Analysis of Human Leukocyte Antigen Classes in Patients with Prostate Cancer and Benign Prostate Hyperplasia

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ABSTRACT:

BACKGROUND:

Certain HLA alleles are occurring in a higher frequency in individuals with particular diseases than in the general population.

METHODS:

HLA-typing for class I and class II antigens expressed by cells of 40 patients with prostatic adenocarcinima (CAP) and 48 patients with benign prostatic hyperplasia (BPH), ranged in age between 48-80 years were detected by lymphocytotoxicity test using 16A, 39B, 7CW, 14DR and 4DQ antisera.

RESULTS:

Patients with BPH showed an increased frequency in HLA DR_{53}, while CAP patients showed an increased frequency in HLA-A_{33} and HLA DR_{53} antigens compared to 100 healthy Kidney donor individual as a control. The increase in HLA- antigens frequency was proved by statistical analysis, relative risk (RR) and etiological function (EF) values estimation.

CONCLUSION:

Possibility in the future, for novel selective immunomodulatory therapeutic strategies which stimulate a clinically significant re-expression of class I protein and associated with CTL responses.

KEYWORDS: HLA, Prostate cancer .

INTRODUCTION:

In recent years there has been considerable interest in the association between HLA antigens and diseases.[1] certain HLA alleles are occurring in a higher frequency in individuals with particular diseases than in the general population. This association between HLA alleles and a given diseases may be quantified by typing the HLA alleles expressed by individuals with the diseases and the HLA alleles of the general population, by comparing the frequency of that alleles in the patients with the alleles frequency in the general population by estimation of the relative risk (RP) value[2] Terasakietal [3] mentioned that there is a weak association between HLA. A28 and HLA-B22 alleles with CAP. Barrry[4] with coworkeus failed to demonstrate a significant HLA-A and Bantigens association with CAP in 1993, carter *et al.*[5] mentioned that the eitology of herediatery CAP results from a single gene passed along in families that confers a greatly increased susceptibility for this diseases to develop and the men with family history of CAP are at a significantly increased risk for this diseases. [6,7] The frequencies of HLA- DR_4 and HLA-DR_1 alleles were reported by[8] to be significantly higher in Japanese men with CAP than in the healthy control group while [9], reported that HLA-A, and HLA-A_2 alleles frequency were decreased or lost in approximately 90% of 34 cases of primary locally invasive CAP.

This raises the possibility in the future, for novel selective immunomodulatory therapeutic strategies which stimulate a clinically significant re-expression of class I protein and associated with CTL responses [9] for these facts we intended to study the pattern of HLA antigens expressed by the cells of prostate cancer patients.

SUBJECTS, MATERIALS, AND METHODS:

Forty patients with newly diagnosed CAP untreated, age range 48-80 years and forty eight males patients with benign hyperplasia (BHP) (age range 50-80 years) were involved in the study.

Samples were collected from six hospitals in Baghdad and Baquba in addition to hundred healthy adults age range from 50-70 years old.

Blood samples: 5 milliliters of blood samples were collected by venepuncture from each patient and control subject in a bottle containing glass beads.

Isolation of peripheral blood lymphocytes: Lymphocytes were separated by density gradient centrifugation as mentioned by (Eremin etal, 1981) 10

Serological typing of HLA: the most widely used procedure for serological detection of HLA-antigens(class 1 and 11), has been the microcytotoxicity test (Biotest data sheet, 1989)

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has been conducted to study type of HLA of our patient.

The assay was performed at Al-Karama hospital.

Statistical analysis: Anovatest, Bonferronit- test and pearson's correlation coefficient were used to analyze the results.

RESULTS:

BPH patients Vs. control As shown in table 1 the antigen frequency of HLA-A_3 increased significantly in BPH patients (27.1%) as compared to control. Such observation was associated with RR value of (3) and EF value of (0.17) (p=0.016). However, the significant concerning HLA-A_3 in BPH patients was to be not significant after correction of p value (0.192) table (2). Similarly the antigen frequencies of H(A-B_{51} and HLA-B_{53}) were significantly increased in those patients (43.8% , 14.6%) as compared to control (21%, 3%) respectively table (1). The frequencies of HLA-CW_7 and HLA-DR_1 antigens were significantly decreased in BPH patients. DR_{53} frequency was significantly increased in BPH patients. Finally HLA-DQ_1 was significantly decreased in BPH patients.

CAP patients Vs. control As shown in table (1) the frequency of HLA-A_2 was significantly decreased in CAP patients compared to control (17.5 Vs 41). In contrast the frequencies of HLA-A_{42} (27.5%) and HLA-A_{33} (35%) were significantly increased in patients than control (12% Vs 13%). As in BPH patients, there was significantly increased in HLA-B_{53}, HLA-Cw_1, table(2). CAP Vs. BPH patients: The results obtained from table(1) revealed that frequency of HLA-A_2 in CAP patients (17.5%) was significantly less than these in BPH patients (37.55).The frequency of HLA-A_{33} in CAP patients (35%) was significantly higher than those in BPH Patients (10.4%) and HLA-DQ_1 antigen frequency in CAP patients was (42.5%) significantly higher than those in BPH patients (12.55).There were no significant differences in the antigen frequencies of remainder HLA-antigens tested. Table2.

Table 1: HLA-antigens frequencies in control, BPH and CAP Groups.

