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Expression of activation markers, HLA class II and IL-2R in acute vascular rejection of human renal allografts

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Abstract. We analyzed the expression of class II antigens on graft tubular cells and the expression of IL-2R on lymphoid cells in 314 prospective aspiration biopsies taken from 30 consecutive patients with histologically verified acute vascular rejection (AVR). Based on histology, two main groups were seen: 11 grafts had features of AVR only and 19 grafts had a combination of AVR and acute cellular rejection (ACR). The AVR findings were also predominant in the latter group. In the grafts with a combination of AVR and ACR, patterns similar to ordinary ACR were seen in class II and IL-2R expression. On the contrary, no class II or IL-2R induction could be seen in the grafts with pure AVR and irreversible rejection. This pattern, demonstrated by immunocytology, suggested that AVR is a heterogenous group of rejections, where different cellular and molecular mechanisms are operating. Humoral mechanisms might be involved in these rejections.

Key words: Class II antigens – IL-2R – Acute vascular rejection – Acute cellular rejection

The association between tubular cell class II induction and renal allograft rejection has been confirmed in several studies [1–3]. We have demonstrated previously that class II induction is associated only with blastogenic inflammation (acute cellular rejection) in the graft [2] but not with nonblastogenic patterns of inflammatory infiltrates. The induction of interleukin-2 (IL-2) receptors on activated lymphoid cells of the inflammatory infiltrate has been demonstrated during acute cellular rejection (ACR) of human kidney transplants [4–5], where it follows closely the pattern of blastogenic inflammation [5]. The induction of these activation markers, class II expression on the tubular cells and IL-2R expression on activated lymphoid cells is thus well established in acute ACR. In acute vascular rejection (AVR), very little is known about the induction of activation markers. To elucidate this question, we have recently analyzed the expression of class II antigens on the graft tubular cells, and the expression of IL-2 receptors on lymphoid cells in serial renal aspiration biopsies taken from 20 consecutive patients with AVR before, during and after acute vascular rejection episodes that were verified histologically [6]. We have now extended the study to 30 consecutive patients with histologically verified acute vascular rejection.

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Materials and methods

A total of 314 aspiration biopsies were obtained from 30 consecutive patients with histologically verified AVR during the first posttransplant month. Altogether 571 renal transplants were performed between 1987 and 1990, at our center. The acute vascular rejections usually occurred early, on days 2 to 31 posttransplant (mean, day 10). The patients were monitored with frequent fine needle aspiration biopsies (FNABs) at 1–3 day intervals, from days 3–30 after transplantation. Altogether 314 aspiration biopsies were performed, mean, 10.4 per patient. Evaluation of class II and IL-2R expression was done by indirect immunoperoxidase staining using monoclonal antibodies. Class II determination was done from 235 biopsies, on average from 8 biopsies per patient and IL-2R determination from 135 biopsies, on average 5 biopsies per patient. Histological biopsies were taken from all 30 patients with AVR throughout the rejection period and after the rejection. Altogether 63 histological biopsies were taken and investigated.

Results

Based on histological findings, the grafts were categorized into four groups: group I ($n = 12$), combination of AVR and ACR, with reversible rejections (REV). Group II ($n = 7$), AVR and ACR with irreversible rejections (IRR). Group III ($n = 3$), pure AVR with REV and group IV ($n = 8$), pure AVR with IRR.

Tables 1 and 2 demonstrate the sequences in tubular cell class II expression and in lymphoid IL-2R expression

Table 1. Sequence of class II expression on tubular cells in the different groups

	Group I ($n=12$)	Group II ($n=7$)	Group III ($n=3$)	Group IV ($n=8$)
Day 5	4±2	14±7	15±5	4±1
Day 0–2	36±6*	39±5	41±9	7±2*
Day 5–7	49±7*	28±7	31±10	7±1
Day 10–15	37±4*	34±9	33±5	5±0*
Day 22–25	12±5	43±3**	24±7	6±1

Percentage of positive tubular cells ± SEM in the aspiration biopsies during the course of AVR
* indicates significant differences ($P<0.001$) between the groups I and IV
** indicates significant differences ($P<0.001$) between the groups I and II

Table 2. Sequence of IL-2 receptor expression in the different groups

	Group I ($n=12$)	Group II ($n=7$)	Group III ($n=3$)	Group IV ($n=8$)
Day 5	0±0	0±0	0±0	0±0
Day 0–2	4±1	4±2	7±2	0.1±0.1
Day 5–7	4±1	6±2	0±0	0.4±0.2
Day 10–15	2±1	3±1	0±0	0±0
Day 22–25	0.4±0.3	4±2	0±0	0.3±0.3

Total number of IL-2R positive cells ± SEM in the aspiration biopsies during AVR

of all 30 grafts in the study. All 19 grafts with a combination of AVR and ACR displayed class II induction and IL-2R expression, closely correlating the blast response of the rejection, with 40–50% positive tubular cells during the 1st week after the onset of rejection, and declining thereafter to prerejection levels in grafts with reversible rejection (group I). In grafts with irreversible rejection (group II), tubular cell class II expression and lymphoid IL-2R expression remained elevated. The same pattern of class II and IL-2R expression was observed in grafts with pure AVR and reversible rejections (group III). On the contrary, a completely different finding was seen in grafts with pure AVR and irreversible rejections (group IV): there was neither class II induction on tubular cells nor IL-2R expression on lymphoid cells. The persistant inflammation was dominated by mononuclear phagocytes, and no blast response could be detected.

Discussion

This study confirmed our earlier observations that in AVR, a close relationship exists between IL-2R and tubular cell class II induction, when AVR is associated with ACR. Furthermore, the study demonstrated that in histologically pure AVR, i.e. without features of interstitial blastogenic cellular rejection, two different patterns of IL-2R and class II expression exist.

All 19 grafts with a combination of AVR and ACR on histology displayed class II upregulation, which was closely associated with IL-2R expression on lymphoid cells and also closely associated with blast cell infiltration in the graft. The local release of gamma interferon and/or other cytokines by the activated lymphocytes and lymphoid blast cells, could be the mechanism responsible for this induction. Also the profile of class II expression would support this concept; in the reversible rejections the blast cells and IL-2R expressing cells disappeared and the tubular cell class II expression returned to pre-rejection level. On the other hand, in the irreversible rejections the blast response and the IL-2R expressing cells persisted as did also the tubular cell class II upregulation. Treatment had no permanent effect on the upregulation in the irreversible rejections.

Completely different findings were seen in the grafts with a pure AVR pattern of histology and irreversible rejection. On immunocytology, none of these grafts demonstrated upregulation of class II antigens on tubular cells or expression of IL-2R on lymphoid cells; also the cytological pattern of inflammation was clearly different. The inflammation was dominated by mononuclear phagocytes, which appeared in these grafts shortly after transplantation. This pattern of inflammation, demonstrated by immunocytology, may represent an entirely different inflammatory cascade, not dominated by the usual T cell driven mechanisms. Humoral mechanisms might be involved in these reactions.

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