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MHC antigens in interferon γ (IFNγ) receptor deficient mice: IFNγ-independent up-regulation of MHC class II in renal tubules

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MHC antigens in interferon γ (IFNγ) receptor deficient mice: IFNγ-independent up-regulation of MHC class II in renal tubules. MHC class II gene products in parenchymal cells, such as tubular epithelial cells in kidney, may play a role in the regulation of autoimmune reactions. Expression of MHC class II in renal tubular cells is normally very low, but it increases considerably under various pathologic conditions. The predominant role of IFNγ in up-regulation of MHC class II expression has been demonstrated repeatedly. We tested the existence of alternative pathways of MHC class II regulation using IFNγ receptor-deficient (IFNγR−/−) mice. Mutant and wild type mice received 50 μg bacterial endotoxin (LPS) i.p. Four days later the kidneys were removed for immunofluorescence examination. In agreement with published results LPS provoked an increase of immunoreactivity for MHC class I and MHC class II in proximal tubules of wild type mice. While MHC class I up-regulation was strictly IFNγ receptor-dependent, up-regulation of MHC II was still evident in mutant mice, although less than in wild type mice. Since injection of IFNγ induced proximal tubular MHC class II expression in wild type mice but not in IFNγR−/− mice, an alternative signaling pathway for IFNγ does not seem to exist. Thus, up-regulation of MHC class II expression in renal tubules does not necessarily require IFNγ. The markedly patchy pattern of immunofluorescence in IFNγR−/− mice suggests that induction of MHC class II after LPS injection may represent renal injury due to shock.

MHC class II gene products in professional antigen-presenting cells, namely B cells, dendritic cells and macrophages, are involved in host defense through presentation to T cells of antigens from invading microorganisms [1]. Except for thymic epithelium [2, 3] the function of MHC class II antigens in non-hematopoietic cells, for instance renal epithelia, is still unclear. A role in host defense is unlikely since those cells obviously do not migrate to lymph nodes, may lack costimulatory molecules [4–6], and express very low levels of MHC class II antigen under normal conditions [4, 7–10]. Nonetheless renal tubular epithelial cells may be capable of antigen presentation *in vitro* provided that MHC class II has been induced by IFNγ [6, 8, 9, 11]. A role of MHC class II antigens in nonhematopoietic cells, including renal proximal tubular cells, has been suggested in triggering of DTH response [12], in inhibition of autoimmunity by anergy or deletion of autoreactive T cells [4, 6, 11] and in the initiation of autoimmunity by activation of autoreactive T cells [4, 9, 13–16]. Induction of MHC class II in tubules is, however, not sufficient for eliciting autoimmune inflammation in the kidney [17].

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Investigations on factors inducing MHC class I and class II expression in nonhematopoietic cells have mainly focused on IFNγ [18]. The availability of mouse mutants defective in the signaling pathway for IFNγ [19] provided an opportunity to investigate the role of this cytokine in the regulation of MHC expression in the kidney. We tested the role of IFNγ in induction of MHC class I and class II antigens following injection of LPS in IFNγ receptor deficient (IFNγR−/−) mice. A single intraperitoneal injection of LPS provokes an increased production of IFNγ [11, 20]. Our data suggest that, while IFNγ plays a role in the regulation of MHC class I and class II, it is not absolutely required for up-regulation of MHC class II in renal proximal tubules following LPS injection.

Methods

Animals

Adult, 6- to 10-week-old female mice of the strain 129/SV, of a homozygous IFNγR−/− strain derived from 129/SV [19] and of a homozygous MHC class II−/− strain derived from C57/B6 [21] were kept under optimal housing conditions (OHC). The colonies were free from the three routinely tested pathogens, Sendai virus, coronavirus and M. pulmonis.

Genotype analysis

The genotypes of the mice were verified by PCR analysis of tail DNA lysate according to standard protocols using the following primers: 5′-CCCATTTAGATCCTACATACGAAACATACGG-3′ (sense) and 5′-TTTCTGTCATCATGGAAAGGAGGGATA-CAG-3′ (antisense). The amplified products were subjected to electrophoresis. On the wild-type allele, the primer amplifies a 190 bp fragment. On the disrupted allele, the amplification encompasses the inserted neomycine resistent gene marker and, therefore, results in an approximately 1300 bp amplification product.

