Oncostatin M pathway plays a major role in the renal acute phase response

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Submitted 23 October 2008; accepted in final form 15 January 2009

Luyckx VA, Cairo LV, Compston CA, Phan WL, Mueller TF. Oncostatin M pathway plays a major role in the renal acute phase response. Am J Physiol Renal Physiol 296: F875–F883, 2009.—The renal acute phase response is traditionally characterized by hepatic synthesis of proteins as an inflammatory response to injury, with interleukin-6 (IL-6) being the key mediator. In contrast, microarray studies in human renal transplantation implantation biopsies indicate a strong acute phase response in the deceased donor kidney, associated with a significant upregulation of oncostatin M receptor β (OSMR). The aim of this study was to determine whether the kidney can generate a strong acute phase response, mediated by the OSM/OSMR gateway. Genes associated with the IL-6 cytokine family and acute phase reactants were analyzed by real-time RT-PCR in four groups of human biopsies spanning a spectrum of renal injury, OSM, OSMR, and fibrinogen β (FGB) were progressively more highly expressed from prenephrectomy, living donor, deceased donor, to discarded donor kidneys, suggesting correlation with severity of injury and local renal synthesis. Acute phase response gene expression was analyzed in human proximal tubular cells in culture in response to OSM. OSM induced a significant increase in expression of FGB, OSMR, serpin peptidase inhibitor A1, IL-6, and lipopolysaccharide binding protein, and a decrease in IL-6R. These changes were mainly attenuated by coinubcation with an OSMR blocking antibody, indicating the OSM effect was mediated through OSMR. OSM also resulted in a significantly altered expression of acute phase genes compared with IL-6 or leukemia inhibitory factor, suggesting that OSM is the predominant cytokine mediating the renal tubular acute phase response. In conclusion, the renal parenchyma is capable of generating a strong acute phase response, likely mediated via OSM/OSMR.

inflammatory response; ischemia and reperfusion injury

THE LIVER has long been thought to be the predominant organ orchestrating the acute phase response through generation of acute phase proteins in response to infection and injury (2, 13, 22, 41, 50). Interleukin-6 (IL-6) and IL-6-type cytokines are the major inducers of this hepatic acute phase response (7, 10, 13, 22, 23, 31, 44). Clinically, circulating IL-6 has been used as a marker of severity of the inflammatory response in critically ill patients (13, 23). IL-6-type cytokines exert their actions via the IL-6 signal transducer (IL-6ST, alias GP130), leukemia inhibitory factor receptor (LIFR), and oncostatin M receptor (OSMR), leading to the activation of Jak/Stat and MAPK pathways (12, 18). IL-6 signaling plays a regulatory role in the proinflammatory response, but also acts as an anti-inflammatory mediator (8, 23). In the short term, a controlled inflammatory response is beneficial, but may become harmful if dysregulated and protracted (25). The acute phase response is therefore critical in determining ongoing injury and inflammation and orchestrating the switch toward healing and repair (8, 51).

We recently reported microarray findings in 87 postreperfusion human kidney transplant biopsies. The transcriptome of deceased donor (DD) kidneys showed a pronounced acute phase response and high expression of gene products not known to be generated by the renal parenchyma, such as fibrinogens, haptoglobin, and serpins (26, 28, 36). In this data-driven unbiased analysis, more that half of the 50 most differentially induced genes between living donor (LD) and DD kidneys were associated with the acute phase response (Supplement Table 1; the online version of this article contains supplemental data), suggesting that the kidney is capable of generating a strong local acute phase response.

Over the long term, DD kidneys, in particular those with delayed graft function, have worse outcomes compared with LD kidneys (52). DDs are subject to catastrophic events which induce a profound systemic inflammatory response, often affecting organs remote from the primary site of injury (23). In addition, brain death, even in the absence of systemic hemodynamic changes, has been shown to induce renal inflammation similar to what observed after ischemia and reperfusion injury (33, 34, 40). The DD organs therefore likely carry a high burden of intrinsic inflammation, further compounded by the inherent ischemia and reperfusion injury of transplantation (1, 37, 39, 40, 45). This high inflammatory burden may be a crucial factor impacting long-term outcomes.

Based on our genome-wide analysis of donor kidneys at the time of implantation, therefore, we hypothesize that the early renal acute phase response, triggered by injury sustained during the peritransplant process, may be pivotal in determining whether the renal parenchyma over the long term is destined toward inflammation and fibrosis, or healing and repair. Moving from bedside to bench, we examined whether cultured human proximal tubule cells can express acute phase response genes in response to the IL-6 family cytokines OSM, IL-6, and LIF.

