

EXPRESSION OF HLA-DR ANTIGEN ON ENDOTHELIAL CELLS IN KIDNEY ALLOGRAFTS

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Summary

The expression of HLA-DR antigen on endothelial and tubular cells was tested in 55 fine needle aspiration biopsies in 30 patients. A three-stage immunoperoxidase technique was used. The first step was to incubate the sections with a mouse monoclonal antibody (DACO M704). There was a positive correlation between the expression of this antigen and the degree of rejection, which may be helpful in the early characterization of rejection.

Introduction

In 1984 Doniach et al [1] demonstrated HLA-DR antigens on thyroid cells in 46 cases of autoimmune thyroid disease. It is possible that the expression of class II antigens is also variable in man. In renal tissue class II antigens were demonstrated on endothelium cells, on dendritic cells and on tubular cells [2,3]. We still have no clear view of the significance of this in renal transplantation. These surface markers might behave like conventional antigens or they could characterize antigen presenting cells.

This study explores whether HLA-DR antigens are constantly expressed on endothelial cells after renal transplantation and whether there is a correlation to the extent of rejection.

Method

Using the method of Häyry [4], 55 fine needle aspiration biopsies were taken from 30 patients after renal transplantation. The indication for biopsy was an increase of the plasma creatinine $>0.05\text{mg}/100\text{ml}$. For immunosuppression combination therapy with Cyclosporin A and steroids was used. The extent of rejection was determined by counting the mononuclear cells according to the increment [4].

HLA-DR antigens were demonstrated by using a three stage immunoperoxidase technique. The first step was to incubate the slides with a mouse monoclonal antibody (Type IgG_{2a}) (DACO M704). This antibody reacts with a determinant present on the β -chain of all HLA-DR molecules. In two further steps we used two immunoperoxidase conjugated antibodies: rabbit anti-mouse, and goat anti-rabbit. After staining with diaminobenzidine the nuclei were stained with haemalaun.

Results

On the basis of the expression of HLA-DR antigens on endothelial cells we formed three groups: in group one (Table I: +) all cells expressed the antigen; in group two (Table I: +/-) there were positive and negative cells, and in group three (Table I: -) only negative cells were found. According to the degree of rejection (Table I: 'R') again three groups were formed: no rejection (0), moderate degree of rejection (1), and strong rejection (>1). In the group without

TABLE I. Degree of rejection (R) and expression of HLA-DR on endothelial cells (HLA-DR +: all cells express the antigen; HLA-DR +/-: positive and negative cells; HLA-DR -: no positive cells) in 55 fine needle aspiration biopsies

No.	R	HLA-DR		
		+	+/-	-
10	0	-	5 (0)	5 (0)
37	1	7 (5)	19 (8)	11 (1)
8	>1	2 (2)	6 (6)	-

Rejection therapy ()

rejection (Table I) HLA-DR antigens were never expressed on all cells. On the contrary, in the group with strong rejection there was no case with only negative endothelial cells. In the group showing moderate rejection we found mixed results, but in this group therapy was necessary only in one case of 11, when HLA-DR antigens were not expressed on all cells (Table I). On the other hand therapy was necessary in five of seven patients expressing the antigen on all endothelial cells. For tubular cells the same results could be demonstrated (not shown in table).

As shown in Table II, there is no correlation between the expression of HLA-DR antigens and the blood concentration of Cyclosporin A.

In one patient we took five biopsies from the allograft. Shortly after transplantation HLA-DR antigens were not expressed on endothelial cells. Three further biopsies taken in the first two months after transplantation showed positive endothelial cells. In this period of time therapy for two rejection episodes was necessary. Six months after transplantation there was no rejection and no HLA-DR antigen positive parenchymal cells could be demonstrated.

TABLE II. Cyclosporin A blood levels and expression of HLA-DR on endothelium cells (HLA-DR +: all cells express the antigen; HLA-DR +/-: positive and negative cells; HLA-DR -: no positive cells) in 55 fine needle aspiration biopsies

HLA-DR	Cyclosporin A level (ng/ml)				
	100-300	300-600	600-800	800-1200	>1200
+	2	2	3	2	-
+/-	2	2	11	7	7
-	-	2	5	4	3
n	4	6	19	19	10

Discussion

Contrary to our expectations the expression of HLA-DR antigens on endothelial cells is variable: we expected the expression of HLA-DR on all endothelial cells [2]. According to Fuggle et al [3] HLA-DR is expressed on the proximal tubular cells in some kidneys. A genetic disposition is discussed. Recently Hall et al [5] published that the expression of HLA-DR on tubular cells is related to immunological events. Our results show that in most cases HLA-DR positive, as well as negative, endothelial and tubular cells appeared.

Regarding clinical aspects, there is a clear tendency that in those cases without any HLA-DR positive parenchymal cells there was no significant rejection of the allograft. In nearly all cases showing positive cells we had to treat rejection episodes. Furthermore we were able to demonstrate in one patient that HLA-DR may be expressed on parenchymal cells in relation to immunological events.

Natural killer cells, found in cases of early rejection [6], may induce the expression of HLA-DR on parenchymal cells by secreting interferons. These cells then either become antigen-presenting cells, stimulating the T-cell system, or the antigen induces the destruction of the cells by cytotoxic lymphocytes.

In summary, the expression of the class II antigen on parenchymal cells is variable and of importance for the rejection of renal allograft. However, these results require to be verified by further studies.

References

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