Antibodies

Rat anti-mouse CD14 serum was a gift from Dr. S. Yamamoto. The other antibodies were rat anti-mouse monoclonals. M5/

114.15.2 against MHC class II antigen (I-$A^{b,d,q}$), and M1/42 against MHC class I antigen were gifts from Dr. H. Hengartner. Anti-LFA-1 was obtained from PharMingen (San Diego, CA, USA) and anti-MHC class II antigen (I-A), clone P7/7, from Serotec (Oxford, UK).

LPS treatment

Six mice were treated per experimental group. Fifty μg of LPS from *E. coli* (serotype 0111:B4; Sigma, St. Louis, MO, USA), dissolved in sterile isotonic saline, were injected intraperitoneally. Control animals received saline alone. Twelve hours, 24 hours or four days after the injection the kidneys were removed under anesthesia with methoxyflurane and shock-frozen in isopentane maintained at the temperature of liquid nitrogen.

Interferon γ treatment

Mice received intraperitoneal injections of 15000 or 60000 units of murine IFNγ dissolved in saline at day 0, 1 and 2. Three wild-type mice and three mutant mice were used for each dosage. Six animals of each population received saline alone. At day 4 the kidneys were removed under anesthesia with methoxyflurane and shock-frozen in isopentane maintained at the temperature of liquid nitrogen. Recombinant murine IFNγ was a gift from Dr. L. Ozmen (Hoffmann-Laroche, Basel, Switzerland).

Immunohistochemistry

Sections of 6 μm thickness were cut on a cryostat and air-dried for storage at −80°C. Fixation in acetone (10 min at 4°C) was performed just before the immunolabeling. After a rinse in Tris-buffered saline (TBS) the sections were incubated for 16 hours at 4°C with the primary antibodies diluted in TBS. The sections were then washed in TBS and incubated for one hour at room temperature with Cy3-labeled goat anti-rat immunoglobulin antibody diluted 1:200. After rinsing in TBS the sections were mounted in Immu-mount (Shandon, Pittsburgh, PA, USA) and examined with a laser scanner microscope.

Results

MHC class II in proximal tubule

Similar immunofluorescence patterns were obtained with two different antibodies against MHC class II, produced by the rat hybridoma clones M5/114 and P7/7, respectively. Figures 1 and 2 show data obtained with the former, since it yielded higher signal intensities. In untreated wild type mice and in untreated IFNγR−/− mice the tubular epithelium was negative in the cortex and only weakly positive tubules were occasionally detected in the outer stripe of the medulla. Generally, the fluorescence was not homogeneous in the few positive tubular profiles, suggesting that only single cells expressed the antigen (Fig. 2D). Strong immunoreactivity was detected in interstitial cells, probably dendritic cells.

Injection of IFNγ in wild type mice resulted in a widespread expression of MHC class II (Fig. 1B). Immunoreactivity in proximal tubules was strong in the cortex and moderate in the outer stripe of the medulla. It was weaker in other tubular structures and in glomeruli. Induction of MHC class II was distinctly less marked with daily doses of 15000 units than with 60000 units. In IFNγ-treated IFNγR−/− mice the distribution pattern of immunolabeling was the same as in untreated mice. Except for a few profiles in the outer stripe, proximal tubules were negative (Fig. 1A).

Four days after injection of LPS, immunoreactivity with MHC class II antibodies was strongly increased in proximal tubules (Figs. 1 and 2). In wild type mice most proximal tubular profiles were labeled in the outer stripe of the medulla and in the cortex. The average intensity of immunofluorescence was higher in the outer stripe than in the cortex, in which the pattern of labeling was patchy. In IFNγR−/− mice immunoreactivity in the outer medulla was similar as in wild type mice, but in the cortex it was distinctly less. In both populations of mice there were marked differences of labeling intensity between neighboring proximal tubules. Likewise within one single profile of a proximal tubule immunoreactivity often varied among neighboring cells, especially in the outer medulla (Fig. 2). Besides proximal tubules, other segments of the nephron were not labeled with MHC class II antibodies after LPS injection. In MHC class II−/− mice the MHC class II antibodies did not yield any signal either in untreated controls or after LPS injection (not shown).

