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Differential expression of HLA-DR, HLA-DP, HLA-DQ and associated invariant chain (Ii) in normal colorectal mucosa, adenoma and carcinoma

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Summary. The expression of MHC class II antigens (HLA-DR, HLA-DP and HLA-DQ) and the associated invariant chain (Ii) was studied in epithelial cells of normal colorectal mucosae, colorectal adenomas and carcinomas, using a sensitive immunoperoxidase technique with monoclonal antibodies on frozen sections. In contrast to class II antigens, Ii was detected in some normal mucosae distant from the tumour. In residual non-neoplastic mucosa adjacent to carcinomas, Ii and class II antigens were induced in the order Ii ≥ HLA-DR ≥ HLA-DP ≥ HLA-DQ, the reactions being most pronounced in cases with inflammatory alteration of the crypts. In 22/37 adenomas and 77/123 carcinomas, Ii expression clearly exceeded class II antigen expression. Class II antigens were found in 20/37 adenomas and 62/123 carcinomas, mostly in a non-coordinate manner, following the above order. A detailed analysis of the expression patterns in normal and neoplastic colon epithelial cells revealed a closer association of HLA-DP with HLA-DQ than of HLA-DR with HLA-DP, or HLA-DQ.

Key words: HLA-D antigens – HLA-D-associated invariant chain – Colonic mucosa – Non-specific colitis – Colorectal neoplasms

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 foreign antigen and induction and regulation of T cell activation (Kaufman et al. 1984; Giles and Capra 1985).

These products are detectable on B cells, activated T cells and some cells of the myelomonocytic lineage, as well as on endothelial cells and a limited number of normal epithelia (Winchester and Kunkel 1979; Daar et al. 1984). In the cells of mesenchymal and epithelial origin in particular, MHC class II antigen expression can be considerably influenced by inductive (e.g., interferons) or inhibitory stimuli (e.g., corticosteroids) (Pober et al. 1983; Todd et al. 1985; Leszczynski et al. 1986). Using monoclonal antibodies (mAbs) with specificity for HLA-D subregion products, differential expression of HLA-DR, HLA-DP and HLA-DQ antigens has been found in many cell types (Gonwa et al. 1983; Natali et al. 1984; Fermand et al. 1985; Carr et al. 1986); on B cells and myelomonocytic cells they appear sequentially in the course of maturation (Edwards et al. 1985; Alonso et al. 1985).

In cytoplasmic compartments, MHC class II α and β chains are associated with the non-polymorphic invariant chain (Owen et al. 1981). Though the respective genes are located on different chromosomes, invariant chain (Ii) and MHC class II antigens were reported to be co-regulated (Claesson-Welsh et al. 1984; Symington et al. 1985); stimuli like interferon-γ cause their concomitant induction (Collins et al. 1984; Momburg et al. 1986a). It has been proposed that Ii may be involved in intracellular transport and recycling of class II molecules (Kvist et al. 1982; Claesson and Peterson 1983).

In contrast with normal colorectal epithelium, an aberrant expression of MHC class II antigens has been shown for colorectal carcinoma (Daar et al. 1982; Rognum et al. 1983; Csiba et al. 1984;

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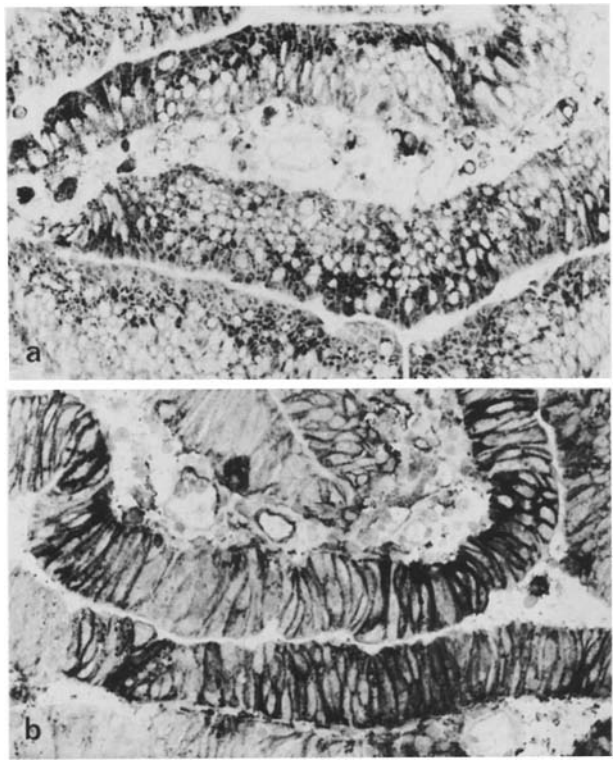

