Virchows Archiv A Pathol Anat (1990) 416:221–228

Virchows Archiv A
Pathological Anatomy and Histopathology

Altered expression of Lewis blood group and related antigens in fetal, normal adult and malignant tissues of the uterine endometrium *

Masaki Inoue, Masahiro Nakayama[1], and Osamu Tanizawa
Department of Obstetrics and Gynecology, Osaka University Medical School, and [1] Department of Pathology, Osaka Medical Center for Maternal and Child Health, Osaka, Japan

Summary. The expression of the Lewis blood group and its related antigens in fetal, normal adult and malignant tissues of the uterine endometrium was examined immunohistochemically using a panel of mouse monoclonal antibodies with specificities for Lewis-a (La), Sialyl Lewis-a (SLa), Lewis-b (Lb), Lewis-X (LX), Sialyl Lewis-X (SLX) and Lewis-Y (LY) antigens. La, SLa and SLX having one fucose residue were detected in a small number of fetal tissues, while Lb and LY having two fucose residues were found in most cases. In the adult endometrium, expression of Lb and LY was considerably lower than those in fetal tissues, although expression of La and SLa was not different between these two tissues. Expression of LX and SLX was pronounced in adult when compared with fetal tissues. Malignant endometrial glands expressed La, SLa, Lb and LY, extensively, while LX and SLX were expressed less than in normal tissues.

Lb and LY can thus be considered oncofetal antigens, extensively expressed in fetal and malignant tissues but not in normal adult tissues. Expression of Lb and LY was greater than that of La and SLA in carcinoma; an increase in the activity of fucose transferase might be associated with malignant transformation in the uterine endometrium.

Key words: Carbohydrate antigen – Lewis blood group antigen – Endometrial cancer – Fucosetransferase

* Supported in part by a Grant-in-Aid for Scientific Research (62480346) from the Ministry of Health and Welfare

Offprint requests to: M. Inoue, Department of Obstetrics and Gynecology, Osaka University Medical School, 1-1-50 Fukushima, Fukushima-ku, Osaka 553, Japan

Introduction

There have been numerous attempts to make cancer-specific monoclonal antibodies in various laboratories but most of the antibodies have been found to have their main activity directed to terminal carbohydrate structures, such as the blood groups, and their related antigens and thus non-cancer specific. A typical example is the monoclonal antibody NS 19-9, obtained by immunization of a mouse with a colon cancer cell line. It is highly reactive with colorectal carcinomas and useful for the serological detection of gastrointestinal and pancreatic carcinomas (Atkinson et al. 1982; Magnani et al. 1983). However, the antigenic determinant recognized by NS 19-9 is a sialylated form of the Lewis-a blood group antigen (Magnani et al. 1982). Another interesting antibody, CSLEX-1, is also directed against Lewis-X, the sialylated form of which is often released into the sera of cancer patients (Kannagi et al. 1986; Kawahara et al. 1985; Saltor et al. 1978; Shi et al. 1984). Other carbohydrate chains belonging to the blood group series have also been shown to be altered in association with neoplastic transformation. These changes include aberrant or blocked synthesis of blood group antigens, either with or without precursor accumulation, an increase or neosynthesis of certain glycolipids with blood group antigenic determinants, and synthesis of sialylated substances bearing blood group carbohydrate chains (Feizi 1985; Hakomori 1984).

Much of our understanding about cell surface glycoconjugates has come from studies on gastrointestinal tissues (Ernst et al. 1984; Itzkowitz et al. 1986; Itzkowitz et al. 1987; Kanai et al. 1987; Sakamoto et al. 1986; Yuan et al. 1985) and the urinary bladder (Cardo-Cordon et al. 1988; Juhl et al.

1986; Linas et al. 1985). Very little is known about the expression of the carbohydrate chains of blood groups and their related antigenic determinants in normal and malignant tissues of the female genital tract. In a previous report, we demonstrated increased expression of the blood group antigen H and Lewis-b in both neoplastic and fetal tissues of the uterine endometrium (Inoue et al. 1987). The present study was designed using a panel of monoclonal antibodies specific for Lewis-a, Lewis-b, Lewis-X, Lewis-Y, and the sialylated forms of Lewis-a and Lewis-X in order to investigate further their immunohistochemical expression and modulation in fetal, normal adult and malignant endometrial tissues.

Materials and methods

Tissue blocks from 73 patients with endometrial cancers were collected from the pathology files of the Department of Obstetrics and Gynecology at Osaka University Medical School, Osaka, Japan. Histologically, these tumours consisted of 51 well-, 14 moderately-, and 8 poorly-differentiated adenocarcinomas. Normal endometrial tissues were also obtained from the surgical specimens of 63 patients treated for uterine myoma at the Department of Obstetrics and Gynecology, Osaka University Medical School. Fetal uterine tissues were obtained at abortion of 29 fetuses of 16 to 25 weeks gestation from the Department of Pathology at Osaka Medical Center for Maternal and Child Health, Osaka, Japan. Tissue samples fixed in 10% formalin and embedded in paraffin were cut into 4- to 6-μm thick serial sections. They were then stained by routine histopathological and immunoperoxidase techniques.

