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Expression of HLA-DR Antigen in Large Bowel Carcinoma

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One hundred large bowel carcinomas were studied immunohistochemically with regard to expression of HLA-DR antigen (DR). One or two sections from each tumor including surrounding normal mucosa were examined by a semiquantitative counting system for tumor cells and mucosal and stromal infiltrates of lymphocytes and mononuclear cells (MNCs) with DR expression and the results were applied Chi-square test. The rate of presence of DR positive (DR^+) lymphocytes in lymphoid nodules and DR^+ lymphocytes / MNC in the adjacent mucosa and stroma in DR^+ carcinoma (50 %) was higher ($P < 0.01$) than in DR^- carcinoma (21.9 %). Thirty-six carcinomas (36 %) were DR^+. Three (75 %) out of 4 DR^+ poorly differentiated carcinomas and six (20 %) out of 30 DR^+ moderately differentiated carcinomas showed homogeneously strong DR^+ expression. There was tendency for poorly differentiated carcinoma to be more homogeneous DR^+ expression. According to Dukes' stage, four (80 %) out of 5 carcinomas in Dukes' stage D were DR^-. An increased infiltration of lymphocytes / MNCs into adjacent mucosa and stroma in large bowel carcinomas is possibly related with DR expression by carcinoma. From the results of this study, we postulated as follows : 1) DR^+ tumor cells may act as antigen-presenting cells, 2) They may have an inhibitory effect for distant metastasis, 3) Poorly differentiated carcinoma expressed more DR^+ homogeneously.

Key Words : *HLA-DR antigen, Large bowel carcinoma, Lymphocytes, Monocytes, Mucosa*

INTRODUCTION

Major histocompatibility complex (MHC) class II molecules (HLA-DR, HLA-DP, HLA-DQ) are involved in a variety of immune functions including presentation of exogenous antigens (Benacerraf, 1981 ; Daar et al., 1984) that have, after endocytosis, been degraded in cell endosomes. These resulting peptides are met by class II molecules in cell endosomes and transported to the cell surface and presented to $CD4^+$ helper T cells (Kaufman et al., 1984 ; Giles and Capra, 1985 ; Hämmerling and Moreno, 1990). DRs are membrane-bound glycoproteins encoded by genes located in the HLA-D region of the MHC (Bodmer and Bodmer, 1984 ; Kaufman et al., 1984 ; Thorsby, 1987). These antigens commonly appear on B-lymphocytes, activated T-lymphocytes, monocytes, macrophages, dendritic cells in lymph nodes, Langerhans cells of the skin, and endothelial cells, and are believed to regulate essential cell interactions in immune re-

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sponses (Benaccrraf, 1985). In addition, DRs can also be present in other tissues that are normal or diseased, specifically DRs have been seen on various malignant tumors where their expression has often been shown to be of prognostic relevance (Ghosh et al., 1986 ; Esteban et al., 1990 ; Sohn et al., 1993). Although the expression of DR in colon tumor has been investigated by previous studies (Moore et al., 1986 ; Norazmi et al., 1989 ; McDougall et al., 1990), these data are conflicting, no conclusion could be drawn on the relationship of DR expression to tumor stage or prognostic parameters. Therefore we performed an immunohistochemical examination using anti-HLA-DR antibody and analysed the expression of DR on colonic epithelia in 100 cases of large bowel carcinoma. The possible functional significance of DR expression on colonic epithelia of large bowel carcinomas is discussed in this paper.

MATERIALS AND METHODS

Case selection

One hundred cases of large bowel carcinoma from 100 patients who were operated on the perioid 1991-1993 at Keimyung University Dongsan Hospital (except one case from 1988 retrieved from the files of the Department of Pathology) were used in this study. We selected cases on the basis of availability of adequate paraffin tissue blocks and clinical information. The representative blocks were selected after reviewing hematoxylin and eosin (H&E) stained paraffin sections and were studied immunohistochemically with special regard to expression of DR. Histological verification and staging were performed on the basis of H&E stained paraffin sections. The medical records and pathological diagnostic sheets were reviewed for an additional follow-up information clinicopathologically.

The age range of the patients and distribution of sex are shown in Table 1.

The anatomical regions of large bowel carcinoma were shown in Table 2.