Fig. 1. Colon adenoma (×200). **a** Staining for the invariant chain reveals the intracytoplasmatic localization of the antigen. **b** In contrast, HLA-DR antigens are detected in the cytoplasma and on the cytomembrane. (Immunoperoxidase stainings of frozen sections using aminoethylcarbazole as the chromogene, faint haematoxylin counterstain, same technique for all photomicrographs)

Momburg et al. 1986b). Recently, Ghosh et al. (1986) reported a non-coordinate expression of HLA-D subregion products in gastrointestinal tumours. However, at present no information is available on the expression of Ii in epithelial neoplasms.

In this report we describe the expression of Ii in normal colorectal mucosa, colorectal adenoma and carcinoma and compare it with the expression of HLA-DR, -DP and -DQ antigens.

Material and methods

The tissue specimens included in this investigation were obtained from patients admitted for large bowel resection or polypectomy at the surgical department of the University of Heidelberg, FRG. They comprised 17 specimens of normal colon or rectal mucosa from sites distant from the tumour (margin of resection), 37 colorectal adenomas and 123 colorectal carcinomas, 43 of which contained remnants of non-neoplastic mucosa. The diagnosis was confirmed on the basis of haematoxylin/eosin stained paraffin sections. The typing, grading and staging of carcinomas was performed according to the classifications given by the UICC (Morson and Sobin 1976; UICC 1987). 23 adenomas were of tubulous, 11 of tubulovillous, and 3 of villous type. The histopathological types of the carcinomas were: adenocarcinoma (93), adenocarcinoma with mucinous differentiation (21), signet ring cell carcinoma (2), adenosquamous carcinoma (1), undifferentiated carcinoma (4) and unclassified (2). 14 carcinomas were graded "well differentiated", 86 "moderately well differentiated", and 23 "poorly differentiated". The anatomical sites of the carcinomas were: caecum (7), ascending colon (23), hepatic flexure (5), transverse colon (6), descending colon (3), sigmoid colon (36), rectum (41) and unknown origin (2).

Representative samples of the tumours and normal large bowel were snap-frozen in liquid nitrogen and stored at −70° C until sectioning. Serial sections of 4–6 µm thickness were cut, extensively air-dried, fixed in acetone for 10 min at room temperature; stained immediately or stored at −20° C for a short time.

The following monoclonal antibodies (mAbs) with specificity for non-polymorphic determinants of HLA class II antigens and for the invariant chain were used: ISCR3 (anti-HLA-DR: Watanabe et al. 1983; Pesando and Graf 1986), B7/21 (anti-HLA-DP: Watson et al. 1983), Tü22 (anti-HLA-DQ: Ziegler et al. 1982; Pawelec et al. 1982) and VIC-Y1 (anti-Ii: Quaranta et al. 1984). ISCR3, Tü22 and VIC-Y1 were kind gifts of L. Graf, Seattle, USA; A. Ziegler, Tübingen, FRG, and W. Knapp, Vienna, Austria, respectively. B7/21 was obtained from Becton Dickinson, Mountain View, CA, USA.