Table 1. Monoclonal antibodies recognizing Lewis antigens and sialylated forms of Lewis-a and Lewis-X antigens

Monoclonal antibody	Antigen	Source
Anti-Lewis-a (Ig M)	Lewis-a	Chembiomed, Ltd. (Edmonton, Canada)
NS 19-9 (Ig Gl)	Sialyl Lewis-a	Dinabot, Ltd. (Tokyo, Japan)
Anti-Lewis-b (Ig M)	Lewis-b	Chembiomed, Ltd. (Edmonton, Canada)
FH-2 (Ig M)	Lewis-X	Dr. S. Hakomori (Seattle, USA)
CSLEX-1 (Ig M)	Sialyl Lewis-X	Dr. P. Terasaki (Los Angeles, USA)
AH-6 (IgM)	Lewis-Y	Dr. S. Hakomori (Seattle, USA)

Tissue localization of antigens was determined immunohistochemically with the avidin-biotin-peroxidase complex (ABC) method (Hsu et al. 1981). Monoclonal antibodies specific for Lewis antigens and the sialylated forms of Lewis-a and Lewis-X are listed in Table 1.

The tissue sections were deparaffinized, hydrated in graded ethanol and immersed in 0.3% hydrogen peroxide to block endogenous peroxidase activity. The slides were then washed in 0.05 M phosphate buffered saline (PBS), pH 7.4, and were subsequently treated with 10% normal goat serum to inhibit nonspecific binding of antisera. The primary monoclonal antibodies were applied for 1 h at room temperature. After rinsing in PBS, the sections were incubated for 30 min with biotin-labeled goat anti-mouse IgG or IgM (Vector Labs, Burlingame, CA, USA). They were then treated with the ABC (Vector Labs) at room temperature. Sites of peroxidase activity were visualized with 0.1% 3,3-diamino-benzidine-tetrahydrochloride containing 0.02% hydrogen peroxide in PBS. The slides were counterstained lightly with haematoxylin. Negative controls included sections incubated with normal mouse serum in place of the primary specific antibody.

The patient's blood type was determined by serological blood typing at the Department of Laboratory Medicine, Osaka University Medical School. However, we were unable to confirm the secretor status of the patients because neither saliva nor gastric secretions were available.

Cellular localization of the antigenic sites was determined by two observers using a double-head light microscope. The relative number of immunoreactive cells was scored from 0 to 4 as follows: score 0, negative; score 1, less than 10%; score 2, 10% to 50%; score 3, 50% to 90%; and score 4, more than 90%. The average score for each group was calculated by the following ratio

$$\frac{\text{Total number of scores}}{\text{Number of cases}}$$

Table 2. Immunoreactivity of Lewis antigens and sialylated forms of Lewis-a and Lewis-X antigens in endometrial tissues

Tissue	Fetus ($n=29$)					Normal adult ($n=63$)					Cancer ($n=73$)				
Staining score	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
Antigen	Number of cases														
Lewis-a	17	7	5	0	0	30	23	9	1	0	15	7	18	26	7
Sialyl Lewis-a	21	8	0	0	0	39	17	7	0	0	19	12	19	15	8
Lewis-b	2	12	13	2	0	34	21	8	0	0	8	9	8	15	33
Lewis-X	28	1	0	0	0	17	25	13	6	2	43	9	18	3	0
Sialyl Lewis X	7	11	11	0	0	1	3	10	30	19	10	6	14	26	17
Lewis-Y	0	1	5	5	17	13	22	12	8	8	2	4	13	22	32

n: number of cases

Results

The results of observation of stained fetal endometrial tissues are shown in Table 1. Sialyl Lewis-a and Lewis-X were observed in only 8 and one of 29 cases, respectively. Positive staining was observed on the luminal surface of a few glands (Figs. 1 B and D). However, Lewis-a, Lewis-b and sialyl Lewis-X were detected in 12, 27 and 22 cases, respectively. Those antigens were mainly positive on the luminal surface and sometimes throughout the cytoplasm of the glandular cells (Figs. 1 A, C and E). Lewis-Y was observed mainly throughout the cytoplasm of the glandular cells in all cases (Fig. 1 F). The antigens which were observed in a majority of the cases tended to be present throughout the cytoplasm of the glandular cells. Interestingly, sialyl Lewis-X and Lewis-Y antigens belonging to type II carbohydrate chain group were expressed more frequently than sialyl Lewis-a and Lewis-b belonging to type I carbohydrate chain group. In addition, expression of the antigens with two fucose residues, i.e., Lewis-Y, and Lewis-b, was pronounced compared to the antigens with one fucose residue, i.e., Lewis-a, sialyl Lewis-a, Lewis-X and sialyl Lewis-X.