Histopathological typing and grading of the tumors were undertaken on the H&E sections. All slides were reevaluated by an observer and compared with the pathologic diagnosis already made. The types of large bowel carcinoma were consisted of 94 cases of adenocarcinoma and 6 cases of adenocarcinoma with mucinous differentiation. Adenocarcinomas were reclassified according to tubular differentiation. The postoperative staging were carried out according to Dukes' stage (Dukes and Bussey, 1958).

Immunohistochemistry of HLA-DR antigen

Immunohistochemical observations were made on the deparaffinized sections (4 μm) which were stained for the presence of DR with commercially available mouse monoclonal antibody for class II HLA-DR antigen (DAKO, Santa Fe, CA ; U.S.A. ; HLA-DR/Alpha) at a concentration of 1 in 30 (streptavidin biotin method).

In brief, HLA-DR immunoperoxidase staining procedure was as follows :

1. Deparaffinized sections were rehydrated and washed in buffer (0.1M PBS).
2. Each section was covered with 3 % H_2O_2 for 5 minutes and washed in buffer.
3. Sections were incubated with protein blocking agent for 10 minutes at room temperature and then incubated with primary antibody (HLA-DR) at 37℃ for 1 hour.
4. Washed in buffer and the tissues covered with biotinized secondary antibody at room temperature for 10 minutes.
5. Washed in buffer and the tissues covered with peroxidase reagent at room temperature for 10 minutes.
6. Washed in buffer, and chromogen solution (AEC) placed on each tissue section.
7. Slides washed in distilled water and covered in Mayer hematoxylin for counterstain.

Table 1. Age range and sex distribution of the patients.

Sex : Male/Female	52/48
Mean age(yr)	52.5
Range(yr)	23-79

Table 2. Site of large bowel carcinoma and sex.

Site of tumor	Male/Female	Total
Cecum	1/1	2
Ascending colon	4/5	9
Transverse colon	4/3	7
Descending colon	1/3	4
Sigmoid colon	17/20	37
Rectum	23/15	38
More than one site	2/1	3
Total	52/48	100

8. Washed in running tap water and cover-slipped with aqueous mounting medium.

Evaluation

DRs were detected within the cytoplasm and on cytomembrane as red color when the stained cells occupied even less than 5 % of all tumor cells in a field, the case was considered to be positive, and cases with no stained cells were considered negative. No necrotic areas of the tumor tissue were taken into consideration. The positive staining of MNCs/lymphocytes in the lamina propria mucosae provided the necessary positive control.

Tumor cells were categorized by their staining with DR according to the following semiquantitative criteria :

group n (none) : no tumor cells stained
group f (focal) : small foci (lesser than 5 %) of all tumor cells in a given section
group p (patchy) : larger clusters of tumor cells weakly or/strongly homogeneously or heterogeneously, stained a greater proportion of tumor cells
group d (diffuse) : all tumor cells strongly and homogeneously stained

Both DR^+ lymphocytes in lymphoid nodules adjacent to carcinoma and also lymphocyte/MNCs in mucosa and stroma adjacent to carcinoma with positive or negative DR expression were thoroughly examined and the results were applied for Chi-square test statistics in order to analyse the correlation between DR expression of tumor cells and DR expression of lymphocytes in lymphoid nodules, and lymphocytes and MNCs in mucosa and stroma adjacent to tumor.

RESULTS

DR expression was cytoplasmic and cytomembranous and more concentrated in the apical portion of columnar cells. Thirty-six out of 100 cases of large bowel carcinoma (36 %) proved to be DR^+. Nine out of 36 DR^+ tumors (25 %) of large bowel carcinomas stained homogeneously with DR, which were composed of 3 out of 4 poorly differentiated carcinomas (75 %) (Fig. 1a) and 6 out of 30 moderately differentiated carcinomas (20 %) and none of 2 well differentiated large bowel carcinomas were stained homogeneously (Table 3). While others were stained heterogeneously, (strong or moderate to faint in strikingly patchy or focal patterns) (Fig. 1b,c). One case showed that poorly differentiated portions of tumor expressed DR strongly and homogeneously, while other well differentiated portions of tumor expressed DR heterogeneously, with various intensity. DR expression according to Dukes' stage (Table 4) showed 35 out of 36 DR^+ large bowel carcinomas were