MATERIALS AND METHODS

Human kidney tissue samples. Informed consent was obtained as approved by the Health Research Ethics Board of the University of Alberta as previously published (28). Eighty seven implant biopsy samples were obtained from 42 DD and 45 LD kidneys, taken intraoperatively within 1 h of revascularization, 3 preclamp LD kidney biopsies were taken before clamping of the renal vessels (PRE), and tissue was obtained from 3 discarded DD kidneys taken after harvesting and during cold storage in UW perfusion solution (DIS).

Microarray processing and analysis of human samples were carried out using our standard protocol previously outlined in detail (28). Gene expression was analyzed using GeneSpring GX 7.3.1 software and KEGG pathway analysis. Microarray expression of genes of

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interest was validated by real-time RT-PCR using the same cDNA samples.

Real-time RT-PCR processing of tissue samples and cultured cells. Total RNA from tissues and cultured cells was extracted using the RNeasy Mini Kit (Qiagen) and reverse transcribed using MMLV reverse transcriptase (Invitrogen). Oligonucleotide primers and probes were synthesized by Sigma or purchased as fluorogenic primer/probe sets (TaqMan Expression assays) from Applied Biosystems. Sigma primers and probes were designed using Applied Biosystems Primer Express 2.0. Genes were selected for analysis based on differential expression on microarray between LD and DD kidneys and known responsiveness to OSM and IL-6 family cytokines (4, 6, 14, 26, 28, 32). Primer sets are listed in Supplement Table 2. Simplex reactions were performed in triplicate for the gene of interest and for the housekeeping gene (HPRT-FAM) in 96-well MicroAmp plates (Applied Biosystems) using the Applied Biosystems 7900HT fast real-time PCR System. Gene transcript levels were calculated according to the ΔΔCT method and expressed as percent HPRT. Variability of HPRT CTs between experimental conditions was low. If CT was not reached by 40 cycles of amplification, expression was considered to be below the limit of detection.

Reagents and antibodies. Tissue culture and real-time PCR reagents were purchased from Applied Biosystems and Invitrogen. Recombinant human OSM (295-OM), IL-6 (206-IL), and the OSM receptor blocking antibody, anti-GP130 (MAB-228), were purchased from R&D Systems. Human LIF was purchased from Chemicon International (LIF1005). Antibodies against human Vimentin (sc-73258), OSMRβ (sc-30010), FGB (sc-H270), N-cadherin (BD Biosciences no. 610920), horseradish peroxidase (HRP)-conjugated secondary antibodies (mouse sc-2005 and rabbit sc-2004) and Actin (C-2) HRP (sc-8432) were obtained from Santa Cruz Biotechnologies.

Cell culture. Immortalized human proximal tubule cells (HK2) were purchased from American Tissue Culture Collection (ATCC). HK2 cells were grown in DMEM/F12 media supplemented with 5% inactivated FBS, 100 U/ml penicillin G, 100 μg/ml streptomycin sulfate, and 0.25 μg/ml amphotericin B [normal medium (NM)], or for the serum starvation condition (SS), in the same media without FBS. Primary proximal tubule cells (PTEC) were purchased from InVitro Technologies. These cells are harvested from DD kidneys. Collagen-coated (BIOCOAT) tissue culture plates were obtained from Millipore. PTEC were grown in InVitroGRO PT medium (In Vitro Technologies), containing 10% inactivated FBS, 100 U/ml penicillin G, 100 μg/ml streptomycin sulfate (Pen/Strep), and 25 mg/ml EGF (Invitrogen). All cells were grown at 37°C in 5% CO2 and subcultured using 0.25% Trypsin/1 mM EDTA. All experiments were done in triplicate and repeated at least two to three times. PTEC were used from passages 2 to 4, and HK2 cells were used at multiple passages. Cells were grown to ~80% confluence in NM and then rinsed with PBS and media were replaced with experimental medium, and incubated for 24 h. At 24 h, plates were rinsed with ice-cold PBS, trypsinized, and harvested for RNA or protein extraction.