The results of observation of stained normal adult endometrial tissues are shown in Table 1. Lewis-a, sialyl Lewis-a, and Lewis-b, which belong to type I carbohydrate chain group, were detected in 33, 24, and 29 of 63 cases, respectively. Although these antigens were present in about half the cases, the luminal surface of a small percentage of cells was faintly stained in a majority of positive cases

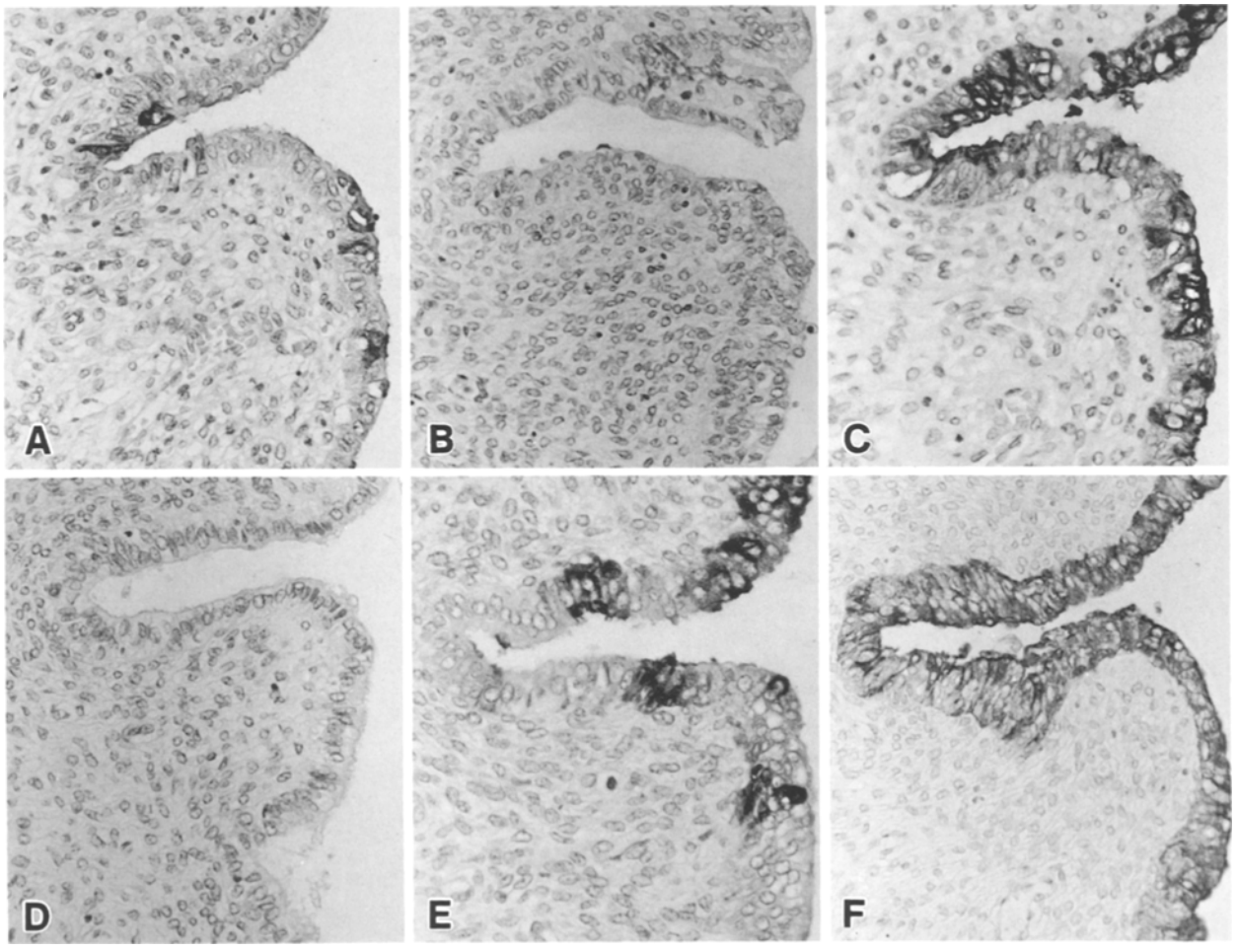

Fig. 1. Localization of Lewis blood group and its related antigens in the fetal endometrium. **A** Lewis-a antigen was expressed in some epithelial cells. **B** Sialyl Lewis-a antigen was not detected in this case. **C** Lewis-b immunoreactivity was observed throughout the cytoplasm in some glandular cells of fetal endometrium exceeding the level of Lewis-a immunoreactivity. **D** Lewis X antigen was not detected. **E** Sialyl Lewis-X antigen was heterologously expressed. **F** Lewis-Y antigen was expressed throughout the cytoplasm of most glandular cells. **A–F:** Immunoperoxidase method ×66

