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IMMUNE SYSTEM IN RENAL INJURY AND REPAIR: burning the candle from both ends?

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Abstract

This brief overview is focused on the inherent duality of immune responses: on the one hand they may induce inflammation and precipitate injury, on the other, a number of examples of participation in organ and tissue repair is growing. These processes will be reviewed from the nephrological standpoint. Specifically, the role of different leukocyte subsets, innate immunity, nitric oxide production, and stem cells, among others, are presented.

Keywords

macrophage; nitric oxide; stem cells; endothelial progenitor cells

Evolutionary view on regeneration

Tissue and organ regeneration in amphibians has for years attracted envious attention of mammalian biologists. Urodels (salamanders, newts) and larval anurans (frogs and toads) are capable of regenerating limbs, tails and other organs or tissues swiftly and scarlessly (1). Elements of such a regenerative prowess are detectable in cutaneous wound healing in embryos and early fetuses (2), but later on wounds heal with scars. Needless to say that scar formation in any organ including the kidney results in architectural distortion and functional compromise. This explains the search for molecular mechanisms of scarless healing of inflammatory lesions and in depth studies of fetal peculiarities of regeneration. It has been found that stimulated fetal fibroblasts produce less IL-6 and IL-8 than fibroblasts from adults, thus accounting for the reduced tissue infiltration by neutrophils and monocytes/macrophages (3). Interestingly, application of TGF- β to fetal wounds results in formation of scars upon wound healing, whereas inhibiting TGF- β formation or action in adult wounds reduces scarring (4,5). Among differences in the composition of the extracellular matrix in fetal wounds, the most prominent are the enrichment in hyaluronic acid and tenascin-C, capable of indirect reduction of activity of serine proteinases, cathepsin G, and inhibiting activation of T-cells and secretion of IL-2 (rev in 1). Collectively, these and other investigations shifted the focus from the relatively static studies into immunologic properties of inflammatory infiltrates toward a more dynamic description of mechanisms for resolution of inflammation.

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Infiltrating inflammatory cells and their role in tissue regeneration

Leukocytes infiltrating glomeruli and tubulointerstitium are a hallmark of renal inflammation (6). This temporary overlap has long been construed as a causative link between leukocytic infiltrate and development of chronic kidney disease and fibrotic complications. Only recently has it become apparent that infiltrating cells also participate in the resolution of a disease. On the one hand, leukocytes are removed, on the other, infiltrating macrophages switch the phenotype from pro-inflammatory to pro-repair. Leukocytes are responsible not only for the first cellular wave of defenses, but may also participate in resolution of the injury, and the impairment of their clearance may result in chronic inflammation (7).

Macrophages, long thought to be both the harbingers and the culprits of inflammatory processes in the kidney and other organs, represent a striking example of the shifting paradigm. Currently, 4 classes of activated macrophages are recognized (rev in 8): 1) Classically activated macrophages are a product of stimulation by $\text{INF}\gamma$ and TLR ligands like microbial products or cytokines $\text{TNF}\alpha$ and IL-1; these cells in turn secrete chemokines and proinflammatory cytokines. 2) Alternatively activated macrophages, a result of their activation by IL-4, IL-13 or glucocorticoids, lack in nitric oxide production, bactericidal activity and histotoxicity, but function in tissue repair. 3) Type II activated macrophages, primed by LPS or CD40 ligand in the presence of IgG immune complexes, are anti-inflammatory as they are characterized by enhanced production of anti-inflammatory IL-10 and reduced production of pro-inflammatory IL-12. 4) Anti-inflammatory macrophages induced by apoptotic cells generate $\text{TGF-}\beta$, PGE_2 and nitric oxide, but are deficient in production of IL-1, IL-6, IL-12 and $\text{TNF}\alpha$. This heterogeneity of activated macrophages and their functions is also seen morphologically based on their localization: glomerular macrophages expressing the chemokine receptor CCR5 are predominantly pro-inflammatory, while interstitially located macrophages have a less inflammatory phenotype (9). However, critical details on the distribution and function of diverse classes of macrophages in various kidney diseases is lacking. Nonetheless, the knowledge on the phenotypical properties of differentially programmed macrophages has already been sifting into therapeutic domain. Wang et al (10) compared classically activated versus alternatively activated macrophages transplanted into mice with adriamycin nephropathy on its outcomes. Classically activated macrophages aggravated the injury, whereas transfusion of alternatively activated cells was renoprotective.