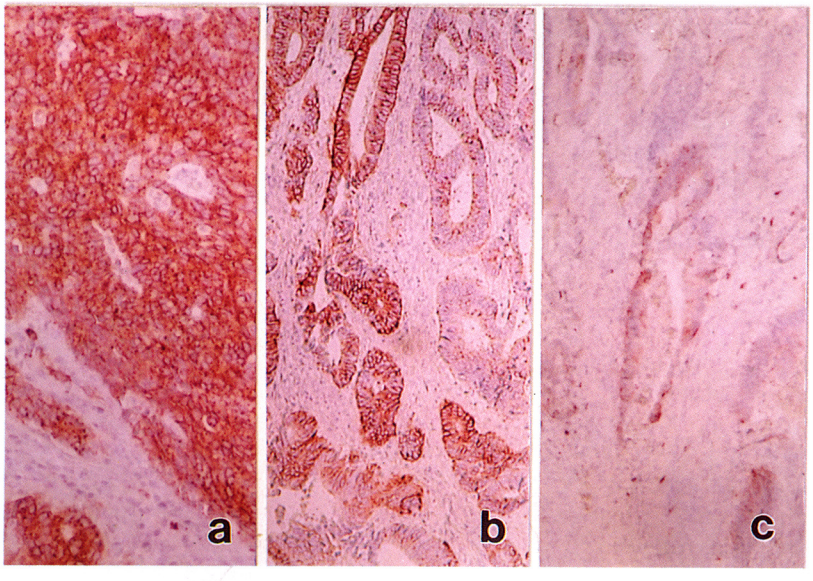

Fig. 1. Immunohistochemical staining for HLA-DR antigen in formalin fixed, paraffin-embedded sections of large bowel carcinomas. Relatively poorly differentiated adenocarcinoma shows homogeneously strong DR expression in diffuse pattern (a). Moderately differentiated adenocarcinomas show heterogeneously strong/weak DR expression in patchy pattern (b) and heterogeneously faint DR expression in focal pattern (c).

Table 3. Histologic grades and staining patterns for HLA-DR in large bowel carcinomas.

Histological grade	HLA-DR expression					
	negative	positive				
	n	f	p	d	Hetero*	Homo**
Well differentiated(n=8)	6	0	2	0	100 %	0 %
Moderately differentiated(n=78)	48	14	10	6	80 %	20 %
Poorly differentiated(n=14)	10	0	1	3	25 %	75 %
Total	64	14	13	9		

n : none, f : focal, p : patchy, d : diffuse
*Heterogeneous expression of DR, **Homogeneous expression of DR

Table 4. HLA-DR antigen expression according to Dukes' stage in large bowel carcinoma.

Duke's stage	HLA-DR expression	
	Negative	Positive
A(n=3)	3(100.0 %)	0
B(n=38)	21(55.2 %)	17(44.7 %)
C(n=54)	36(66.6 %)	18(33.3 %)
D(n=5)	4(80.0 %)	1(20.0 %)
Total(100)	64(64.0 %)	36(36.0 %)

classified as Dukes' stage B and C and only one out of 36 DR^+ large bowel carcinomas was in stage D showing focal heterogeneous expression. Four (80 %) out of 5 large bowel carcinomas in Dukes' stage D showed no DR expression, this was a higher percentage than that of stage B and C. In this study it was evident that lymphoid nodule formation and increased infiltrates of lymphocytes and MNCs were present in mucosa adjacent to tumor and also in intraneoplastic as well as perineoplastic stroma regardless of DR expression of tumor cells (Fig. 2a). The results of statistical analysis of the rate of presence of DR^+ lymphocytes and mononuclear cells in lymphoid nodules and in the adjacent mucosa and stroma in DR^+ large bowel carcinomas showed significant correlation (Table 5) with the rate of DR expression of tumor cells. The rate of presence of DR^+ lymphocytes in lymphoid nodules (71.9 %) was significantly higher ($P < 0.01$) in DR^+ large bowel carcinomas than DR^- large bowel carcinomas (28.1 %).