PTEC and HK2 cells were cultured as above, with the addition of OSM at 25 ng/ml to either NM or SS for 24 h. This dose of OSM was chosen based on a prior publication by Nightingale et al. (32). These authors found a high concentration of OSM in peripheral blood mononuclear cell-conditioned medium and went on to show that culture of HK2 cells in the presence of OSM induced epithelial-to-mesenchymal transition (EMT). Their dose-response curves showed 25 ng/ml to be an optimal OSM concentration. Most other papers examining the effects of OSM on endothelial cells, lung epithelial cells, and liver cells use concentrations ranging from 10 to 100 ng/ml (16, 27). To examine whether OSM effects are mediated via the OSMR, cells were cultured with the addition of OSM alone (25 ng/ml), an excess of the OSMR blocking antibody, GP130 antibody, alone or OSM + GP130 antibody (38). In other experiments, cells were exposed to either NM or SS in the presence of OSM (25 ng/ml), IL-6 (25 ng/ml), or LIF (100 ng/ml) for 24 h. The concentrations of these cytokines were chosen based on published comparison to OSM in induction of fibrinogen synthesis in human liver cells (36).

Protein extraction and Western blotting. Cell pellets were lysed in RIPA buffer (Santa Cruz Biotechnologies) containing complete protease inhibitor (Boehringer Mannheim). Protein concentration was determined by BCA assay (Sigma). Twenty to forty micrograms of whole cell lysate were separated on 7.5–10% SDS-PAGE gels, transferred to PVDF membrane, and probed with antibodies to Vimentin and N-cadherin, as markers of transition from epithelial-to-mesenchymal phenotype, to OSMRβ, and the acute phase protein FGB. Immunoblots were detected using ECL (Amersham). Actin was used as a loading control. Densitometry was performed using Quantity One software (Bio-Rad) averaged over three blots.

Statistical analysis. Microarray results were analyzed as outlined previously (28). PCR gene expression among experimental groups was analyzed using the Student’s t-test and ANOVA assuming significance at a P value of ≤0.05 [Kirkman TW (1996) Statistics to Use; http://www.physics.csbsju.edu/stats/].

RESULTS

High expression of acute phase response genes in the DD kidney implant transcriptome. As previously reported, the transcriptome of 87 renal implant biopsies (45 LD, 42 DD) strongly differentiated samples from LD and DD, with over half of the 50 most upregulated genes in DD kidneys representing acute phase proteins (Supplementary Table 1). Further unsupervised analysis of the transcriptome revealed strong clustering of LD kidneys separately from DD kidneys (Supplementary Fig. 1), and of two distinct groups of DD kidneys, one with high and one with low risk of poor early function (28). The IL-6 family cytokine receptor OSMRβ was among the most highly differentially expressed genes, and of the IL-6 family cytokine receptors, OSMRβ best separated DD from LD kidneys (P < 0.001) (28). Furthermore, OSMRβ was significantly more highly expressed in DD kidneys at highest risk of delayed graft function, suggesting a correlation with renal injury (Supplementary Fig. 1) (28). Taken together, the transcriptome findings suggest that the renal acute phase response is likely mediated predominantly via the OSMR rather than through IL-6R or LIFR.

Validation of microarray findings with real-time RT-PCR. Transcript levels of the selected acute phase response genes were examined in eight randomly selected DD and LD implant biopsy samples previously used in the microarray analysis (28). Patterns of gene expression were conserved between microarray and RT-PCR, validating our microarray findings (Table 1).

Transcript levels of OSM/OSMR-associated genes in human kidney tissue with varying degrees of injury. To investigate whether degree of injury may be proportional to degree of upregulation of the acute phase response genes, transcript levels were measured in four groups of human kidney biopsy samples: three LD preclamp, prenephrectomy (PRE), three discarded (DIS), eight randomly selected DD and LD postimplant kidneys. These samples are presumed to reflect a spectrum of degree of injury from worst to best: DIS > DD > LD > PRE. Table 2 shows that expression of OSM, OSMRβ, and FGB reflects this spectrum with lowest transcript levels in the PRE and highest in the DIS organs. In addition, LBP and SERPINA1 follow a similar pattern, with low levels in LD organs and high levels in DD organs, likely reflecting degree of injury and brain death. FGB and SERPINA1 show the highest
levels in the DIS organs, supporting a strong local generation of these transcripts in the injured kidneys, independent of reperfusion, i.e., absence of circulating cells. LIF, LIFR, and IL-6R transcript levels are highest in the DIS organs, but reperfusion, i.e., absence of circulating cells. LIF, LIFR, and OSMR transcripts in the injured kidneys, independent of these conditions (43). Transcripts associated with the acute phase response genes identified in kidney biopsies were detected in two lines of human PTEC (HK2 and PTEC), supporting a tubular origin of these inflammatory response genes. Both cell lines displayed an overall similar transcript pattern under normal (NM) and SS conditions, although levels in PTEC tended to be higher. Compared with culture under normal conditions, SS alone was consistently associated with small, but significantly, increased expression of OSMRβ, IL-6, IL-6R, LIF, and LIFR compared with NM conditions in both cell types (P < 0.001; Fig. 1). OSM transcript levels were extremely low at baseline and tended to increase with SS. It is likely, however, that OSM is not expressed at high levels by PTEC and in the kidney is rather produced by other cell types, e.g., circulating or infiltrating leukocytes (9, 47).