Lymphocytes and dendritic cells, major players in adaptive immunity, participate significantly in renal diseases (8). IL-12 and IL-18 program naïve CD4^+ T cells to become Th1 lymphocytes which promote delayed-type hypersensitivity reactions. Microenvironment enriched in IL-4 and IL-13 predisposes to T cell differentiation into Th2 cells promoting allergic responses. Th1-driven immune responses are prominent in severe crescentic glomerulonephritis, whereas Th2-mediated reactions are responsible for antibody formation and participate in the pathogenesis of immune complex glomerulonephritis (rev in 13). Modulation of injury or repair can be achieved through modulation of cytokine microenvironment, so that administration of IL-12 or deficiency of IL-4 exacerbate the disease, whereas the inverse cytokine profile ameliorates it. Regulatory T cells, a subset of T cells responsible for the maintenance of tolerance, protect the kidney against nephrotoxic anti-GBM serum nephritis (14). In contrast, deficiency of regulatory T cells, induced by thymectomy performed in lupus-prone New Zealand mixed 2328 mice on the 3rd day of life, accelerates development of autoimmune disease (15). In the field of transplantation, regulatory T cells limit immune response to mismatched human leukocyte antigen DR antigens (16). An unexpected increase in the level of regulatory T cells was observed after rituximab (anti-CD20 antibody) therapy, being perhaps partially responsible for the anti-inflammatory effect and reduction in proteinuria (rev in 8). Dendritic cells specializing in presentation of antigens to T cells (immunologic synapse), may have diverse functions in renal disease. They interact with T cells via CD80 and CD86 surface

antigens with CD25 on T cells, and these interactions may exert opposite effects: CD80 deficiency is renoprotective against anti-GBM disease, CD86 deficiency exacerbates it, whereas combined deficiency has no discernible effect (17).

Contribution, if any exists, of *B-cells* and *eosinophils* to tissue repair remains insufficiently understood. On the other hand, *mast cells* participate in renoprotection, possibly through the fibrinolytic mechanism and their role in remodeling. Thus, mice deficient in mast cells appear to have worse morphologic and clinical manifestations of anti-GBM disease (18).

Endothelial-myofibroblast transformation

We have recently obtained evidence of endothelial-mesenchymal transdifferentiation in the course of inhibition of nitric oxide synthase by a pathophysiologically important antagonist, asymmetric dimethylarginine (ADMA). Cultured endothelial cells treated with ADMA showed inhibition of eNOS and Flk-1 expression and enhanced expression of α -smooth muscle actin, calponin and fibronectin, all markers of smooth muscle/mesenchymal cells. These cells overexpressed TGF- β and CTGF, as well as endostatin (19).

Significant literature exists on the role of epithelial-mesenchymal transdifferentiation in development and progression of fibrosis (20–23). Yet, the role of endothelial-mesenchymal transdifferentiation in vascular regression and fibrosis remains unexplored. It has been appreciated that during embryonic development Flk-1-positive vascular progenitor cells have a potential to differentiate into either endothelial or smooth muscle cells (24). DeRuiter et al (25) have documented the potential of embryonic endothelial cells to transdifferentiate into mesenchymal cells expressing smooth muscle cell markers. These observations posed a broader question on the potential single progenitor cell type for endothelial and smooth muscle cells and the possibility of conversion of endothelial to smooth muscle cells during adulthood. In vitro studies of cultured bovine and human endothelial cells showed that gamma-irradiation, mitomycin C, or FGF deprivation induce endothelial transdifferentiation into smooth muscle cells (26,27). There is indication that similar processes may occur in vivo during neointimal formation in patients with transplant arteriosclerosis – α -SM actin-positive neointimal cells are derived from recipient's circulating endothelial progenitors (28). Our data demonstrate that ADMA induces the loss of endothelial differentiation markers, such as eNOS and Flk-1 while increasing the expression of mesenchymal markers such as calponin and fibronectin. Inhibition of NO synthesis also led to the increased expression of collagen XVIII/endostatin, TGF- β and CTGF in cultured endothelial cells and in the non-hypertensive animal model. Exposure of cultured endothelial cells to either endostatin or TGF- β mimicked the effect of ADMA, suggesting their role in effecting endothelial-mesenchymal transformation. Interestingly, up-regulation of TGF- β in HUVEC was achieved by both ADMA and endostatin. This may be due to the existence of two independent pathways (TGF- β -mediated and endostatin-mediated), both triggered by ADMA, in switching the endothelial phenotype toward the mesenchymal. Alternatively, this could be explained by the ability of endostatin to up-regulate TGF- β . Since there was no significant additive effect in the combined action of ADMA with either TGF- β or endostatin, nor there was any significant additive effect of the combination of endostatin with TGF- β , the data are consistent with the second scenario, namely, the ADMA-induced up-regulation of endostatin, leading to the generation of TGF- β . The validity of this deduction will require future confirmation.