The rate of presence of DR^+ lymphocytes/MNCs in intraneoplastic and adjacent mucosa and stroma was also significantly higher ($P < 0.05$) in DR^+ large

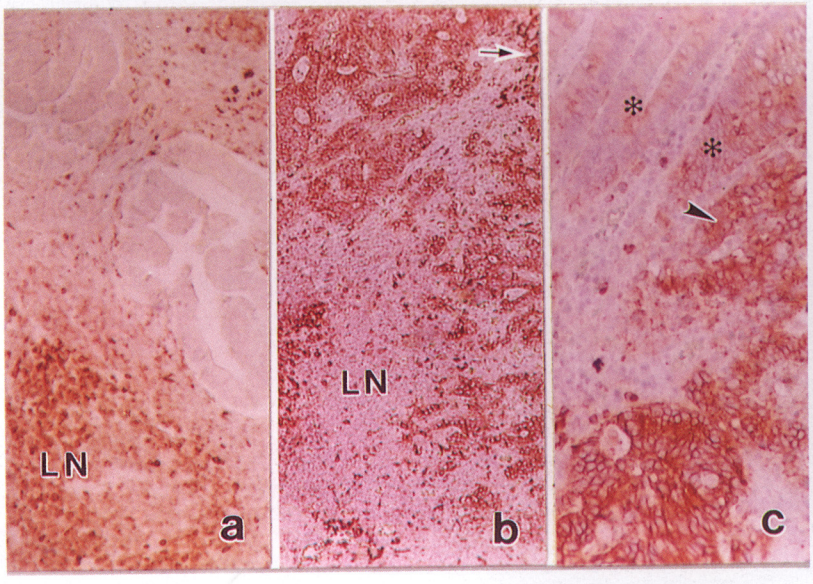

Fig. 2. Diffuse stromal infiltrates of DR^+ lymphocytes in between D R^- carcinoma cells and in lymphoid nodules (LN) (a). Increased infiltrates of DR^+ lymphocytes in intraneoplastic stroma (arrow) and lymphoid nodule (LN) adjacent to homogeneously strong DR^+ carcinoma (b). DR^+ normal-looking cells of crypts (*) immediately adjacent to DR^+ carcinoma (arrow head) (c).

Table 5. The rate of presence of DR^+ lymphocytes in lymphoid nodules and DR^+ lymphocytes/mononuclear cells in the adjacent mucosa and stroma in DR^+ large bowel carcinomas.

	HLA-DR expression in large bowel carcinomas (−)	(+)	P value*
a (−)	46(71.9 %)	14(38.9 %)	P < 0.01(P=0.001)
(+)	18(28.1 %)	22(61.1 %)	
b (−)	21(32.8 %)	4(11.1 %)	P < 0.05(P=0.016)
(+)	43(67.2 %)	32(88.9 %)	
a/b (−/−)	17(26.6 %)	0	P < 0.001(P=0.001)
(+/−)	4(6.3 %)	4(11.1 %)	
(−/+)	29(45.2 %)	14(38.9 %)	
(+/+)	14(21.9 %)	18(50.0 %)	

a : lymphocytes in lymphoid nodule
b : lymphocytes/mononuclear cells in adjacent mucosa and stroma, (−) : DR^-, (+) : DR^+
*Chi-square test

bowel carcinoma (88.9 %) than those with DR^- large bowel carcinomas (67.2 %).

The combined evaluation of rates of presence of both DR^+ lymphocytes in lymphoid nodules and DR^+ lymphocytes/MNCs in mucosa and stroma adjacent to large bowel carcinomas in relation to carcinoma was significantly higher ($P < 0.001$) in DR^+ large bowel carcinomas (50 %) (Fig. 2b) than these with DR^- large bowel carcinomas (21.9 %).

The mucosal epithelial cells distant from the DR^+ tumor expressed no DR, but normal looking cells of glands and crypts, and atypical cells of crypts immediately adjacent to the DR^+ tumor expressed DR (Fig. 2c).

Fence-like stromal infiltrates of DR^+ lymphocytes/MNCs along the margin of invading front tumor (Fig. 3) were present.