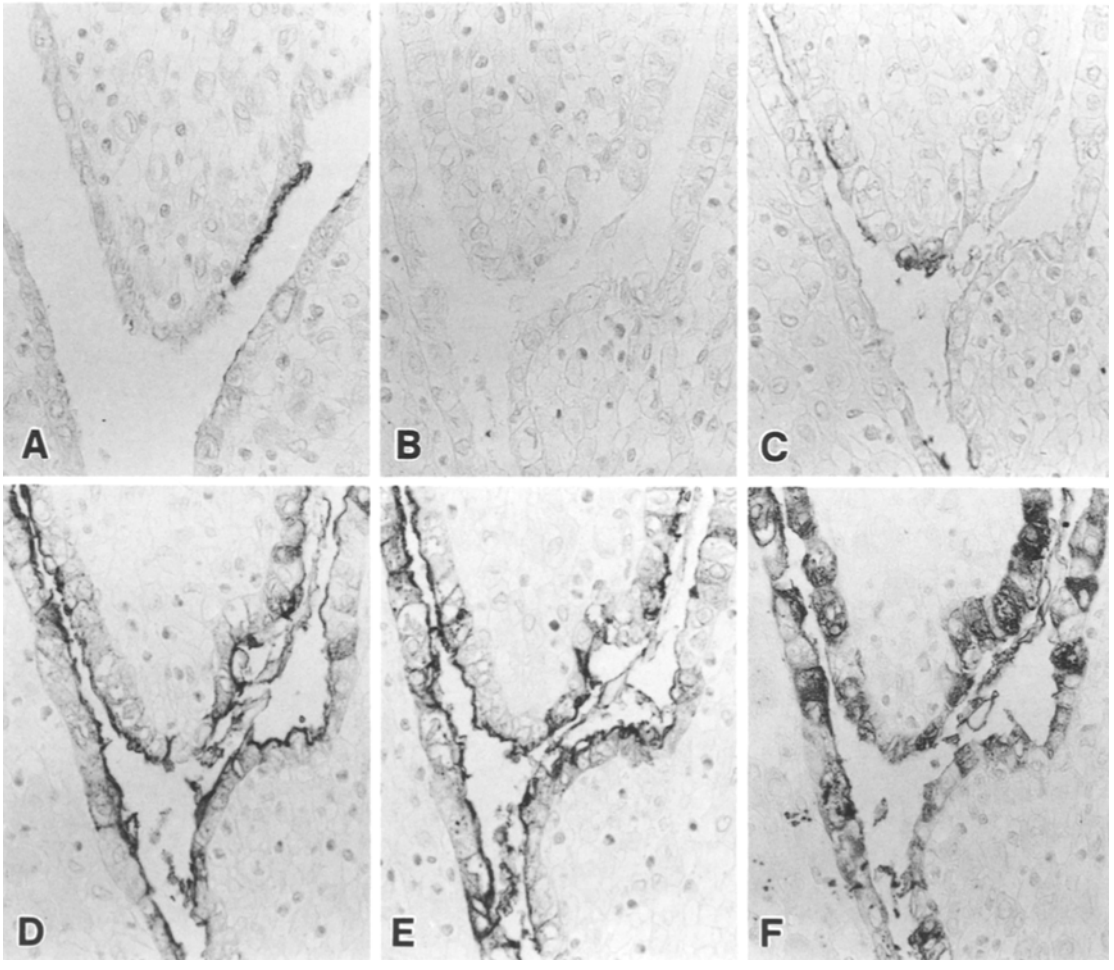

Fig. 2. Localization of Lewis blood group and its related antigens in normal adult endometrium. **A–C** Lewis-a (**A**), sialyl Lewis-a (**B**), and Lewis-b (**C**) were expressed in the apical portion of a few cells. **D–F** Lewis-X (**D**), sialyl Lewis-X (**E**), and Lewis-Y (**F**) were expressed throughout the cytoplasm of most cells. **A–F:** Immunoperoxidase methods ×100

(Figs. 2A–C). Lewis-X, sialyl Lewis-X and Lewis-Y, which belong to type II carbohydrate chain group, were detected in 46, 62 and 50 cases, respectively. The staining was observed in a greater percentage of cells in each case, although the proportion of positive cells varied from case to case. The antigens were expressed mainly throughout the cytoplasm of the glandular cells of basal layer and surface lining epithelium. They were sometimes positive in the supranuclear lesion of the cytoplasm (Fig. 2D–F).

The results obtained by tissue staining during the proliferative and secretory phases of the endometrium are summarized in Fig. 3. Expression of Lewis-X antigen was pronounced somewhat in the proliferative endometrium, while the expression of the other antigens did not differ between these phase.

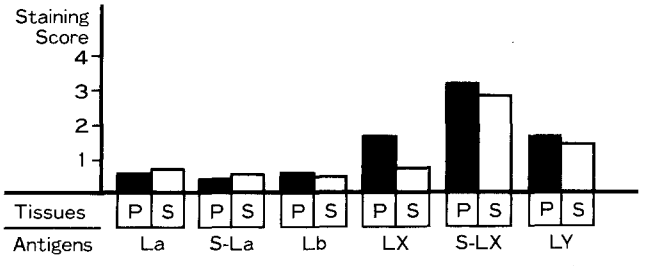

Fig. 3. Staining scores of Lewis blood group and its related antigens in the proliferative and secretory phases of normal endometrium. Staining score, Refer to "Materials and methods"; La, Lewis-a antigen; SLa, Sialyl Lewis-a antigen; Lb, Lewis-b antigen; LX, Lewis-X antigen; SLX, Sialyl Lewis-X antigen; LY, Lewis-Y antigen. P, Proliferative phase of endometrium; S, Secretory phase of endometrium

The results of observations of stained endometrial cancer are shown in Table 1. Expression of Lewis-a, sialyl Lewis-a, Lewis-b, Lewis-X, sialyl