Modulated fibroblasts expressing some features of smooth muscle cells, myofibroblasts, are the pivot for post-inflammatory remodeling and/or scarring of the parenchyma. The process commences with the formation of proto-myofibroblasts, expressing stress fibers containing β - and γ -cytoplasmic actins, later differentiating into myofibroblasts containing α -smooth muscle actin (α -SMA) (29), which correlate with the disease progression. This process is governed by transforming factor- β 1 (TGF- β 1) and dependent on the presence of fibronectin

splice variant ED-A. Growth hormone inhibits TGF- β 1-induced formation of myofibroblasts (30). In addition to fibroblasts, pericytes, smooth muscle cells and epithelial cells may give rise to myofibroblasts (21). There is growing evidence that a leukocyte subpopulation of circulating bone-marrow-derived precursor cells, fibrocytes, can be recruited to the inflammatory sites and differentiate into myofibroblasts (31) which can participate in tissue repair or contribute to fibrosis, as it has been shown in liver (32).

The N-terminal sequence AcEEED of the α -SMA is necessary for its polymerization (33). Consequently, this peptide conjugated with the membrane-permeating carrier has been found to inhibit incorporation of α -SMA into stress fibers and to suppress collagen type I synthesis by myofibroblasts (34). It remains to be shown that administration of this peptide is associated with the reduction in renal fibrosis. Interestingly, myofibroblasts obtained from α -SMA-knockout mice are highly motile, proliferative and synthesize more type-I procollagen than the wild-type cells. In vivo, these mice subjected to unilateral ureteral obstruction (UUO), a model of renal interstitial fibrosis, as well as Habu snake venom injection, a model of mesangioproliferative glomerulonephritis, exhibited enhanced fibrosis, increased number of proliferating interstitial cells and type-I procollagen expression (35). Yet in another model, adriamycin nephropathy, blockade of p38 and TGF- β 1/Smad signaling pathways decreased myofibroblast transformation, improved functional renal recovery and attenuated fibrosis (36). Obviously, the issue is far from being settled, however, these discrepancies and unexpected findings should alert investigators to the multitasking by the same signal-initiating pathway placed at diverse biological contexts.

Humoral mechanisms of repair

Apart from cellular mechanisms of resolution, autocoids are attracting attention as checkpoint controllers of the inflammation (37). An emerging paradigm is related to the activity of cyclooxygenase-2 (COX-2), the source of pro-inflammatory PGE2 and PGD2. Although pathogenic at the initiation of inflammation, these eicosanoids are necessary for the subsequent stimulation of 15-lipoxygenase in neutrophils (38). Its product, lipoxins, the trihydroxy-tetraene-containing eicosanoids generated in the process of cell-cell interaction, provide local anti-inflammatory signaling resulting in a switch from PMN to monocytic, non-flogistic infiltrate. In addition, dietary omega-3 polyunsaturated fatty acids (PUFA) can be converted by COX-2 into potent anti-inflammatory and pro-resolution compounds resolvins and protectins (39), capable of halting the inflammatory infiltration and promoting the resolution of inflammation. Most recently, an additional COX-2-mediated and hematopoietic PGD2 synthase (hPGD2S)-dependent mechanism has been described: in vivo synthesis of PGD2 and 15-deoxy-delta12-14 PGJ2 (40) capable of resolving acute inflammation.