DISCUSSION

From the results of this study it is clear that the gain of DR in large bowel carcinomas differ from non-

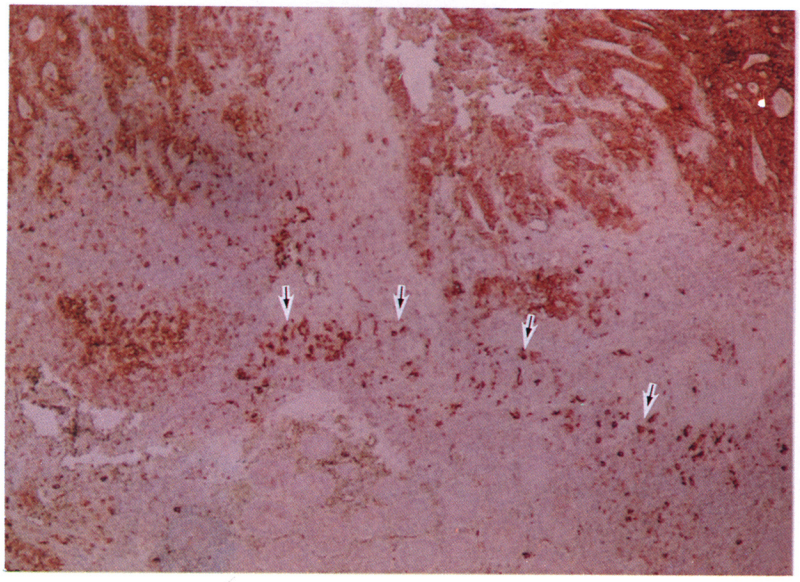

Fig. 3. Fence-like stromal infiltrates of DR^+ mononuclear cells and lymphocytes (arrows) along the periphery of carcinomas apposing the margin of nonneoplastic glands below.

malignant colonic tissue. The expression of DR by human colonic epithelium has also been described in various inflammatory bowel disease such as Crohn s disease and ulcerative colitis (Selby et al., 1983 ; Hirata et al., 1986 ; Fais et al., 1987 ; McDonald and Jewell, 1987 ; Ouyang et al., 1988). It is not clear whether these DRs are synthesized by epithelial cells themselves or whether they are passively adsorbed onto the cell surface. However, the exact reason for the expression of MHC class II antigen in some tumors remains unknown.

In this study there was an increase in the number of MNCs and lymphocytes in the mucosa and development of lymphoid nodules with or without follicle formation in the mucosa and stromal tissue adjacent to the tumor in the majority of cases. Such an increase of MNCs into the lamina propria with an aberrant expression of HLA-DR antigen had been characterized in chronic bowel disease (Selby et al., 1983) and some adenoma and adenocarcinoma of the large bowel (Allen and Hogg, 1985 ; Lampert et al., 1985 ; Umpleby et al., 1985 ; Momburg et al., 1986). Bedossa et al.(1990) also reported that in hyperplastic polyps of large bowel, lymphocytes are increased in the lamina propria, with predominance of the CD4 subset in close contact with DR^+ pericryptal fibroblast, which could act as antigen presenting cells involved in immune cell-mediated reaction. They concluded that this increase of lymphocyte component is a result from a homing phenomenon of circulating lymphocytes rather than a local proliferation because of lack of Ki-67-positive cells.

In this study the rate of appearance of DR^+ lymphocytes (61.1 %) in lymphoid nodules and DR^+ lymphocytes/MNCs (88.9 %) in adjacent mucosa and stroma to carcinoma was significantly higher ($P < 0.01$ and $P < 0.05$) in DR^+ large bowel carcinomas than in DR- large bowel carcinomas (28.1 % and 67.2 % respectively). Thus we assumed that these MNCs and lymphocytes were probably closely related to occurrence of the epithelial DR. Spencer et al.(1986) reported that HLA-DR-positive gut epithelium is strictly associated with adjacent lymphoid tissue, suggesting that products from local MNC are responsible for HLA-DR induction. Lowes et al.(1992) proved that mucosal MNC released a cytokine that induced epithelial DR expression, and the cytokine responsible has the characteristic of IFN-γ. The presence of DR on/in tumor cells is a prerequisite for activation of the $CD4^+$ T cells and the release of cytokines, such as TNF-α, INF-γ. These cytokines and growth factors regulate HLA gene expression via distinct mechanisms.