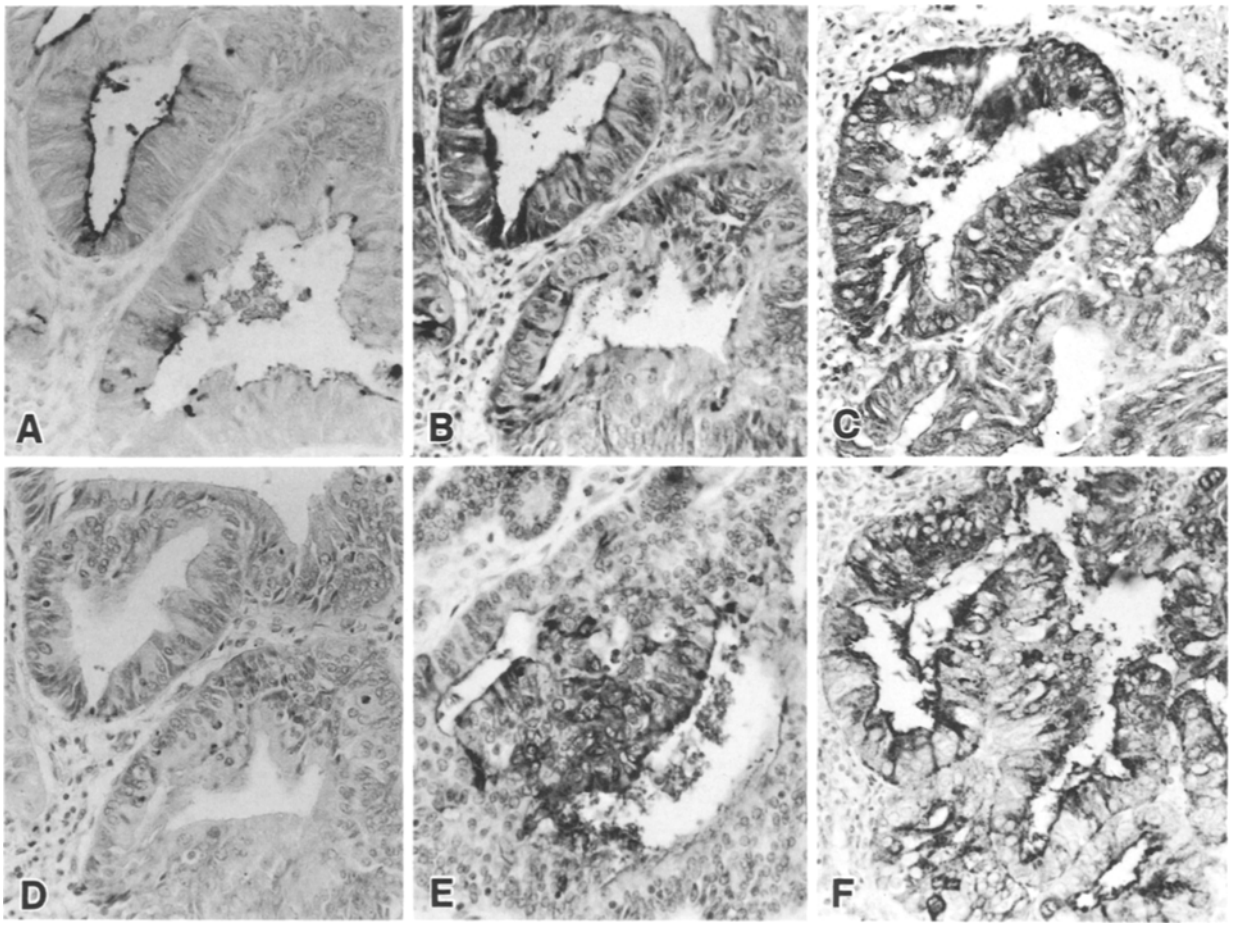

Fig. 4. Localization of Lewis blood group and its related antigens in endometrial cancer tissues. **A** Lewis-a antigen was expressed mainly in the apical cytoplasm of cancer cells. **B** Sialyl Lewis-a antigen was expressed in the apical cytoplasm and also throughout the cytoplasm of many cancer cells. **C** Lewis-b antigen was expressed throughout the cytoplasm of many cancer cells. **D** Lewis-X antigen was not detected in this case. **E** Sialyl Lewis-X antigen was detected in the cytoplasm of some cancer cells. **F** Lewis-Y antigen was detected in the cytoplasm of most cancer cells and the luminal contents of the glands. (Immunoperoxidase methods × 50)

Lewis-X and Lewis-Y antigens was demonstrated in 58, 54, 65, 31, 63, and 71 of 73 cases, respectively. Lewis-b, sialyl Lewis-X and Lewis-Y antigens were strongly expressed, with more than 50% of cancer cells being positive in more than half of the cases. Lewis-Y antigen was detected in all cases except for two patients who did not express any of the antigens tested, although Lewis-X antigen was detected in limited cases. These antigens were observed to be distributed mainly in the cytoplasm of the cancer cells and also in the apical cytoplasm and luminal contents of the glands. The proportion of positive cells varied from case to case and from area to area in the same case. Positive and negative cell aggregates coexisted adjacent to each other in some areas, while in other areas, a single positive cell or a few aggregated positive cells were scattered among negative cells (Figs. 4A–F).

The correlation between the cellular distribution of antigens and the degree of histological differentiation are summarized in Fig. 5. Generally, poorly-differentiated tumours showed less antigen expression, with 4 of 8 cases being negative for the 5 antigens other than Lewis-Y. However, Lewis-Y antigen was still expressed in poorly differentiated tumours, although it was negative in 2 cases which did not express any of the antigens tested.