HlA- antigens	Control (n=100)		BPH (n=48)		CAP (n=40)	
	N	%	N	%	N	%
HLA-A Locus 1	22	22.0	7	14.6	3	7.5
2	41	41.0	18	37.5	7	17.5
3	11	11.0	13	27.1	8	20.0
11	13	13.0	10	20.8	8	20.0
23 (9)	8	8.0	2	4.2	1	2.5
24 (9)	12	12.0	11	22.9	11	27.5
26 (10)	12	12.0	5	10.4	4	10.0
28	13	13.0	2	4.2	2	5.0
29	3	3.0	1	2.1	1	5.5
30	16	16.0	2	4.2	2	5.0
32	8	8.0	4	8.3	3	7.5
33	13	13.0	5	10.4	14	35.0
HLA- B locus 7	13	13.0	3	6.3	3	7.5
8	12	12.0	3	6.3	3	7.5
14	3	3.0	1	2.1	1	2.5
17	5	5.0	1	2.1	1	2.5
18	8	8.0	4	8.3	4	10.0
27	2	2.0	2	4.2	0	0.0
35	19	19.0	10	20.8	9	22.5
40	3	3.0	2	4.2	1	2.5
41	12	12.0	4	8.3	2	5.0
44 (12)	13	13.0	2	4.2	3	7.5
45 (12)	3	3.0	2	4.2	2	5.0
49 (21)	9	9.0	2	4.2	1	2.5
50 (21)	11	11.0	2	4.2	4	10.0
51 (5)	21	21.0	21	43.8	13	32.5
52 (5)	3	3.0	1	2.1	3	7.5
53	3	3.0	7	14.6	8	20.5
60	1	1.0	0	0.0	0	0.0
62 (15)	2	2.0	1	2.1	1	2.5
63 (15)	4	4.0	1	2.1	0	0.0
73	1	1.0	0	0.0	1	2.5

Table 2: Significant variations of HLA-antigen in patients with BPH, CAP and control.

Groups	HLA-antigen	RR	EF	PF	X^2	P	Pc
BPH vs. control	A3	3	0.17		5.831	0.016	0.192[NS]
	B51 (5)	2.9	0.27		7.953	0.005	0.1[NS]
	B53	5.5	0.11		5.713	0.017	0.34[NS]
	Cw7	0.3		0.22	6.011	0.014	0.084[NS]
	DR1	0.3		0.18	6.282	0.012	0.132[NS]
	DR35	7.1	0.22		12.082	0.001	0.011
	DQ1	0.4		0.15	4.177	0.041	0.164[NS]
CAP vs. control	A2	0.3		0.28	6.565	0.010	0.120[NS]
	A24 (9)	2.8	0.17		4.755	0.029	0.348[NS]
	A33 (19)	3.6	0.25		8.287	0.004	0.048
	B35	8.1	0.17		8.736	0.003	0.060[NS]
	Cw1	14.1	0.11		5.666	0.017	0.102[NS]
	Cw7	0.3		0.22	5.177	0.023	0.138[NS]
	DR53	6.3	0.21		9.908	0.002	0.022[NS]
CAP vs. BPH	A2				4.126	0.042	0.504[NS]
	A33 (19)				7.052	0.008	0.096[NS]
	DQ1				9.227	0.002	0.008[NS]

RR = Relative risk.
EF = Etiological fraction
PF = Preventive fraction
X^2 = Chi- square test, Significance >3.84.
P= Probability, Significance <0.05
Pc = Corrected probability
NS= Not significant variation

DISCUSSION:

It has been suggested that heredity may be an etiologic factor in the development of CAP because there are many cases of familial CAP have been reported [5][6][7]. There is a relationship between CAP and some alleles of HLA antigens , these MHC class II epitopes are particularly important because there is increasing evidence from both human and animal studies that CD4+ T cells are required for the generation and maintenance of a cytolytic CD8+ antitumor immune response [9 .10].

In the present study, we found that there were a significant associations in BPH patients with HLA-A_3, HLA-B_{51}, HLA-B_{53} and HLA-DR_{53} alleles with a RR value of >1. While there were a significant associations with HLA-Cw_7, HLA-DR_1 and HLA-DQ_1 alleles but with RR value of <1. These observation were in contrary to the findings mentioned by [7] who reported that the HLA-DR_1 alleles has been detected in (74%) of the familial BPH more than healthy controls (64%).

In CAP patients there were a significant associations with HLA-A_{24} - HLA-A_{33}, HLA-B_{53}, HLA-Cw_1 and HLA-DR_{53} with RR >1. There were a significant associations with HLA-A_2 and HLA-Cw_7 but with RR <1. Our findings seem to correlate different HLA antigens with the disease when compared with other works[6][7].

Recognition of tumor cells by cytolytic T lymphocytes depends on cell surface MHC class I expression. As a mechanism to evade T cell recognition, many malignant cancer cells, including those of prostate cancer, down-regulate MHC class I. For the majority of human cancers, the molecular mechanism of MHC class I down regulation is unclear, although it is well established that MHC class I down-regulation is often associated with the down-regulation of multiple genes devoted to antigen presentation(12) .

In general the initiation of the two diseases (CAP and BPH) seem to require HLA-DR_{53}.

On the other hand the deficiency of HLA-A_2 fits well with the results of [9].

This alleles seems to generate CTL against oligoepitope peptide of prostate specific antigen in CAP patients. Heterogeneity of the two diseases (CAP and BPH) was different with respect to HLA-antigens distribution and HLA-DQ_1 the land mark of such heterogeneity with (P_6) significance value of 0.008, therefore there was no relationship between the two different diseases [13].

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