**Acute phase response genes are expressed in cultured human PTEC and increase under serum-starved conditions.** The renal tubules are the major compartment impacted by ischemia and reperfusion injury in the kidney and are likely highly represented in biopsy samples (24). We therefore sought to evaluate whether acute phase response genes are expressed in tubule cells in culture. Preliminary RT-PCR analysis revealed largely similar patterns of acute phase gene expression in cultured PTEC compared with the implant biopsy samples (data not shown). We used 24 h of SS as a cellular stress, previously shown to induce injury and apoptosis in immortalized human kidney proximal tubule (HK2) cells cultured under similar conditions (43). Transcripts associated with the acute phase response genes identified in kidney biopsies were detected in two lines of human PTEC (HK2 and PTEC), supporting a tubular origin of these inflammatory response genes. Both cell lines displayed an overall similar transcript pattern under normal (NM) and SS conditions, although levels in PTEC tended to be higher. Compared with culture under normal conditions, SS alone was consistently associated with small, but significantly, increased expression of OSMRβ, IL-6, IL-6R, LIF, and LIFR compared with NM conditions in both cell types (P < 0.001; Fig. 1). OSM transcript levels were extremely low at baseline and tended to increase with SS. It is likely, however, that OSM is not expressed at high levels by PTEC and in the kidney is rather produced by other cell types, e.g., circulating or infiltrating leukocytes (9, 47).

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in accordance with prior publications, and having a definite effect on APR gene expression. As shown in Fig. 1, under normal conditions, 25 ng/ml OSM consistently induced a significant increase in the transcript levels of FGB, OSMRβ, GP130, IL-6, LIF, LIFR, SERPINA1, and lipopolysaccharide-binding protein (LBP), and a significant decrease in IL-6R. A small increase in OSM expression occurred only under NM conditions. Similar, and numerically greater, changes were induced under SS/OSM conditions for most acute phase response genes. Percent increase with OSM relative to baseline was similar under NM and SS conditions, with the exception of a greater percent increase in FGB under SS conditions. These results confirm that OSM is indeed an inducer of acute phase response genes in renal tubular cells. As responses were similar in HK2 and PTEC (data not shown), most subsequent experiments were conducted using HK2 cells.

Effect of OSM is blocked by coadministration of an OSMR blocking antibody. To determine whether the observed increases in acute phase response gene expression upon stimulation with OSM are mediated via the OSMR, HK2 cells were cultured under NM or SS conditions in the presence of 25 ng/ml OSM alone, a molar excess of GP130 antibody alone, and OSM + excess GP130 antibody, for 24 h. Figure 2 shows the changes in gene expression under SS conditions. OSM-induced changes in transcript levels are largely abrogated or significantly attenuated in the presence of a greater percent increase in FGB under SS conditions. These results confirm that OSM is indeed an inducer of acute phase response genes in renal tubular cells. As responses were similar in HK2 and PTEC (data not shown), most subsequent experiments were conducted using HK2 cells.

OSM has a greater effect on induction of renal acute phase response gene expression than IL-6 or LIF in HK2 cells. To test whether OSM is the predominant acute phase response cytokine acting on the renal proximal tubular epithelium, HK2 cells were cultured in the presence of OSM (25 ng/ml), IL-6 (25 ng/ml), and LIF (100 ng/ml) for 24 h. These concentrations have previously been shown to have similar potency to induce FGB synthesis in liver cells (36). Figure 4 shows the changes in gene expression with exposure to each cytokine under SS conditions, which were largely similar to those seen under NM conditions. Expression of FGB, OSMRβ, GP130, and LBP was significantly increased by OSM compared with IL-6 or LIF under both NM and SS conditions. Expression of LIFR and SERPINA1 was significantly increased with OSM vs. IL-6 and LIF predominantly under SS conditions. No differences in transcript expression were observed with stimulation by all three cytokines for IL-6 and LIF under NM or SS conditions, which were largely similar to those seen under NM conditions. Expression of IL-6R was significantly reduced by OSM compared with IL-6 and LIF. Compared with baseline NM or SS medium with no supplementary cytokines, IL-6 stimulation resulted in an increased expression of the
IL-6R under SS conditions ($P = 0.03$), LIF stimulation resulted in a small increase in expression of OSMRβ ($P = 0.03$) under NM, and an increase in LIFR ($P < 0.005$) under SS conditions.