The results obtained from this study are summarized in Fig. 6. The average staining scores of Lewis-b, and sialyl Lewis-X in fetal tissues were 1.5 and 1.2, respectively. Lewis-Y was expressed in all fetal tissues, with an average staining score of 3.3. However, Lewis-a, sialyl Lewis-a, and Lewis-X showed less expression. Lewis-X in particular was only faintly positive in just one case. In adult endometrium, expression of Lewis-b and Lewis-Y

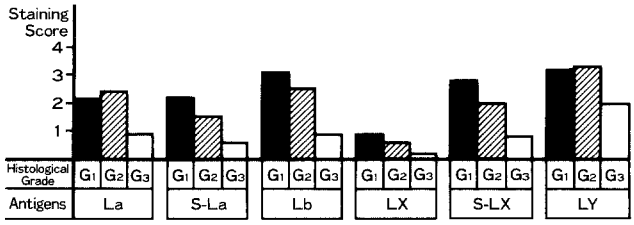

Fig. 5. Staining scores of Lewis blood group and its related antigens in endometrial cancer tissues distributed according to the histological grade. Staining score, Refer to "Material and methods"; La, Lewis-a antigen; SLa, Sialyl Lewis-a antigen; Lb, Lewis-b antigen; LX, Lewis-X antigen; SLX, Sialyl Lewis-X antigen; LY, Lewis-Y antigen; Gl, Well-differentiated adenocarcinoma; G2, Moderately-differentiated adenocarcinoma; G3, Poorly-differentiated adenocarcinoma

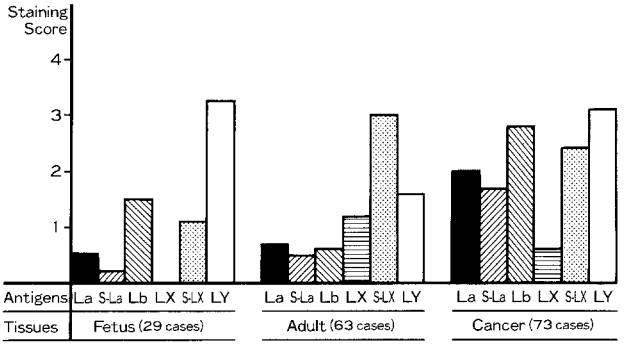

Fig. 6. Summary of Lewis blood group and its related antigens in human endometrial tissues. Staining score, refer to "Materials and methods"; La, Lewis-a antigen; SLa, Sialyl Lewis-a antigen; Lb, Lewis-b antigen; LX, Lewis-X antigen; SLX, Sialyl Lewis-X antigen; LY, Lewis-Y antigen

was considerably lower than that in fetal tissues. Conversely, expression of Lewis-X and sialyl Lewis-X was pronounced in adult endometrial tissues. Lewis-a and sialyl Lewis-a showed the same expression in both tissues. In cancer tissues, the malignant glandular cells reexpressed Lewis-b and Lewis-Y, extensively with their two fucose residues. Expression of Lewis-a and sialyl Lewis-a was also greater in cancer tissues than in normal adult endometrial tissue. However, expression of the antigens having two fucosyl residues, Lewis-b and Lewis-Y, was greater in cancer tissues than expression of the antigens with one fucosyl residue, Lewis-a and sialyl Lewis-a. Lewis-X and sialyl Lewis-X were somewhat more weakly expressed in cancer tissues compared to normal tissues. Consequently, amplified expression of the type I carbohydrate chain in malignant cells was greater than that of the type II chain, although Lewis-Y was detected in many cancer cells.

Discussion

The Lewis "family" of antigens consists of carbohydrate antigenic structures which are formed by sequential addition of specific monosaccharides to the carbohydrate side chains of glycolipids and glycoproteins. The Lewis-a determinant contains L-fucose joined to the C4 position of the subterminal N-acetylglucosamine in a type I chain. The Lewis-b determinant, also based on the type I chain, has two fucosyl residues joined to adjacent sugars, one linked (1–4) to N-acetylglucosamine as in the Lewis-a determinant and the second linked (1–2) to the β-galactosyl residue. Lewis-X and Lewis-Y antigens are stereoisomers of Lewis-a and Lewis-b antigens, respectively, having the fucose molecules bound to a Type II sugar chain terminus. The sialylated forms of Lewis-a and Lewis-X have a sialic acid moiety bound (2–3) to the galactose residue of Lewis-a and Lewis-X antigens, respectively (Hakomori 1984; Watkins 1980). These well-characterized carbohydate antigens are extremely useful markers for examining what antigenic alteration may be associated with malignant transformation. This is the first study to investigate the expression of the Lewis blood group and its modified antigens systematically in human endometrial tissues.

In the present study, Lewis-a and Lewis-b were strongly expressed in endometrial cancer. Lewis-b was also expressed in the endometrial epithelium of the fetus. As we have already pointed out, Lewis-b is surmised to have a carcinoembryonic character (Inoue et al. 1987). The increased expression of Lewis-b in ovarian cancer specimens and colonic cancer specimens has been reported by other investigators (Ernst et al. 1984; Orodonez et al. 1987; Sakamoto et al. 1986; Yuan et al. 1985). Conversely, disappearance of Lewis-a and Lewis-b has been reported in cancer tissues of the pancreas and bladder, and disappearance is a marker for poor prognosis (Itzkowitz et al. 1987; Juhl et al. 1986; Linas et al. 1985). With regard to the liver, it has been suggested that Lewis-a and Lewis-b antigens may be involved in renewal of the biliary duct epithelium rather than in cancer development (Kanai et al. 1987). As described above, the patterns of expression of Lewis-a and Lewis-b antigens differ depending on the organ. However, many investigators have pointed out a correlation between Lewis-b antigen expression and cancer (Ernst et al. 1984; Hakomori et al. 1983; Hakomori 1984; Hakomori 1985). Comparison of the intensity of expression of Lewis-a and Lewis-b antigens in endometrial cancer tissues revealed that Lewis-b antigen expres-

sion was clearly stronger than that of the Lewis-a antigen, indicating, as was also reported by Hakomori et al. (Hakomori et al. 1983; Hakomori 1984; Hakomori 1985), an increased fucose-transferring activity of the type I sugar chain in endometrial cancer.