After rehydration with phosphate buffered saline (PBS), the frozen sections were incubated for 1 h with culture supernatants or purified mAb at appropriate dilutions. The sections were then incubated with biotinylated anti-mouse immunoglobulin (1:50) and streptavidin peroxidase complex (1:100) (both from Amersham, High Wycombe, UK) at room temperature for 30 min. In order to avoid cross-reactions; the second antibody was used in the presence of 5% pooled human IgG. All incubation steps were carried out in a humid chamber at room temperature and followed by rinsing with PBS and a further 10-min-wash with PBS. The binding of antibody was visualized by incubating with 0.4 mg/ml 3-amino-9-ethylcarbazole (Sigma, St. Louis, MO, USA), 5% dimethylformamide (Sigma) and 0.015% H_2O_2 in 0.1 M acetate buffer, pH 5.2, for 10 min. The sections were counterstained with Harris' haematoxylin and mounted with glycerol gelatine.

Intrinsic positive controls for the immunoreactivity of Ii and class II mAbs were interstitial dendritic cells, endothelial cells and macrophages that indicated by their staining the reliability of the reaction and thus excluded false negative results. Negative controls were performed by omitting the primary antibody. Endogenous peroxidase activity of occasional granulocytes was not blocked because it was easily distinguishable from specific immunostaining.

Immunoperoxidase staining of normal and neoplastic colorectal epithelial cells were evaluated by two observers applying the following semiquantitative scoring system. 5, all cells positive; 4, distinctly more positive than negative cells; 3, positive and negative cells in about equal proportions; 2, distinctly more negative than positive cells; 1, small subset (<5%) positive; 0, all cells negative.

Results

The expression of MHC class II subregion products and of the associated invariant chain (Ii) was studied in epithelial cells of normal colorectal mucosae, colorectal adenomas and carcinomas by immunohistology on serial frozen tissue sections.

Table 1a. Expression of Ii, HLA-DR, HLA-DP and HLA-DQ in 17 specimens of normal colorectal mucosa (distant from the tumour)

Score	Ii	DR	DP	DQ
5[a]	0[b]	0	0	0
4	1	0	0	0
3	2	0	0	0
2	3	0	0	0
1	4	0	0	0
0	7	17	17	17

[a] Immunoreactivity of epithelial cells: 5 all cells positive; 4 distinctly more positive than negative cells; 3 positive and negative cells in about equal proportions; 2 distinctly more negative than positive cells; 1 small subset (<5%) positive; 0 all cells negative
[b] Number of cases

Table 1b. Expression of Ii, HLA-DR, HLA-DP and HLA-DQ in 33 cases of non-neoplastic normal mucosa adjacent to carcinoma or adenoma

Score	Ii	DR	DP	DQ
5	7	2	2	0
4	3	1	0	0
3	18	4	2	2
2	3	4	1	2
1	1	2	1	1
0	1	20	27	28

Table 1c. Expression of Ii, HLA-DR, HLA-DP and HLA-DQ in 18 cases of non-neoplastic colitic mucosa adjacent to carcinoma

Score	Ii	DR	DP	DQ
5	16	11	5	3
4	2	1	0	0
3	0	5	3	4
2	0	1	3	2
1	0	0	1	1
0	0	0	6	8

Table 1d. Expression of Ii, HLA-DR, HLA-DP and HLA-DQ in 37 colorectal adenomas

Score	Ii	DR	DP	DQ
5	0	0	0	0
4	4	0	0	0
3	5	1	0	0
2	7	5	1	1
1	13	14	9	3
0	8	17	27	33

Table 1e. Expression of Ii, HLA-DR, HLA-DP and HLA-DQ in 123 colorectal carcinomas

Score	Ii	DR	DP	DQ
5	16	4	2	1
4	18	10	5	2
3	17	7	6	1
2	25	15	11	8
1	26	26	22	17
0	21	61	77	94

Characteristically, the cellular binding pattern of mAb VIC-Y1 revealed cytoplasmic location of Ii (Fig. 1a), while class II antigens were detected within the cytoplasm and on the cytomembrane (Fig. 1b). The results of the semiquantitative evaluation of the staining are summarized in Table 1a–e. In all normal mucosae and adenomas, and in all but one carcinoma, stainings with at least one of the mAbs used was heterogeneous, that is to say, positive and negative epithelial cells occurred on the same section among the epithelial cells of a given type. As a common feature to every serial immunostaining, HLA-DQ-positive subsets of epithelial cells were always completely included in HLA-DP-positive subsets, which were always completely included in HLA-DR-positive subsets, which in turn were always entirely covered by Ii-positive subsets; in short: Ii ≥ HLA-DR ≥ HLA-DP ≥ HLA-DQ (Fig. 4a–c).