MHC class I in proximal tubule

In untreated animals (Fig. 3A) immunoreactivity for MHC class I was detected in vessels and in scattered interstitial cells, probably representing leukocytes. Few proximal tubules were weakly labeled in the wild type (not shown) but not in the IFNγR−/− mice. In wild type mice injection of IFNγ provoked a widespread, strong up-regulation of MHC class I immunoreactivity in proximal tubules, in glomeruli and in endothelia of peritubular capillaries as well as of vasa recta (not shown). IFNγ had no effect on MHC class I in IFNγR−/− mice. Four days after LPS injection immunolabeling of proximal tubules in wild type mice was moderate to strong in the cortex (Fig. 3C), whereas it remained undetectable or weak in the outer medulla (not shown). In IFNγR−/− mice proximal tubules remained unlabeled (Fig. 3B).

CD14 in proximal tubules

The distribution pattern of the LPS receptor CD14 in kidney was similar in IFNγR−/− mice as in wild type mice, in controls as well as in LPS-treated animals. In kidneys of untreated animals interstitial cells, probably representing dendritic cells, displayed a weak immunoreactivity (not shown). Twelve hours after injection of LPS additional labeling was found in the brush border of the proximal tubule. It was stronger in the outer stripe of the medulla than in the cortex (Fig. 4A). The tubular immunoreactivity was no longer detectable 24 hours after injection of LPS (Fig. 4B).

Discussion

The purpose of the present study was to assess the role of IFNγ in the regulation of expression of MHC class I and class II in renal tubular cells by using IFNγR−/− mice. The most striking finding was that MHC class II antigen expression could be induced by LPS injection in proximal tubules of mice lacking the IFNγ receptor. This is the first direct evidence of IFNγ-independent induction of MHC class II in a non-hematopoietic cell type *in vivo*. Up-regulation of MHC class I, however, was clearly dependent on IFNγ in that model.

MHC class I is constitutively expressed in all cell types, however at very variable levels [10]. MHC class II is constitutively expressed at high levels in B cells and dendritic cells [22], whereas it is normally undetectable in other cell types. The expression of

