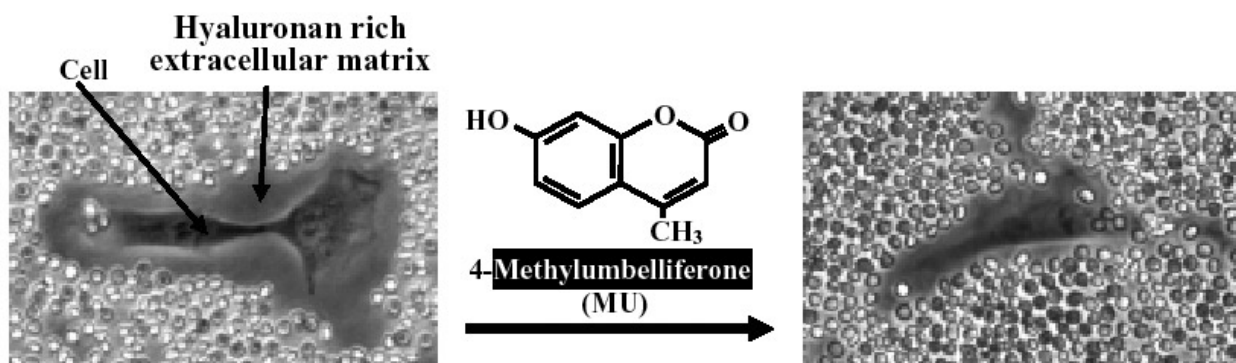
University School of Medicine, and obtained a Ph.D. at the same university in 1990 under the supervision of Prof. Masahiko Endo. In 1986 and 1987, he studied with Dr. Karl Schmid at Boston University Medical Center. He was Assistant Professor in the Department of Biochemistry, Hirosaki University from 1990-1991, and Associate Professor from 1991-2002. From 2002, he has been Professor in the same department. His research interests are the biological functions and structures of proteoglycans and glycosaminoglycans, especially chondroitin sulfate proteoglycans. His recent major research has focused on the glycotecnological approach for proteoglycan synthesis with reconstructed glycosaminoglycans using endo-type glycosidases.



Ikuko Kakizaki graduated from the Faculty of Pharmaceutical Sciences, Hokkaido University, Japan in 1992, and received her MS degree from the graduate school of the same university in 1994. She graduated from the graduate school of Hirosaki

University, School of Medicine, Japan and received her Ph. D in 1998. She started her professional career as an Instructor in the Department of Biochemistry, Hirosaki University, School of Medicine in 1998 under the supervision of Prof. Masahiko Endo, and from 2002, under Prof. Keiichi Takagaki. She studied in the Department of Biochemistry and Molecular Biology, Pennsylvania State University College of Medicine for 8 months in 2003 under the supervision of Profs. Veer P. Bhavanandan and D. Channe Gowda. Her research interests are the biosynthesis and degradation of glycosaminoglycan, especially hyaluronan. Her recent research has focused on the inhibitor of hyaluronan synthesis

Figure 1 Inhibition of hyaluronan rich extracellular matrix formation by MU Cell 4-Methylumbelliferone(MU)
Hyaluronan rich extracellular matrix



Hyaluronan is a high molecular weight glycosaminoglycan composed of repeating disaccharide units of -GlcUA β -(1 \rightarrow 3)-GlcNAc β -(1 \rightarrow 4)-. This molecule is one of the major components of the extracellular matrices, and is involved in many biological processes, including not only maintaining homeostasis of cells, but also tumor invasion and cancer metastasis. Specific inhibitors of hyaluronan synthesis would help us understand the role of hyaluronan and serve as valuable therapeutic agents to prevent the malignant alteration of disorders associated with abnormal increase of hyaluronan synthesis. We previously found that 4-methylumbelliferone (MU) inhibits hyaluronan synthesis specifically and demonstrated one of the MU-mediated inhibitory mechanisms of hyaluronan synthesis in mammalian cultured cells. Experiments using cultured B16F-10 melanoma cells showed that MU inhibits the formation of cell surface hyaluronan, resulting in suppression of adhesion and locomotion of the cells. We succeeded in generating mice with hyaluronan-knock-down extracellular matrices

by oral administration of MU. When B16F-10 melanoma cells were injected into the lateral tail vein of the hyaluronan-knock-down mice, tumor metastasis to liver was suppressed by 30% compared to that of MU-unadministered mice. The suppression of metastasis to liver was more marked when MU-treated melanoma cells were injected into the lateral tail vein of untreated mice. These data suggest the possibility of applications of MU in clinical medicine for the prevention of tumor metastasis based on its inhibitory effect on hyaluronan synthesis.

When cell surface hyaluronan, as a biological barrier, of cultured pancreatic cancer cells, KP1-NL, was decreased by MU treatment, the enhancement of the growth inhibition by an anticancer drug was observed. *In vivo* simultaneous administration of MU and an anticancer drug to tumor-bearing mice by the inoculation of KP1-NL cells into the spleen decreased tumor growth in the spleen more than did the anticancer drug alone. Therefore, a possibility that MU can be applied as an adjuvant in cancer chemotherapy was also suggested.

Keywords: Hyaluronan, synthesis, inhibitor, 4-Methylumbelliferone