Colorectal mucosa from sites distant from carcinoma (mostly derived from the margins of resection) showed no histopathological anomalities. Ii was expressed in epithelial cells in 10 of the 17 specimens studied (Table 1a), however, the predominantly weak staining was confined to the basal parts of the crypts, the middle parts were less frequently stained, and the upper parts and surface epithelium were unreactive (Fig. 2a). In 5 cases, the epithelium was only focally positive. These foci were not more than haphazardly associated with lymph follicles. No reactions for HLA-DR (Fig. 2b), HLA-DP and HLA-DQ antigens were observed.

Residual untransformed mucosa was evaluated on the same section in 39 cases of carcinoma and 4 cases of adenoma. In 18 of the 39 cases, mucosa adjacent to carcinoma or at least parts of it exhibited the signs of non-specific colitis with mucous cell depletion, elongation of crypts, and a considerable inflammatory cell infiltrate. In 29 of 39 carcinomas and in 4 adenomas the entire adjacent mucosa or parts of it were morphologically unaltered and were therefore termed "normal". Except for one negative case, Ii was expressed in crypt epithelial cells to varying extents (Table 1b). The predominantly strong staining started from the basis of the crypts and reached different levels in individ-

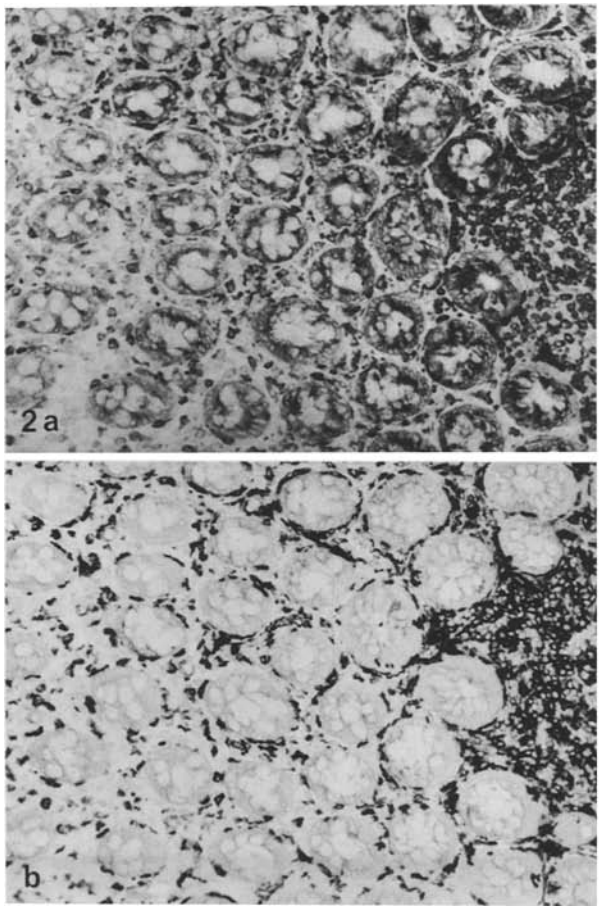

Fig. 2. Serial sections of normal colonic mucosa, distant from a carcinoma (×125). **a** Ii is expressed in the basal parts of the crypts, lymphocytes of an intramucosal lymph follicle and some interstitial dendritic cells of the lamina propria. **b** Colon epithelium is completely devoid of HLA-DR while lymphocytes and interstitial dendritic cells are heavily stained

