O-124 The availability of oligosaccharides on cell surface as possible markers for cancer stem cells

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癌幹細胞特異的な糖鎖マーカーの探索

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Cancer stem cells (CSCs) are defined as a minor population which possesses prominent abilities to self-renew, generate differentiated progenies and form new tumors. Over the last decade, a number of studies have implicated CD133 as a marker for CSCs. However, several studies have suggested that CD133 expression might not be limited to CSCs. Thus, identification of other specific markers for CSCs has received significant attention. Oligosaccharides modify proteins and lipids on cell surface and their structures dramatically change during carcinogenesis. In this study, we examined the availability of oligosaccharides as possible markers for CSCs. We isolated CSCs from a human hepatoma cell line, based on the expression of newly-identified protein markers for CSCs and examined oligosaccharide structures on these cells by lectin microarray. In addition, the expression of glycosylation-related genes in these cells was also examined by DNA microarray. These analyses revealed distinctive oligosaccharide structures in CSCs. In further analyses, we will clarify the roles of the oligosaccharides in tumorigenic capacity of CSCs and evaluate its availability as possible markers for CSCs.

Keyword: cancer stem cell

Oral Sessions

Room 6 Sep. 22 (Wed.) 15:30-16:20

11-2 Glycosylation and glycosyltransferase (2)
糖鎖および糖転移酵素 (2)

Chairperson: Yoji Nagashima (Dept. of Mol. Path., Yokohama City Univ. Grad. Sch. of Med.)

座長：長嶋 洋治（横浜市大・院医・分子病理学）

O-125 Role of histone H3 trimethylation in induction of sialyl Lewis x expression in colon cancer

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大腸癌のシアリルルイスX発現誘導におけるヒストンH3トリメチル化の役割

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Colon cancer cells show decreased expression of sulfated normal glycan called sialyl 6-sulfo Lewis x, and strongly express the cancer-associated glycan, sialyl Lewis X (Izawa et al., Cancer Res, 2000). We recently showed that this is due to a reduced transcription of sulfate transporter gene, *DTDST*, in cancers (Yusa et al., Cancer Res, in press). The *DTDST* transcription is suppressed in cancers through epigenetic silencing mechanisms involving histone modification. The results of ChIP assays indicated prominent trimethylation of H3K27, followed by that of H3K9 and H4K20 of the *DTDST* gene promoter. A histone methylation inhibitor, DZNep, induced a significant *DTDST* transcription, which was further enhanced by the combination of DZNep and HDAC inhibitors. Induction of *DTDST* transcription using tet-off system led to inhibition of cell proliferation. In normal colonic tissues, the *DTDST* gene products were detected in differentiated epithelial cells, but not in undifferentiated colonic crypt cells. These results suggest close involvement of histone H3 methylation of the *DTDST* gene in sialyl Lewis x expression and in enhanced proliferation of colon cancer cells.

Keywords: Sulfotransferase, transporter

O-126 Glycoproteomic approach for serobiomarker discovery of various carcinoma

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グライコプロテオミクスによる各種がん血清バイオマーカーの探索

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It is quite difficult to discover early stage cancer serobiomarker using proteomics by comparing the amount of serum protein, because the amount of cancer-derived proteins occupy quite small portion of total serum proteins. Furthermore, most of them are the same kinds as those produced by noncancerous cells. However, it is well known that glycan structure on the proteins derived from cancer cells is altered from those of normal cells. Therefore, we constructed an integrated strategy to discover serobiomarkers systematically by focusing structural alteration of glycans on specific proteins (FEBS J. 2010 277, 95-105). First, we applied this workflow to discover serobiomarkers for HCC. Culture media glycoproteins were analyzed by lectin microarray for selection of a characteristic lectin. Using the lectin column, glycopeptides were captured from the media and identified by LC/MS in a high throughput manner. Glycan profiles were confirmed by lectin microarray. Thus, we could discover many biomarker candidates carrying cancer-associated glycans. This work was supported by "Medical Glycomics: MG" project in New Energy and Industrial Technology Development Organization (NEDO) in Japan.

Keywords: glycosylation, biomarker

O-127 Induction of cancer cell-specific cell death and alteration of sugar chain synthesis pathways by fucoidan extract

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酵素消化低分子化フコイダン抽出物による癌細胞特異的細胞死及び糖鎖合成経路の改変誘導

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Fucoidan is sticky fucose-rich sulfated polysaccharides derived from seaweeds such as Konbu or Mozuku. Low molecular weight fucoidan extract (LMWFE) digested by abalone glycosidases exhibited anti-invasion and anti-angiogenesis effects. LMWFE is now widely used for therapy of terminal cancer patients in Japan. Recently, we found that LMWFE induced cancer cell-specific cell death, which is enhanced by concanavalin A (Con A), a lectin recognizing mannose moiety of polysaccharides. LMWFE enhanced the Con A reactivity of human fibrosarcoma HT1080 cells but not of TIG-1 cells, human normal fibroblasts. An N-acetylglucosaminyl-transferase V (GnT-V) exhibits an important role on the formation of branch chain of beta-1,6-GlcNAc and relates to invasion and metastasis of cancer cells. A transcription factor Ets-1 is also deeply related to invasion and metastasis via expression of extracellular matrix degradation enzymes. LMWFE suppressed the gene expression of GnT-V and Est-1 but did not affect the ER stress pathway, suggesting that LMWFE suppressed the malignant properties of cancer cells including alteration of sugar chain synthesis pathways and induced cancer-specific cell death.

Keywords: Fucoidan, GnT-V

O-128 The uptake of iron, crucial for cellular proliferation and survival, maintained by STEAP3 in cancer

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STEAP3によって調節される癌細胞内貯蔵鉄量

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Iron is essential for cell proliferation and survival based on its involvement of DNA and ATP synthesis. Tumor cells especially require more iron supply than normal cells even in decreased serum iron of patients with cancer. STEAP3 is known to relate to uptake of iron from extracellular milieu. We previously reported the overexpression of STEAP3 increased intracellular iron storage and showed potency to survive in iron-depleted medium in vitro. Furthermore, the augmentation of *steap3* mRNA induced by iron-deprivation indicated that STEAP3 maintained the amount of cellular iron. In the present study using clinical sample, we revealed that *steap3* was more expressed in colorectal cancer tissue than in normal colorectal mucosa. In addition, the iron storage of colorectal cancer tissue stored more iron than that of normal tissues. These findings suggest that cancer cells increase STEAP3-expression and subsequently import iron effectively, which maintains their proliferating and surviv-