EVALUATION OF NOVEL GLYCOCONJUGATE MOLECULES AS PROMISING ANTI-CANCER AGENTS

Ahmad Faried1*, Leri S. Faried2, Shinji Hashimoto1, Kaori Tsuboi1, Takayuki Asao1, Hiroyuki Kuwano1, and Shin Yazawa1, 3

1Department of General Surgical Science (Surgery I); 2Department of Gynecology and Reproductive Medicine, Graduate School of Medicine, Gunma University, Japan; 3Tokushima Research Institute, Otsuka Pharmaceutical Co. Ltd., Japan

*afaried@med.gunma-u.ac.jp

INTRODUCTION. The accumulation of sialylated and/or fucosylated antigens like SLX and YB-2 is known to occur on the surface of human colorectal carcinoma cells (1, 2). Treatment of the cancer cells with exogenous sugar acceptors as primers induced the suppression of such antigen expressions, reduced their metastatic potential and increased the susceptibility of the cancer cells to anticancer treatment (2, 3). Recently, sugar-cholestanols prepared as primers for a variety of cancer cell lines have also been demonstrated to have anti-cancer actions against those cancer cells (4). In this study, we evaluated chemically synthesized GlcNAc derivatives with cholestanol as an anti-cancer agent and also investigated the molecular basis of the sugar-cholestanol to induce apoptosis of cancer cells.

METHODS. In this study, we obtained chemically synthesized GlcNAc derivatives with cholestanol as an aglycon and evaluated their anti-cancer potential, in vitro by cell proliferation inhibition assay. Next, we used a mouse experimental model of peritoneal dissemination for our further in vivo experiment. Liposomes or cyclodextrin containing aforementioned sugar-cholestanols could be used for both evaluations.

RESULTS. GlcNAcβRcholestanol (R=Gal or (-), GlcNAcβRChol) was obtained as encapsulated liposomes and clathrate cyclodextrin. By increasing the concentration of the sugar-cholestanol in the culture medium, the viability of a series of colorectal cancer cells was found to decrease significantly together with the occurrence of apoptotic changes in a short period of time. Surprisingly, such changes were hardly induced by cholestanol itself in the same form. When mouse colorectal cancer cells, (colon26) were
treated with the sugar-cholestanol, GlcNAcβChol was found to be taken into a cell and was associated with the following molecular-based changes in the cells: loss of mitochondrial membrane potential and release of cytochrome c accompanied by a time dependent increase in the initiator caspase-9 activation, then activation of caspase-3 and PARP to execute the apoptotic cell death. The DNA ladder and the nucleic fragmentation were observed at the same time in these cells. Evaluation of GlcNAcβRChol encapsulated liposomes were also undertaken using a mouse experimental model of the peritoneal dissemination using colon 26 cells which indicated that tumor growth was markedly reduced and the survival rate was dramatically enhanced.

**DISCUSSION.** Newly synthesized sugar-cholestanols have been demonstrated to induce apoptosis in different types of cancer cell lines. Although the mechanism of such an induction with GlcNAcβRChol is not fully elucidated, it must be involved in the mitochondrial-intrinsic pathways. This novel feature of glycoconjugates with cholestanol should have clinical application as a promising anti-cancer agent for prevention and treatment of human carcinoma, especially peritoneal dissemination.

**ACKNOWLEDGMENTS.** This work was supported in part by Grants-in-Aid (to A.F., and No.40212469 to T.A.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan and by a Grant-in-Aid for Scientific Research (C) No.15591730 (to L.S.F.) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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