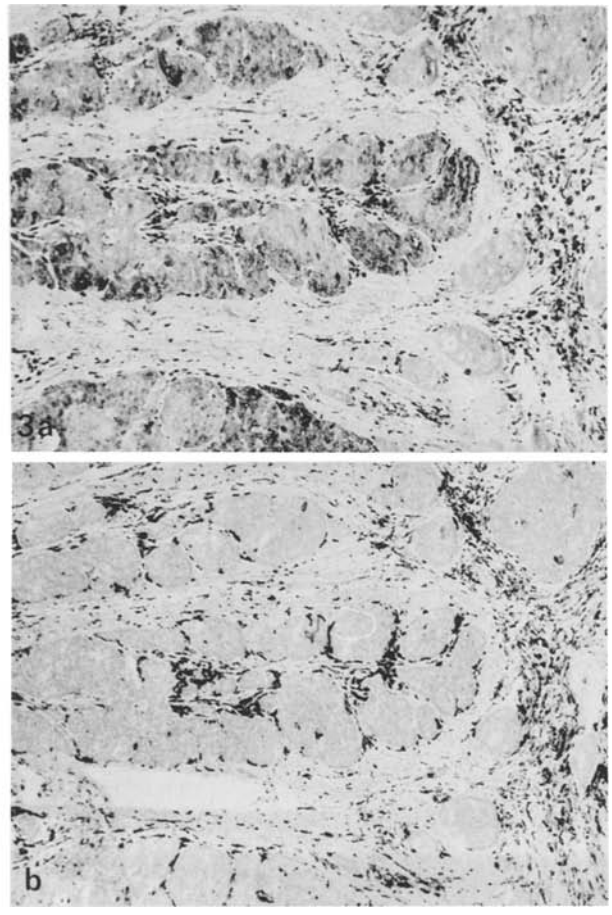

Fig. 3. Serial sections of a moderately well differentiated adenocarcinoma (×50). **a** Ii is expressed in the majority of tumour cells and in inflammatory cells of the tumour stroma. **b** In contrast, no HLA-DR antigens are detectable within the neoplastic population

ual cases. In 7 cases, every non-neoplastic epithelial cell was labeled (Fig. 5a). Staining for HLA-DR, HLA-DP and HLA-DQ revealed positive epithelial cells at a considerably lower frequency (Fig. 5b–c). In the majority of cases, normal tumour-adjacent mucosa was non-reactive for class II antigens.

With regard to residual untransformed mucosa apparently involved by reactive colitis, only 2 cases showed a heterogenous staining for Ii (Table 1c). In the remaining 16 cases, all non-neoplastic epithelial cells were Ii-positive, which was the case for HLA-DR in 11 cases, for HLA-DP in 5 cases and for HLA-DQ in 3 cases. There were cases with completely HLA-DP$^-$ or HLA-DQ$^-$ colitic mucosa adjacent to carcinoma, but no Ii$^-$ or HLA-DR$^-$ cases.

In the 37 colorectal adenomas studied, expression of Ii was detected in 29 cases (Table 1d). The heterogenous reaction varying from a majority of tumour cells stained (score 4) (Fig. 3a) to small foci of tumour cells stained (score 1). None of the adenomas expressed Ii in the entire neoplastic population. With considerably decreasing frequency, Ii-positive tumour cells were also stained for HLA-D subregion products (Fig. 3b) in the order HLA-DR → HLA-DP → HLA-DQ.

The expression of invariant chain and class II antigens was more pronounced in colon carcinoma cells than in benign lesions (Table 1e). 16 carcinomas were completely Ii-positive and there were relatively more carcinomas than adenomas with staining scores 4 and 3. The number of carcinomas attributed to staining scores 5 to 1 decreased in the order Ii → HLA-DR → HLA-DP → HLA-DQ.