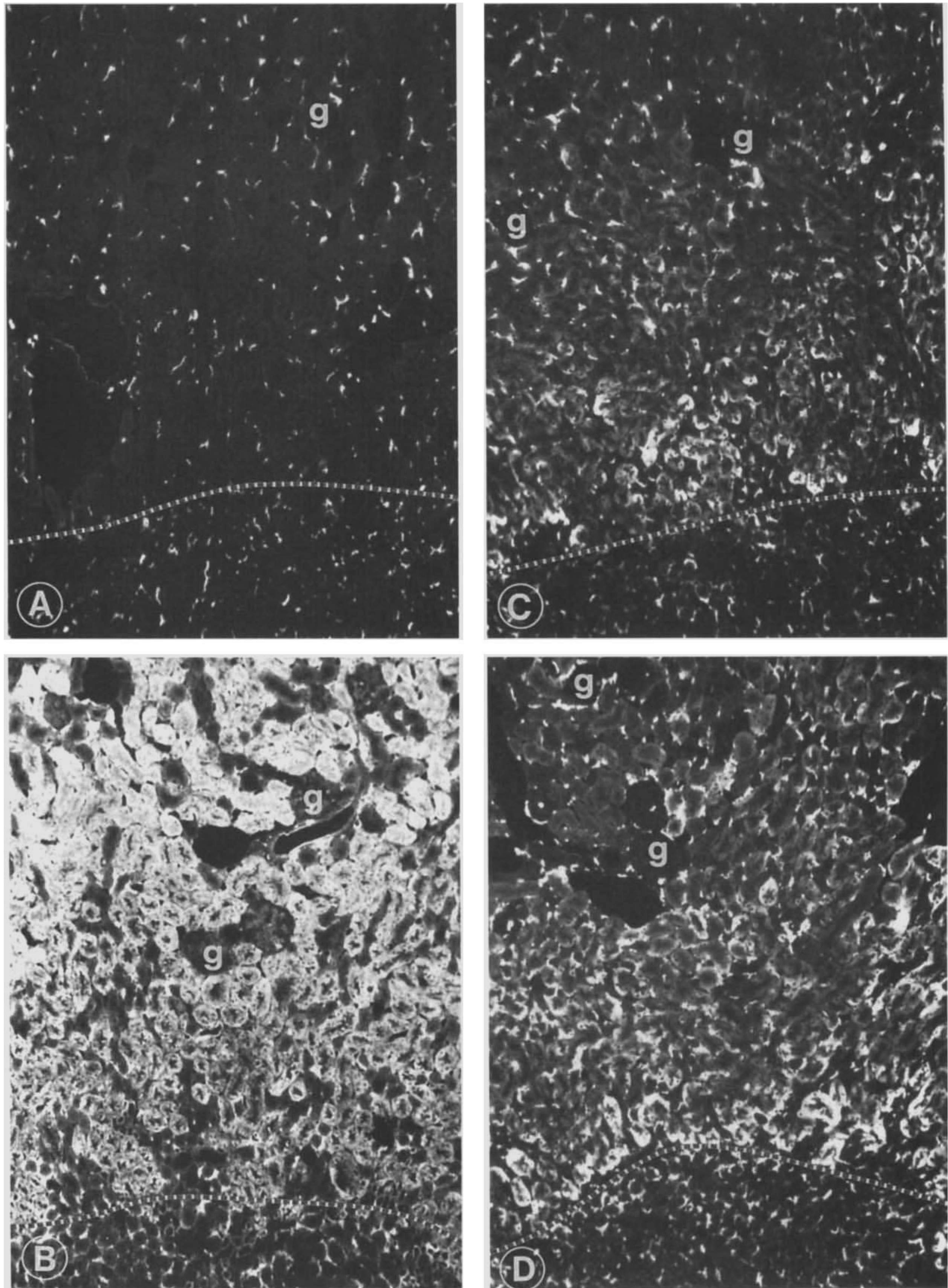

Fig. 1. *MHC class II immunoreactivity in kidneys of IFNγR−/− mice* (**A, C**) *and of wild-type mice* (**B, D**) *treated with IFNγ (A, B) or LPS (C, D).* Untreated wild-type and mutant mice displayed similar immunoreactivity patterns as the IFNγ-treated IFNγR−/− mice (A). The approximate border between outer stripe and inner stripe of the medulla is indicated by a dotted line. Some glomeruli are marked (g) in order to indicate the presence of cortex on the section. Magnification: ×100