Recent studies have placed sphingolipids, including ceramide, sphingosine and sphingosine-1-phosphate (S1P), at the centre stage of biological processes specifically related to signal transduction and determination of cell fate, in which their levels change in a highly regulated temporal and spatial manner (98). Possessing opposite actions on cell death and survival, ceramide and S1P represent the key players of the concept of "sphingolipid rheostat (sphingostat)", as a determinant of cell fate (99). Our findings are consistent with this concept: proapoptotic action of elevated ceramide when it is unopposed by S1P, dominates the early response to nonenzymatically glucated long-lived proteins like collagen I. Furthermore, our data suggest that the anti-apoptotic action of S1P, in conjunction with the elevated level of ceramide, could result in cell senescence, marking the later response to glycated collagen I (100).

Nitric oxide, immunity and renal inflammation and regeneration

Inducible nitric oxide synthase in macrophages is activated by cytokines or microbial compounds and generates large amounts of NO, which exerts antimicrobial and anti-inflammatory effect. This simple paradigm has shifted to a more complex role of iNOS due to the recognition of the fact that iNOS-generated NO appeared to be protective during the acute phase of leishmaniasis, but resulted in the worsening of the lesions in the chronic phase (41). This expanded role of NO may explain the findings that inhibition of iNOS in the rat model of autoimmune interstitial nephritis aggravated renal injury (42). In this model iNOS may function as “a negative feedback regulator of the autoimmune T_H1 cell response and thereby protect host against immunopathological sequelae” (43). On the other hand, inhibition of iNOS in rats receiving renal allograft appeared to protect the graft from tubulointerstitial injury and improved graft function and survival (44) implicating high levels of NO in acute rejection. Similarly, we have demonstrated that selective inhibition of iNOS using oligodeoxynucleotides protected the kidney against ischemic injury (45). Administration of this selective inhibitor of iNOS resulted also in the improvement of eNOS function necessary for prevention of thrombosis and survival of endothelial cells. Interestingly, when LPS was used to induce acute renal injury, the same oligodeoxynucleotides did not appear to be protective (unpublished data).

Innate immune responses and renal injury and repair

Apart from recognizing bacterial, fungal, parasitic or viral molecular patterns, Toll-like receptors (TLR) appear to have several endogenous molecular ligands, such as mRNA, hypomethylated CPG-DNA, some extracellular matrix molecules, heat shock protein 60/70, and Tamm-Horsfall protein (THP), and they are expressed in various combinations in different segments of the nephron (rev in 46). Activation of these receptors has been implicated in the pathogenesis of infection-induced renal disease, like pyelonephritis, and infection-induced flares of the existing renal disease. Moreover, THP acting via TLR4 may activate dendritic cells, whereas biglycan has been recognized as a ligand for TLR-2 and -4; its effects are totally abolished in a double TLR-2/-4 knockout mice (47). The same is true for chronic allograft nephropathy. The role of TLR4 in fatty acid-induced insulin resistance has been discovered by Shi et al (48). These authors fed TLR4 knockout and control mice a high fat diet, observed protection of TLR4 $-/-$ mice, and were able to demonstrate that TLR4 in adipocytes and macrophages was activated by fatty acids, thus contributing to pro-inflammatory signaling and development of insulin resistance in these obese mice. In two mouse models of cryoglobulinemic membranoproliferative glomerulonephritis, TLR3 and TLR4 expression was significantly increased, with TLR4 localized to nephritic podocytes where it may regulate production of inflammatory cytokines and contribute to immunemediated injury (49). In a mouse model of acute renal ischemia, injury was much attenuated in TLR2 $-/-$ mice (50). Another group, however, implicates TLR4 in kidney injury: TLR4 $-/-$ mice were protected against renal ischemia (51). Ischemia-induced cyto- and chemokine response was found to be dependent on tubular TLR4 and responsible for the induction of inflammation and kidney injury.

Our group has developed a modification of “Danger Model” hypothesis explaining the involvement of innate immunity in acute renal injury and repair. We have previously demonstrated (52,53) that uric acid, a product of ubiquitous xanthine oxidase activity, is one of the early postischemia released substances. Uric acid level in the peripheral circulations surges within minutes after reperfusion and returns to baseline within 1 h in mice. This surge is causatively associated with the mobilization of endothelial progenitor and hematopoietic stem cells, both capable of accelerating regeneration. It appears that uric acid acts on TLR2 and TLR4 receptors to induce exocytosis of Weibel-Palade bodies in endothelial cells, which,

depending on the severity of ischemia, may induce, with varying intensity, either mobilization of stem cells or predominantly pro-inflammatory response.