In order to describe relationships between the expression of the four antigens studied, the set of

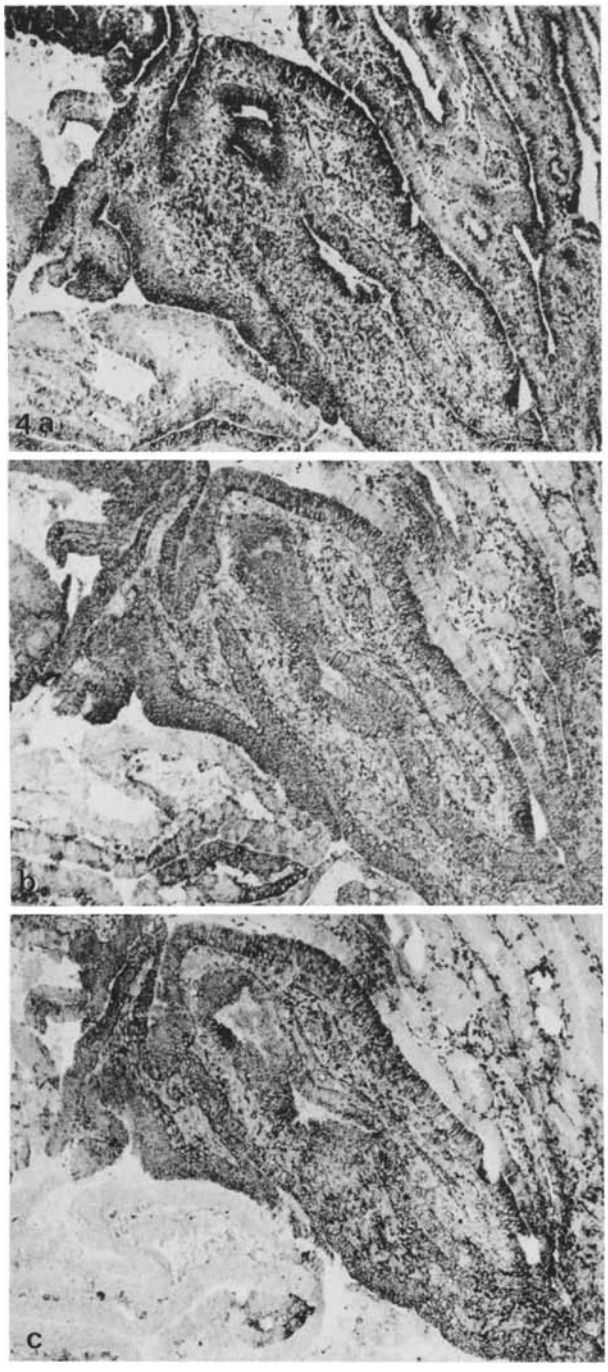

Fig. 4. Serial sections of a tubulo-villous adenoma stained for Ii (**a**), HLA-DR (**b**) and HLA-DP (**c**); (×39). Tumour cells depicted in the upper right corner differentially express Ii and class II antigens: they are predominantly Ii^+, the minority of them expresses HLA-DR, and a still smaller subset of them is $HLA\text{-}DP^+$. Other parts of the tumour (*center*) are equally stained for the three antigens