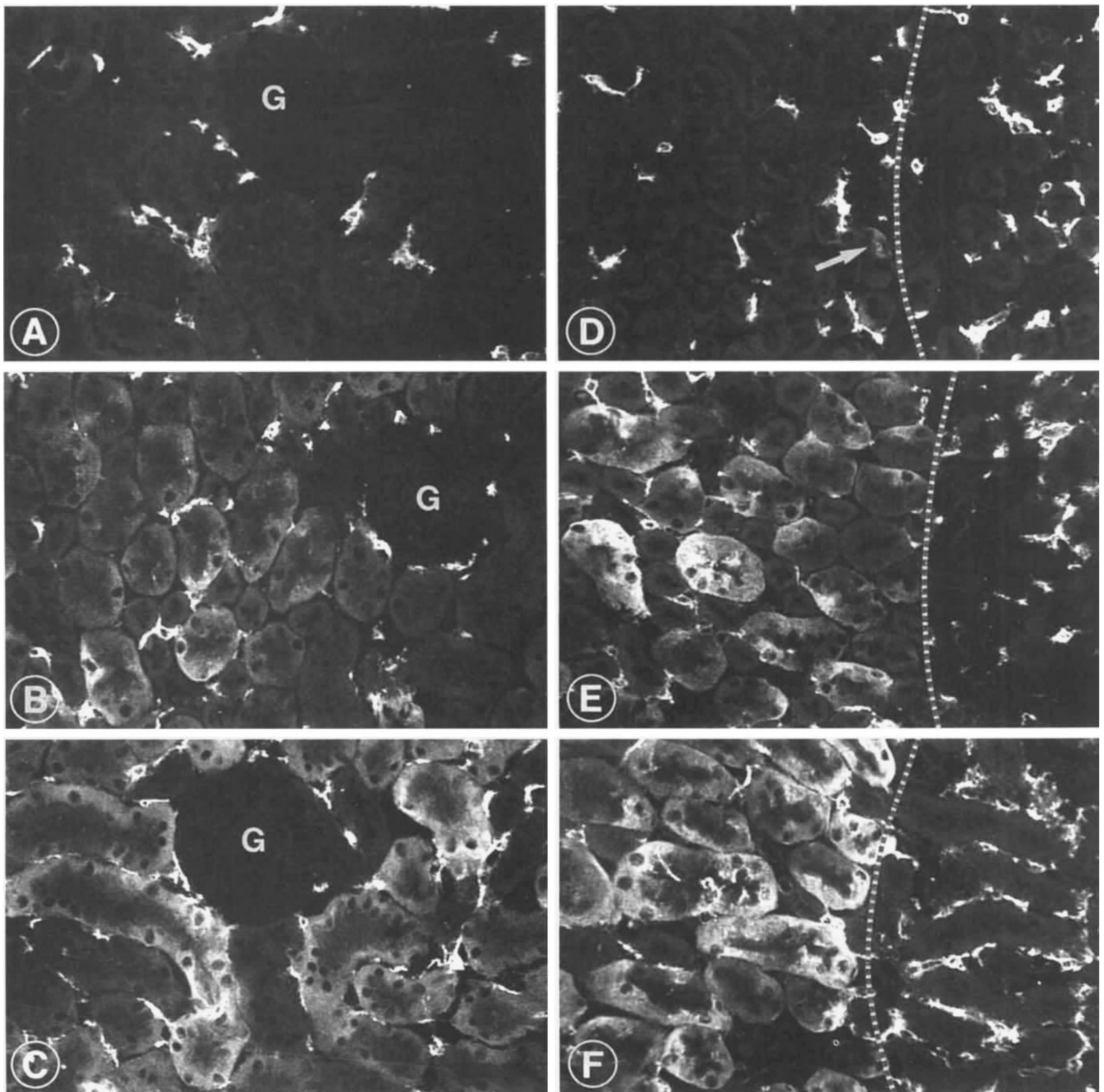

Fig. 2. *MHC class II immunoreactivity in renal cortex* (**A–C**) *and outer medulla* (**D–F**). **A, D.** Untreated IFNγR−/− mice; untreated wild type mice display the same labeling pattern; arrow points to a single labeled cell in a proximal tubule. **B, E.** LPS-treated IFNγR−/− mice. **C, F.** LPS-treated wild type mice. The approximate border between outer stripe and inner stripe is indicated by a dotted line. G: glomerulus. Magnification ×360

MHC class II may be up-regulated under various conditions in parenchymal cell types of several tissues. This occurs in the kidney in autoimmune diseases [9, 23, 24], in infection [8], during rejection of allografts [25] as well as after application of toxic agents like streptozotozin [26, 27], LPS [20, 28, 29] or $HgCl_2$ [30].

IFNγ plays a major role in up-regulation of MHC class II in renal tubular epithelial cells. This has been demonstrated by injecting IFNγ to rodents [8, 29, 31, 32] and by treating cells in culture with IFNγ [6, 11, 12, 33, 34]. Likewise IFNγ antibodies inhibit the induction of MHC class II in renal tubular cells *in vivo* [20, 28–30, 35, 36] as well as *in vitro* [37]. When MHC class I expression was investigated in those studies it was found to respond to IFNγ in the same way as MHC class II in proximal tubules [27, 28, 30, 32, 34–36]. A role of cytokines other than IFNγ in the regulation of MHC class II expression in renal tubular cells has not been demonstrated so far [9].

