

Control of Synthesis and Functional Analysis of Pericellular Hyaluronan Matrix

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Hyaluronan is a high molecular weight glycosaminoglycan composed of thousands of repeating disaccharide units of GlcUA β (1, 3)GlcNAc β (1, 4) and is synthesized by hyaluronan synthase, which is a membrane associated enzyme. This simple-structured 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 these disorders associated with abnormal increase of hyaluronan synthesis. We found that 4-methylumbelliferone (MU) inhibits hyaluronan synthesis specifically and demonstrated one of the MU-mediated inhibitory mechanisms of hyaluronan synthesis. In this lecture, we will introduce experiments using hyaluronan-knock-down mice that we generated by administration of MU. These experiments provided information that MU inhibits cell adhesion and locomotion of cultured cells of melanoma, a well known skin cancer, and their metastasis to other organs, which suggests the possibility of applications of MU in clinical medicine for the prevention of cancer metastasis based on its inhibitory effect on hyaluronan synthesis. Moreover, when cell surface hyaluronan of pancreatic cancer cells was decreased by MU treatment, the enhancement of the efficacy of an anticancer drug was observed. Therefore, a possibility that MU can be applied as an adjuvant in cancer chemotherapy was also suggested.