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Principal Investigator: Naoki Itano

Grant Title: Hyaluronan metabolism-dependent stress tolerance in cancer stem cells

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研究課題：がん幹細胞におけるヒアルロン酸糖代謝依存的なストレス耐性機構の解明

研究報告：

(a) 要旨：

Cancer stem cells (CSCs) have been implicated in cancer recurrence due to their resistance to chemo- and radio-therapies. Prolonged exposure of CSCs to such stresses may elevate the cellular stress response and strengthen tolerance to stress stimuli. Therefore, elucidating the stress responses of CSCs will provide insights into ameliorating cancer relapse and therapeutic resistance. Our previous studies have shown that hyaluronan overproduction promotes cancer cell stemness by accelerating hexosamine biosynthesis pathway (HBP) flux. HBP regulates protein glycosylation through the supply of UDP-*N*-acetylglucosamine (UDP-GlcNAc) as a donor substrate. *N*-linked protein glycosylation is important for quality control of glycoproteins in the endoplasmic reticulum (ER), and its failure induces unfolded protein response (UPR). Thus, hyaluronan biosynthesis is thought to induce UPR by competing with *N*-glycosylation for UDP-GlcNAc because the synthesis of this huge molecule requires a large amount of UDP-GlcNAc. Here, we analyzed UPR in hyaluronan-overproducing breast cancer cells. When cancer cells were treated with tunicamycin (TM), an inhibitor of *N*-glycosylation, hyaluronan overproduction enhanced TM-induced UPR. To investigate whether hyaluronan overproduction enhanced UPR through the consumption of cellular UDP-GlcNAc, we measured cellular levels of nucleotide sugars in control and HA-overproducing cancer cells by ion-pair reversed-phase HPLC. Of the detected nucleotide sugars, UDP-GlcNAc was found to be reduced in HA-overproducing cancer cells relative to control cells. Furthermore, exogenous D-glucosamine (GlcN) supplementation suppressed the TM-induced UPR coincident with substantial increase in the cellular UDP-GlcNAc pool. Therefore, the present findings suggest that hyaluronan production enhances the ER stress response of cancer cells through changes in *N*-glycosylation, providing a new perspective on the elucidation of the stress response of CSCs.