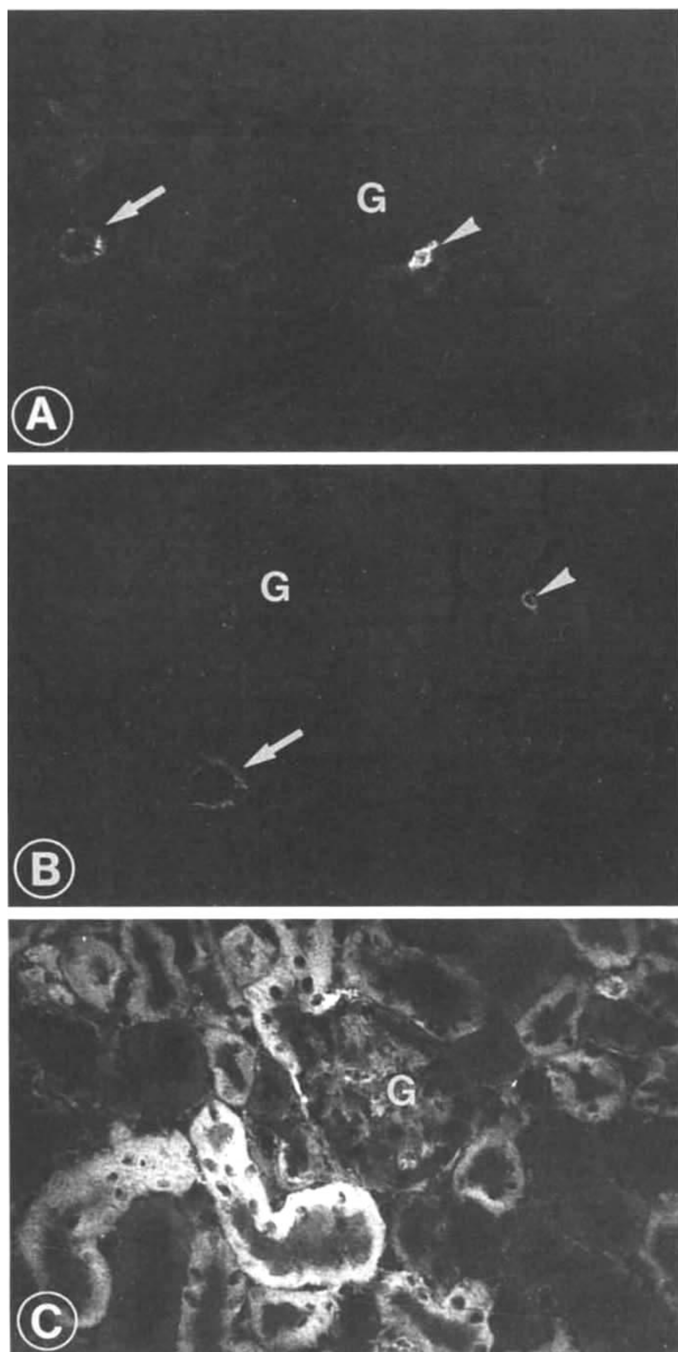

Fig. 3. *MHC class I immunoreactivity in renal cortex.* **A.** Untreated wild type; untreated IFNγR−/− display a similar labeling pattern. **B.** LPS-treated IFNγR−/−. **C.** LPS-treated wild type. Arrows: arterioles; arrowheads: leukocytes; G: glomerulus. Magnification ×360

The lower levels of tubular MHC class I and class II antigen upregulation by LPS in IFNγR−/− animals compared to the wild type is compatible with the known role of IFNγ in controlling the expression of MHC antigens. This is particularly true for MHC class I, the up-regulation of which was abolished by the deletion of the IFNγ receptor. However, LPS provoked a clear increase of MHC class II immunoreactivity in IFNγR−/− mice. Two lines of evidence indicate that the immunoreactivity represented MHC class II antigens. First, two anti-MHC class II antibodies (clone P7/7 and clone M5/114) recognizing different epitopes yielded the same pattern of immunofluorescence. Second, there was no immunoreactivity in tubules of MHC class II-deficient mice after LPS injection.