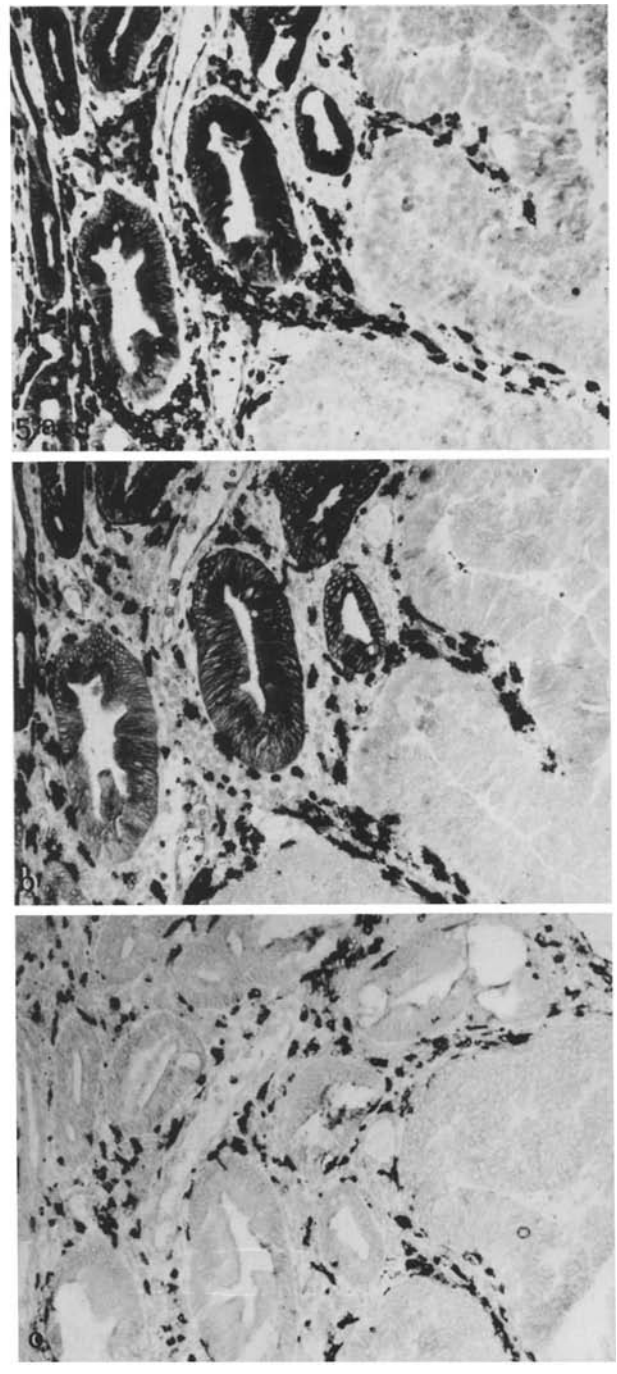

Fig. 5. Serial sections showing non-neoplastic mucosa with features of colitis adjacent to a carcinoma, stained for Ii (**a**), HLA-DR (**b**), and HLA-DQ (**c**); (×100). This individual tumour does neither contain Ii nor class II antigens. The colitic mucosa, however, is strongly stained throughout for Ii and HLA-DR illustrating an induction of these antigens in the course of inflammation while HLA-DP (not shown) and HLA-DQ are not induced. Apparently, the tumour cells are refractory to stimuli leading to antigen induction in untransformed epithelial cells

Table 2. Patterns of Ii, HLA-DR, HLA-DP and HLA-DQ expression

	Carcinoma	Adenoma	Adjacent mucosa		Distant mucosa	Σ
			normal	colitic		
Ii > DR > DP > DQ	6	2	0	0	0	8
Ii > DR > DP = DQ	14	8	7	3	0	32
Ii > DR = DP > DQ	6	1	1	0	0	8
Ii > DR = DP = DQ	51	11	21	4	10	97
Ii = DR > DP > DQ	7	0	0	1	0	8
Ii = DR > DP = DQ	8	4	1	5	0	18
Ii = DR = DP > DQ	7	2	1	2	0	12
Ii = DR = DP = DQ	24	9	2	3	7	45

Staining scores of individual cases were attributed to patterns describing the modes of coexpression of Ii and HLA-D subregion products. The table shows that non-coordinate expression of Ii occurs frequently, and that HLA-DP and HLA-DQ are more often coexpressed than HLA-DR and HLA-DP, or HLA-DR and HLA-DQ

staining scores of each individual case was attributed to one of the 8 patterns given in Table 2, which indicate the mode of coexpression. In only 45 of the 228 cases of carcinoma, adenoma, colitic and normal mucosa were the staining scores for Ii, HLA-DR, -DP and DQ identical. The most frequent pattern of non-coordinate expression was Ii > DR = DP = DQ (97 cases) followed by Ii > DR > DP = DQ (32 cases) and Ii = DR > DP = DQ (18 cases). The tissues with non-coordinate expression of HLA-DR and HLA-DP add up to 66, those with non-coordinate expression of HLA-DP and HLA-DQ add up to 36, and in 145 cases Ii and HLA-DR were differentially expressed.