In the present study, almost no Lewis-X antigen was detected in the fetal endometrium, and even with the endometrial cancer specimens, this antigen was detected in only a few specimens. In the adult normal endometrium, however, in the basal stratum of the endometrium in the secretory phase, the whole of the endometrium in the proliferative phase and the covering epithelium were extensively positive for Lewis-X antigen in terms of both the number of cells and the number of specimens. The present findings differ greatly from reports that the Lewis-X antigen level was increased in cancer tissues (Fox et al. 1983; Gong et al. 1985; Itzkowitz et al. 1986; Shi et al. 1984; Yuan et al. 1987). However, some authors have surmised that Lewis-X is an antigen relating to the growth and differentiation of cells since no difference was detected in the level of this antigen between cancer (Sakamoto et al. 1986) and normal tissues of the colon and since it was not detected in the normal biliary ductal epithelium but was detected in proliferating biliary ductal epithelium in the liver undergoing regeneration after trauma (Kanai et al. 1987). In addition, Lewis-X antigen was first discovered as a stage-specific embryonic antigen and is considered to be an antigen involved in the differentiation of cells during embryogenesis (Saltor et al. 1978; Shi et al. 1984). Therefore, it can be surmised that, in the endometrium, Lewis antigen is associated with proliferation and differentiation of cells rather than cancer development.

Lewis-Y antigen was detected at a high level in most specimens of the fetal endometrium and endometrial cancer, but it was detected at a relative low level in the normal endometrial specimens. Thus, Lewis-Y antigen can be surmised to be a carcinoembryonic antigen in the endometrium, similar to Lewis-b antigen. A similar finding has been reported for distal colon (Abe et al. 1986). The present finding that Lewis-Y antigen expression was pronounced but Lewis-X antigen expression was decreased in cancer tissues compared with normal tissues suggests that there is an increase in fucose-transferring activity in the type II sugar chain as well in endometrial cancer tissues.

The patterns of expression of the sialylated forms of Lewis-a and Lewis-X antigens in the endometrial tissues are quite similar to those of Lewis-a and Lewis-X antigens, respectively, although the expression of sialylated Lewis-X antigen was more pronounced than that of Lewis-X antigen in all specimens. Sialylation of sugar residues on the cell surface might not be involved in carcinogenesis of the uterine endometrium.

The findings can be summarized as follows. The expression of Lewis-a and Lewis-b (type I sugar chains) was increased in cancer. The expression of Lewis-b, which has two fucose residues, was more pronounced than that of Lewis-a, which has one. The expression of Lewis-X antigen (type II chain) was less in cancer tissues, although increased expression of Lewis-Y antigen was observed. This is because amplification of Lewis-b antigen expression in cancer tissues is greater than that of Lewis-Y antigen. These findings suggest that increases in the amount of type I sugar chains and in fucose-transferring activity are oncodevelopmental changes in the Lewis "family" of antigens. However, it is not clear whether such cancer-related changes occurring in the terminal sugar chain structure are caused by stepwise addition of sugar residues by the action of a transferase in the same fashion as seen in normal tissues. The biological significance of the above-described changes and the effects of the Lewis blood group phenotype in individuals remain to be investigated.

Acknowledgments. We thank Dr. S. Hakomori and Dr. P. Terasaki for providing the monoclonal antibodies, AH 6 nd FH 2, and the monoclonal antibody, CSLEX-1, respectively. We also thank Miss N. Kawasaki for her valuable assistance in preparing this manuscript.

References

Abe K, Hakomori S, Ohshiba S (1986) Differential expression of difucosyl type 2 chain (Le Y) defined by monoclonal antibody AH-6 in different locations of colonic epithelia, various histological types of colonic polyps and adenocarcinomas. Cancer Res 46:2639–2644

Atkinson BF, Ernst CS, Herlyn M, Steplewski Z, Sears H, Koprowski H (1982) Gastrointestinal cancer-associated antigen in immunoperoxidase assay. Cancer Res 42:4820–4823

Cardo-Cordon C, Reuter VE, Lloyd KO, Sheinfeld J, Fair WR, Old LJ, Melamed MR (1988) Blood group-related antigens in human urothelium: Enhanced expression of precursor, Le^x, and Le^y determinants in urothelial carcinoma. Cancer Res 48:4113–4120

Ernst C, Atkinson B, Wysocka M et al. (1984) Monoclonal antibody localization of Lewis antigens in fixed tissue. Lab Invest 50:394–400

Feizi T (1985) Demonstration by monoclonal antibodies that carbohydrate structures of glycoproteins and glycolipids are onco-developmental antigens. Nature 314:53–57