Induction of MHC class II antigen after LPS treatment in IFNγR−/− mice was unexpected since in the same experimental model anti-IFNγ antibodies have been reported to block the induction of MHC class I and class II antigens [28, 29]. It is possible that an IFNγ-independent pathway of induction of MHC class II antigen exists, that is more efficient in the mouse strain 129/SV, compared to the strains used by others in similar experiments. It may also be hypothesized that the deletion of the IFNγ receptor leads to an alternative pathway for regulation of MHC class II. Absence of IFNγ signaling might for instance drive the cytokine pattern of T helper cells from Th1- towards Th2-type response. However interleukin-4, the only typical Th2 cytokine known to up-regulate MHC class II expression in hematopoietic cell types [18], had no effect on tubular cells in culture [33]. In the same study TNF was also without effect on MHC class II in tubular cells.

To test whether induction by LPS treatment of MHC class II in the IFNγR−/− mice might be due to IFNγ acting via an alternative, still unknown receptor, we treated mice with murine recombinant IFNγ. Since MHC class II was induced in the wild type mice but not in the IFNγR−/− mice, tubular expression of MHC class II in the mutant mice after LPS treatment seems to be truly independent of IFNγ. Differences among renal zones in the tubular expression of MHC class II after stimulation with IFNγ on the one hand and with LPS on the other hand further support the presumption that the induction by LPS is not mediated by IFNγ. Indeed, after IFNγ treatment, tubular MHC class II immunoreactivity was clearly higher in the cortex than in the outer stripe of the medulla. An inverse pattern was observed after LPS injection. Furthermore, after LPS, in contrast to IFNγ treatment, the intensity of immunofluorescence is very variable among proximal tubules as well as among cells within one tubule. That patchy pattern does not suggest a response to a systemic factor. It rather resembles the pattern of tubular injury caused for instance by hypoxia or toxic agents. Thus, LPS-induced up-regulation of MHC class II in proximal tubule might be a consequence of renal injury due to shock [38]. In that respect it is interesting that heat shock and cadmium induce expression of MHC class II in proximal tubular cells *in vitro*, possibly through HSP 70 [39]. In wild type mice, the effect of LPS on MHC class II expression might be a consequence of two independent events, namely on the one hand renal injury and on the other hand the release of IFNγ. However, the lower level of tubular MHC class II immunofluorescence in IFNγR−/− mice compared to wild type mice does not necessarily reflect a direct role of IFNγ in regulation of tubular MHC class II expression after injection of LPS. The systemic shock in response to LPS injection is much less in the mutant mice [40]. Thus, not only the levels of various cytokines, but also renal function might be affected differently by LPS in the two populations of mice. Besides renal dysfunction due to shock, a direct effect of LPS on proximal tubule seems possible since after LPS injection the brush border displays transiently immunoreactivity for the LPS receptor CD14. Tubular CD14 immunoreactivity was found sixteen hours [41] and twelve hours (present study) after