Thirty-six cases (36 %) out of 100 large bowel carcinomas expressed DR in our series, this result is lower than 76.92 % (20 out of 26) of Norazmi et al. (1989), 52 % (52 out of 100) of Anderson et al.(1993), 50 % of Durrant et al.(1987) and 41.37 % (12/29) of Garcia-Espejo et al.(1986). The reason for the different results may be partly due to the number of examined tumor sections or different methods such as indirect immunofluorescence, and different brand of antigen for DR detection, but it is rather difficult to speculate on the underlying mechanism. These DR-bearing epithelial cells can stimulate the mixed lymphocyte reaction, and present (auto)antigens (Braudtzaeg et al., 1989). Thus, the expression of MCH class II antigen may have a modulating effect on the immune response to tumor possibly by helping in the presentation of tumor-associated antigen to the T-lymphocytes. Green et al.(1977) suggested that the immunological abnormalities noted within the tumor are a result of the changed nature of the epithelium, such as altering or interfering with the normal interactions between epithelial and lymphoid tissue in the gut.

In this study the extensive infiltration of DR^+ MNCs and lymphocytes forming a fence-like boundary apposing the margin of invading front carcinoma and peritumoral lymphocytic infiltration appears to be a morphological manifestation of host immunological response to prevent further tumor invasion. The increased number of MNCs in the periphery of these tumors could also indicate better host immunologic defense mechanisms against the tumor. This suggests DR^+ MNCs and lymphocytes play an important role in the immune network that regulates further invasion. Two patterns, homogeneous and heterogeneous, DR expressions were noted, and these patterns were related to the degrees of differentiation. Epithelial DR expression was more homogeneous in poorly differentiated tumors whereas DR expression was heterogeneous in patchy patterns with various intensities in higher differentiation (moderate to well differentiated tumors). These findings agree with previous studies (Daar et al., 1982 ; Rognum et al., 1983 ; Durrant et al., 1987).

Durrant et al.(1987) reported that aneuploid tumors expressed DR with significantly stronger intensity ($P < 0.005$) than diploid tumors ; only one of the

aneuploid tumors stained heterogeneously whereas over half of the diploid tumors showed this patchy expression, and 80 % of the aneuploid tumors expressed DR antigen whereas only 27 % of diploid tumors expressed this antigen.

In this study homogeneously strong DR expressions of cancer cells were more frequently in poorly differentiated carcinoma (75 %) compared to moderately differentiated carcinoma (20 %). One case showed two distinct patterns in expression of DR within a section ; the portion of poorly differentiated tumor cells revealed homogeneously strong expression of DR while the portion of well differentiated tumor cells expressed DR heterogeneously with various intensities. This possibly resulted from the presence of divergent clones of neoplastic cells within the same tumor, some of these clones showed different histologic patterns and phenotypes (Stemmerman et al., 1994). Thirty-five (97.2 %) out of 36 DR^+ tumor were in Dukes' stage B and C, and 1 (2.7 %) out of 36 DR^+ tumor were in Dukes' stage D showing focal heterogeneous expression. Distant metastatic carcinomas were mostly DR^-. This finding was agreed with the report of Thompson et al.(1982). From these findings we assumed that perhaps tumors were maintained and seed by cell surface DR^- tumor cells which may be easy to escape immune recognition. Sadanaga et al. (1994) reported that DR may prevent tumor invasion, whereas the negative expression of DR antigen may facilitate tumor invasion in esophageal squamous cell carcinoma. In accordance with previous reports (Daar et al., 1982 ; Rognum et al., 1983 ; Csiba et al., 1984 ; Momburg et al., 1986 ; Ghosh et al., 1986 ; Moore et al., 1986 ; Degener et al., 1988) we found DR absent from normal colonic mucosa distant from DR^+ large bowel carcinoma, but DRs were detected on normal and abnormal crypt cells in the transitional mucosa immediately adjacent to the DR^+ large bowel carcinomas, even in the absence of an inflammatory infiltrate or morphological change in crypts characteristic of colitis. We assume that minute changes had taken place, not yet being discernible on morphological grounds, leading to variations in the immunophenotype. From the results of this study and in accordance with other reports (Moore et al., 1986, Nagura, 1992 ; Sato et al., 1993) it is reasonable to assume that the possible functions for DR on large bowel carcinoma and its adjacent mucosa are :

1. A role in antigen presentation. Tumor cells expressing DR may act as antigen-presenting cells and present the so-called abnormal self to host cells.
2. An inhibitory effect for distant metastasis, which may results in effect of an antigen by DR^+ tumor cells which may be faciliated for immune recognition.
3. Better differentiated tumor expressed less DR heterogeneously whereas poorly differentiated tumor expressed more DR homogeneously.

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