Fox N, Damjanov I, Knowles BB, Solter D (1983) Immunohistochemical localization of the mouse stage-specific embryonic antigen 1 in human tissues and tumors. Cancer Res 43:669–678

Gong F, Hirohashi S, Shimosato Y, Watanabe M, Ino Y, Teshima S, Kodaira S (1985) Expression of carbohydrate antigen 19-9 and stage-specific embryonic antigen 1 in nontumorous and tumorous epithelia of the human colon and rectum. JNCI 75:447–454

Hakomori S, Kannagi R (1983) Glycosphingolipids as tumor-associated and differentiation markers. JNCI 71:231–251

Hakomori S (1984) Tumor-associated carbohydrated antigens. Ann Rev Immunol 2:103–126

Hakomori S (1985) Aberrant glycosylation in cancer cell membranes as focused on glycolipids: Overview and perspectives. Cancer Res 45:2405–2414

Hsu SM, Raine L, Fanger H (1981) Use of avidin-biotin-peroxidase complex (ABC) in immunoperoxidase techniques: A comparison between ABC and unlabeled antibody PAP procedures. J Histochem Cytochem 29:577–580

Inoue M, Sasagawa T, Saito J, Shimizu H, Ueda G, Tanizawa O, Nakayama M (1987) Expression of blood group antigen A, B, H, Lewis-a and Lewis-b in fetal, normal and malignant tissues of the uterine endometrium. Cancer 60:2985–2993

Itzkowitz SH, Yuan M, Fukushi Y et al. (1986) Lewis X and sialylated Lewis X-related antigen expression in human malignant and non-malignant colonic tissues. Cancer Res 46:2627–2632

Itzkowitz SH, Yuan M, Ferell LD, Ratcliffe RM, Chung YS, Satake K, Ueyama K, Jones RT, Kim TS (1987) Cancer-associated alterations of blood group antigen expression in the human pancreas. JNCI 79:425–434

Juhl BR, Hartzen SH, Hainau B (1986) Lewis-a antigen in transitional cell tumors of the urinary bladder. Cancer 58:222–228

Kanai T, Hirohashi S, Upton MP, Ino Y, Shimosato Y (1987) Expression of Lewis blood group antigens in cancerous and noncancerous liver. Jpn J Cancer Res 78:968–976

Kannagi R, Fukushi Y, Tachikawa T, Noda A, Shin S, Shigeta K, Hirajwa N, Fukuda Y, Inamoto T, Hakomori S, Imura H (1986) Quantitativ and qualitative characterization of human cancer-associated serum glycoprotein antigens expressing fucosyl or sialy-fucosyl type 2 chain polylactosamine. Cancer Res 46:2619–2626

Kawahara M, Chia D, Terasaki PI, Roumans A, Sugich L, Wermes M, Iguro T (1985) Detection of sialylated Lewis-X antigen in cancer sera using a sandwich radioimmunoassay. Int J Cancer 36:421–425

Linas C, Lange PH (1985) Lewis antigens in normal and neoplastic urothelium. Am J Pathol 121:176–182

Magnani JL, Nilsson B, Brockhaus M, Zopf D, Steplewski Z, Koprowski H, Ginsburg VA (1982) Monoclonal antibody-defined antigen associated with gastrointestinal cancer is a ganglioside containing sialylated Lacto-N-fucopentaose II. J Biol Chem 257:14365–14369

Magnani JL, Steplewski Z, Koprowski H, Ginsburg V (1983) Identification of the gastrointestinal and pancreatic cancer-associated antigen detected by monoclonal antibody 19-9 in the sera of patients as a mucin. Cancer Res 43:5489–5492

Ordonez NG, Freedman RS, Herlyn M (1987) Lewis and related tumor-associated determinants on ovarian carcinoma. Gynecologic Oncology 26:1–20

Sakamoto J, Furukawa K, Cordon-Cardo L, Yin BWT, Retting WJ, Oettgen HF, Old LJ, Lloyd KO (1986) Expression of Lewis a, b, X and Y blood group antigens in human colonic tumors and normal tissues and in human tumor-derived cell lines. Cancer Res 1986; 46:1553–1561

Saltor D, Knowles BB (1978) Monoclonal antibody defining a stage-specific mouse embryonic antigen (SSEA-1). Proc Natl Acad Sci [USA] 75:5565–5569

Shi ZR, McIntype LJ, Knowles BB, Solter D, Kim YS (1984) Expression of carbohydrate antigen, stage-specific embryonic antigen 1 in human colonic adenocarcinoma. Cancer Res 44:1142–1147

Yuan M, Itzkowitz SH, Palekar A, Shamsuddin AM, Phelps PC, Trump BF, Kim YS (1985) Distribution of blood group antigens A B H Lewis-a and Lewis-b in human normal, fetal and malignant colonic tissue. Cancer Res 45:4499–4511

Yuan M, Itzkowitz SH, Ferrell LD, Fukushi Y, Palekar A, Hakomori S, Kim YS (1987) Expression of Lewis X and sialylated Lewis-X antigens in human colorectal polyps. JNCI 78:479–488

Watkins WM (1980) Biochemistry and genetics of ABO, Lewis, and P blood group systems. Adv Hum Genet 10:1–136

Received August 14, 1989 / Accepted August 23, 1989