**Exposure to OSM induces expression of genes associated with EMT.** PTEC were used for this experiment with the presumption that early physiologic changes may be more pronounced than in immortalized HK2 cells. PTEC were cultured under NM or SS conditions in the presence or absence of 25 ng/ml OSM, with or without GP130 antibody, for 24 h. Western analysis was performed on whole cell lysates for vimentin and N-cadherin expression. Vimentin expression increased significantly after exposure to OSM under both conditions and was partially attenuated in the presence of the GP130 antibody (Fig. 5). This finding is consistent with a loss of epithelial phenotype and a switch to a mesenchymal phe-
notype induced by OSM, via the OSMR, as previously shown by others (32, 38). There was a trend toward reduced N-cadherin expression, seen with loss of epithelial phenotype, upon exposure to OSM (not shown), also consistent with development of EMT, but this was small, likely because of the short duration of OSM exposure.

**DISCUSSION**

Our findings show that the human kidney can generate a strong intrinsic acute phase response correlating with the severity of injury, and most likely mediated via OSMRβ signaling. In a genome-wide transcriptome analysis, OSMRβ was the most highly differentially expressed IL-6 family cytokine receptor between DD and LD kidneys and correlated with early functional outcome (28, 52). Our PCR-based analysis in a spectrum of donor kidneys confirmed the association of OSMRβ with degree of tissue injury in human kidneys. This finding is consistent with transcriptome changes seen in the postischemic rat kidney, in which OSMR was among the 25 most upregulated genes at 6 and 36 h after ischemia and reperfusion injury (15). OSMR expression has not been reported in human kidneys. In contrast, in donor human hearts IL-6R mRNA was found to be significantly upregulated, and in a porcine model, brain death was associated with increased IL-6 mRNA in heart, lung, and kidney (45). These data suggest organ- and species-specific patterns of acute phase response signaling.

Incubation of renal proximal tubular cells with OSM induced expression of acute phase response genes such as SERPINA1, FGB, or LBP, which are traditionally associated with hepatic rather than intrinsic renal synthesis. The effect of OSM was enhanced by SS suggesting a greater propensity to generation of the acute phase response, or a synergistic effect with a proinflammatory environment, under conditions of cellular stress. These data demonstrate that the human renal tubular epithelium itself is capable of generating an acute phase response. Similar effects have been shown in cultured liver and endothelial cells (6, 41). The exact roles of each of the acute phase proteins cannot be deduced from this study, but local generation of acute phase reactants is likely crucial for a rapid
coordinated inflammatory response to injury, before the liver has had time to generate a systemic response (13).

Coincubation of cells with OSM together with the GP130 antibody reduced or abolished OSM-induced gene expression, suggesting that upregulation of the acute phase response genes is mediated through the OSMR. Stimulation of cells with LIF, known to signal via OSMR type I (heterodimer of LIFR/GP130), had a far lesser effect than stimulation with OSM, which would suggest predominant signaling of OSM via the type II receptor (heterodimer of OSMRβ/GP130) (47). LIF and LIFR expression, however, have been found to be associated with the repair response in a rat model of ischemia and reperfusion injury (53). The short incubation period in our culture experiments may therefore have missed a delayed LIF effect. LIF and LIFR expression did increase after stimulation with OSM in our model, suggesting that OSM could play a role in promoting renal recovery via upregulation of LIF/LIFR.

Incubation of PTEC with IL-6 did not induce acute phase response gene expression. This result was not unexpected given our transcriptome finding of low IL-6R expression and known low IL-6R expression in the kidney (31). Renal responsiveness to IL-6 has been described, however. At the whole animal level, IL-6 has been found to augment renal injury in response to ischemia and reperfusion injury as well as to nephrotoxins, but to enhance recovery when administered as a IL-6/sIL-6-R fusion protein, via trans-signaling (31, 35). The IL-6/sIL-6R complex can activate GP130 in cells not expressing IL-6R (11). It is possible, therefore, that IL-6 trans-signaling may play a role in modulation of the renal epithelial acute phase response. In our model, OSM stimulation did increase IL-6 expression. In the injured kidney, therefore, one may speculate that OSM-induced IL-6 expression may result in leukocyte recruitment, local formation of the IL-6/sIL-6R complex, and augmentation of the renal acute phase response (21).