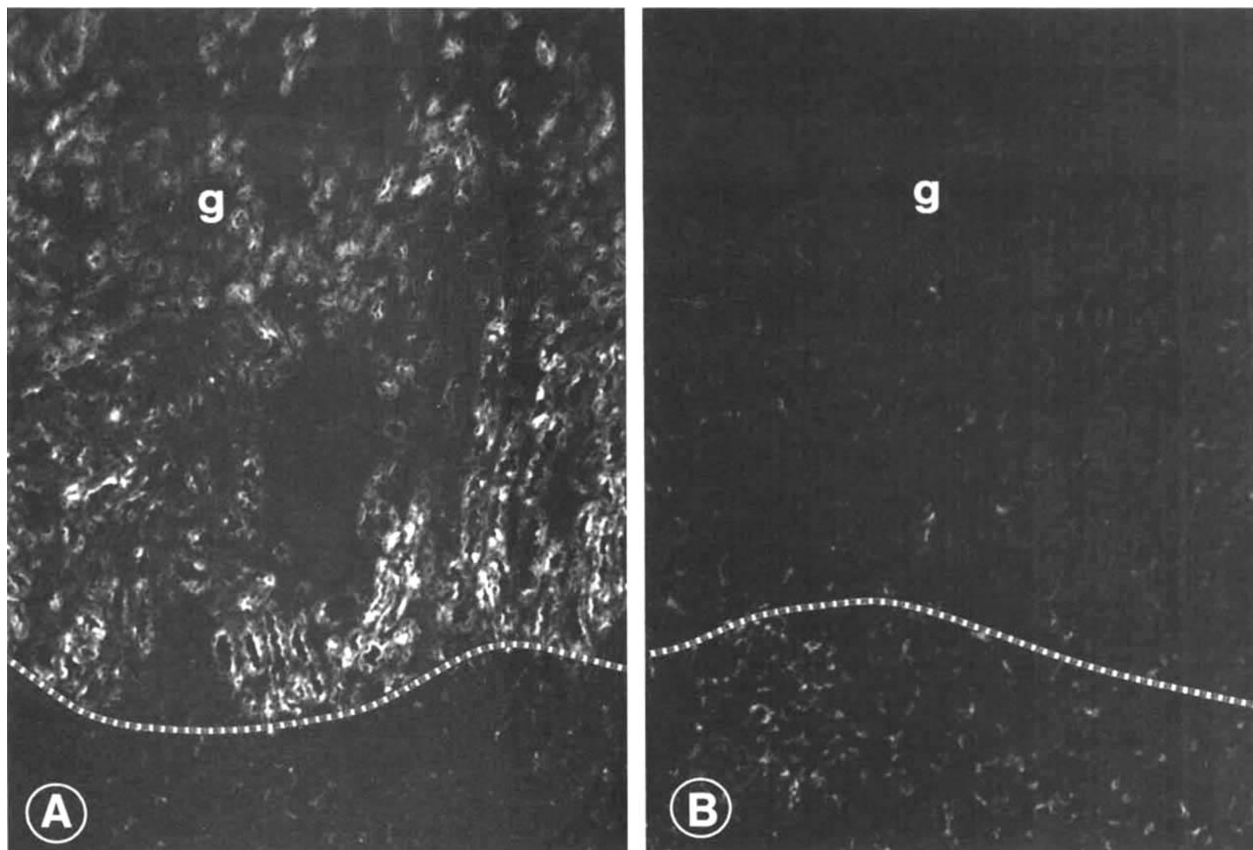

Fig. 4. *CD14 immunoreactivity in kidneys of wild-type mice 12 hours* (**A**) *and 24 hours* (**B**) *after injection of LPS.* The approximate border between outer stripe and inner stripe is indicated by a dotted line. g: glomerulus. Magnification ×100

injection of LPS and it was undetectable after twenty-four hours. The similarity in the distributions of MHC class II and of tubular CD14 in LPS-treated mice, both being restricted to the proximal tubule and both showing maximal levels in the outer stripe, is compatible with an induction of MHC class II via direct interaction of LPS with proximal tubular cells. The molecular weight of the LPS-binding protein, which mediates the interaction of LPS with CD14, is about 60 kD. Thus it may be filtered in the glomerulus and have access to CD14 at the brush border of the proximal tubule. However, there exists to our knowlege no report of a direct induction of MHC class II by LPS in any cell type.

In conclusion, the present observations in mice lacking the IFNγ signaling pathway suggest the existence of an IFNγ-independent pathway for upregulation of MHC class II in renal proximal tubules. In contrast, IFNγ seems to be required for LPS-induced up-regulation of MHC class I. IFNγR−/− mice may be useful for identification of cytokines or other signals involved in IFNγ-independent regulation of MHC II expression.

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