As revealed by statistical analysis, there was no significant correlation between type, grade, stage and site of the carcinomas on the one hand and their staining scores for Ii, HLA-DR, HLA-DP and HLA-DQ on the other (data not shown). Likewise, the histological types of adenomas did not correlate with Ii or class II antigen expression.

Discussion

The present investigation demonstrates that MHC class I antigens and the associated invariant chain are differentially expressed in normal and neoplastic colonic epithelial cells. In contrast to HLA-DR, -DP and -DQ, Ii could be detected in normal colonic mucosa, although this expression was inconstant. In parallel with a de novo expression of MHC class II antigens, Ii expression is substantially enhanced in residual mucosa adjacent to colorectal tumours, both without and, in a even more pronounced manner, with inflammatory change. Finally, in 22/37 colorectal adenomas and 77/123 carcinomas Ii expression distinctly exceeded class II antigen expression.

So far, only a few human tissues have been studied for the presence of invariant chain. Quaranta et al. (1984) reported a concomitant expression of Ii and HLA-DR in peripheral blood, B cells and monocytes as well as in Kupfer cells and Langerhans cells. Volc-Platzer et al. (1984) studying keratinocytes in various disease states, and Hansson et al. (1986) studying smooth muscle cells in atherosclerotic plaque found no differences between the tissue reactivities for HLA-DR and Ii. An $Ii^+/HLA\text{-}DR^-$ phenotype, however, was reported to occur rarely in thyroid epithelial cells in Hashimotos thyroiditis (Möst et al. 1986). Moreover, B lymphoma cells occasionally express Ii in the absence of HLA-DR, -DP and -DR (Momburg et al. 1987). To our knowledge, this is the first report on differential Ii and MHC class II antigen expression in normal human tissue. This finding, together with the excessive Ii expression in colorectal epithelium under pathological conditions, is suggestive of a differential regulation of the Ii gene and the HLA-D genes in certain tissues. Previous studies using defective variants of erythroid and B lymphoblastoid cell lines with cultured human endothelial cells and dermal fibroblasts have indicated a co-regulated transcription of these unlinked genes (Long et al. 1984; Collins et al. 1984; Symington et al. 1985). The detection of Ii in the absence of class II antigens speaks in favour of previously suggested ideas that Ii may have additional functions other than facilitating transport and processing of class II molecules (Sekaly et al. 1986; Koch et al. 1987).

In accordance with other reports (Daar et al. 1982; Rognum et al. 1983; Csiba et al. 1984; Momburg et al. 1986b; Ghosh et al. 1986) we found class II antigens absent from normal colon mucosa distant from the tumour. HLA-DR, HLA-

DP and HLA-DQ were, however, found in normal mucosa adjacent to the tumour. Interestingly, even in the absence of an inflammatory infiltrate and the morphological changes in crypts characteristic of colitis, HLA-DR antigens could often be detected in these crypts, and so but more rarely could HLA-DP and HLA-DQ. We assume that minute changes had taken place, not yet being discernible on morphological grounds, however, leading to variations in the immunophenotype. In this context, the invariant chain appears to be an even more sensitive marker for a presumptive "minimal change colitis".

In agreement with Ghosh et al. (1986) we found the de novo expression of class II subregion products in colorectal adenomas and carcinomas to follow the hierarchy HLA-DR ≥ HLA-DP ≥ HLA-DQ strictly indicating a sequential induction in the sequence HLA-DR → HLA-DP → HLA-DQ. A more detailed analysis of the patterns of non-coordinate class II antigen expression (Table 2) revealed a closer association of DP and DQ expression than of DR and DP expression in colon epithelial cells. Since differential functions of class II subregion products have not been disclosed with certainty, the significance of this finding remains unclear at present.

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