OSM expression levels were extremely low in cell culture and in the microarrays, suggesting either a short early burst of OSM synthesis that was missed by the time of implantation biopsy and/or, more likely, an extrarenal source, e.g., from infiltrating cells and circulating OSM (9, 47). Serum levels in patients have seldom been reported but significantly increased OSM levels have been described in the setting of infections, sepsis, and acute respiratory distress syndrome (16, 21, 27). A single study in patients with septic shock found OSM levels up to 1,000 pg/ml (16) and are reported to be “higher,” but unpublished, by others (27). What circulating and tissue levels may be in the setting of brain death or local inflammation, relevant to a DD renal allograft, are unknown. In experimental models of injury and inflammation, OSM has been shown to stimulate leukocyte recruitment, adhesion, and migration and possibly contribute to the temporal switch between acute and chronic inflammation (17, 27). In both cardiac and liver injury models, OSM has been found in areas of tissue repair (17, 29). Differences in biological activity of OSM have, however, been noted among species making it difficult to speculate at this stage on its overall effect in the human kidney (14, 46, 47). To our knowledge, this is the first study to describe the OSM/OSMR in the human kidney and its role in generation of the renal acute phase response.

Two recent in vitro studies demonstrated a role for OSM/OSMR in induction of EMT in human PTEC by activating the Jak/Stat pathway and ERK1/2 signaling (32, 38). An emerging paradigm in progressive native kidney disease, as well as in chronic allograft dysfunction, suggests that inflammatory mediators, in response to diverse forms of injury, result in EMT and subsequent fibrosis (3, 30, 49). This paradigm is partially borne out by the observation that even advanced renal fibrosis is always associated with inflammatory infiltrates (42). Whether EMT occurs as an independent phenomenon, or is the precursor of progressive fibrosis in the transplanted kidney, however, remains somewhat controversial. An association between markers of EMT at 3 mo and early transplant ischemia and inflammation has been described in DD kidneys (19, 20, 48). The role of OSM/OSMR in initiation of EMT and the development of fibrosis over time in the DD kidney cannot be deduced from our study, but remains a plausible hypothesis that is the subject of ongoing studies.

A major strength of this study is its translational nature. We took results from in vivo unsupervised microarray analysis of human transplant biopsies enriched with clinical phenotypes to generate and test a hypothesis in vitro. In addition, our findings confirm and extend the array-based studies in transplantation, but are also highly relevant to the broader field of acute kidney injury. There are, however, several limitations inherent in our study. We recognize that cell culture models of ischemia and reperfusion injury are very poor correlates of in vivo tissue responses and that SS is an extremely mild cellular stress. Similarly, our use of OSM at 25 ng/ml may be considered supraphysiologic. Our preliminary dose-response analysis, however, did show a significant, although smaller, increase in acute phase response gene expression at lower OSM concentrations, suggesting a continuum of induction of acute phase response genes by OSM. The higher OSMR expression found in the most injured kidneys would be consistent with this observation. These potential limitations therefore do not deter from our overall conclusions. Our aim was not to attempt to reproduce the in vivo situation, but to test whether the renal tubular epithelium, which is a major target of ischemic renal injury, is capable of generating an acute phase response, and whether this would be modulated by OSM. Our findings support these hypotheses. We do not exclude, however, that other cell populations in the kidney may also participate in the renal acute phase response.

Inflammation is a critical response in injured tissue, augmenting the host defense against infection, initiating tissue repair, allowing adaptation to stress, and promoting healing (25). The inflammatory response, however, may also lead to less favorable outcomes, by augmenting the immune response and enhancing risk of organ rejection, as well as leading to healing in the form of fibrosis instead of reestablishment of normal parenchyma (1, 5, 25, 42). To our knowledge, our data are the first to highlight the importance of an intrinsic renal inflammatory response and to suggest that OSM/OSMR signaling is likely a relevant, but thus far underappreciated, pathway with pathophysiologic relevance for the renal parenchyma. Further studies are required to define its role in the balance between injury and repair in the kidney and impact on long-term transplant function.

ACKNOWLEDGMENTS

We are grateful to the patients and families who consented to participate in the study and the collaboration of the staff of the HOPE organ procurement program in Edmonton. We are grateful to the Ballermann and Halloran
REFERENCES