Another recently identified target of uric acid is represented by NALP3 inflammasome (101). This cytoplasmic pathway, closely cooperating with membrane-associated Toll-like receptor pathways responsible for production of proIL-1 β protein, is responsible for activation of caspase-1 and cleavage of active IL-1 β . This step relies on the assembly of inflammasomes consisting of a NALP protein, an adaptor and caspase-1 (102). Among NALP proteins, NALP3 is known to have a broad range of ligands, from bacterial products to various non-microbial danger-associated molecular patterns (DAMPs), such as ATP, urate crystals, reduced intracellular potassium concentration and others (103). Obviously, this pathway has a major role in innate immunity and inflammatory responses to non-specific stressors, however, its role, if any, in regeneration remains unexplored.

Stem cell-induced repair

Mesenchymal stem cells (MSC, also known as stromal cells) appear to be ubiquitous (54,55). Due to the reduced level of expression of MHC class I and II antigens, the lack of expression of the T cell co-stimulatory molecules CD80 and CD86, and the ability to maintain dendritic cells in the immature state, MSC are immunologically privileged (rev in 56). Moreover, MSC suppress production of IL-2 by activated T cells and inhibit differentiation of cytotoxic T cells. These actions are achieved in part by diverse secretory factors of MSC: IL-10 and PGE2 prostaglandins, hepatocyte growth factor (HGF), and a potent immunosuppressive enzyme indoleamine-2,3-dioxygenase (57).

Transplantation of MSC exerted renoprotective effect in a model of ischemic acute renal failure (58), which occurred early in the course of the disease, was independent of stem cell differentiation, and was most probably due to the paracrine activity of MSC. Our group confirmed these findings. Using clonal MSC line, isolated from Tie-2/GFP mice and previously characterized (59), Chen, Park et al (60) infused these cells to mice subjected to unilateral renal ischemia and detected their preferential engraftment of the ischemic, but not contralateral kidney. In addition, in bilaterally ischemic mice, MSC infusion resulted in the accelerated recovery of renal function at days 2–3, compared to non-treated mice. The level of VEGF in the kidney was elevated by MSC treatment. Within 2 weeks infused cells partially differentiated toward endothelial or smooth muscle cell (pericyte) lineage. In vitro and in vivo studies confirmed the potential of MSC to differentiate toward angiogenic cells and participate in angiogenesis and vasculogenesis. Preferential engraftment of MSC to the ischemic tissue is governed by stromal cell-derived factor-1 (SDF-1, aka CXCL12), a chemokine produced by ischemic kidney or myocardium and attracting cells expressing CXCR4 (61). The latter subject, as well as the origins of mobilized MSC remain debatable and are beyond the scope of this review.

Endothelial progenitor cells (EPC)

A landmark study on EPCs and new vessel formation has provided an impetus for their use in stem cell transplantation (62). Human circulating CD34⁺ cells were demonstrated to differentiate *in vitro* into cells with endothelial-like properties. Moreover, administration of the cells to athymic nude mice with hind limb ischemia resulted in the integration of transplanted cells into capillary vessels and improved collateral circulation. The idea that such cells derive from the hematopoietic stem cell in the bone marrow has been strongly supported in the murine system where transplantation of a single hematopoietic stem cell repopulated the bone marrow and the endothelium of retinal blood vessels following experimental retinal ischemia (63). Comparable results have been published by others (64). The exact nature of EPC still needs to be elucidated and there is an ongoing debate whether these cells represent

a structurally and functionally homogeneous population (65). Although the bone marrow has been shown to be a principal source of EPCs, it is probably not the only one, since stem/progenitor cells with endothelial cell-like properties have been isolated from different tissues including peripheral blood, adipose and cardiac muscle tissue (66). The sources of endothelial progenitor cells are many, including, in addition to Sca+ bone marrow hemangioblasts and side-population CD34-cells, many tissue-resident (e.g. adventitial, skeletal muscle, adipose tissue, spleen, etc) progenitors and circulating peripheral blood VEGF-R2+, CD34+-mononuclear cells (rev in 67).

Mobilization of endothelial progenitor cells

Mobilization of EPC from their respective niches can be accomplished by mechanical injury and ischemic stress through generation of hypoxia-inducible factor-1-regulated release of vascular endothelial growth factor, erythropoietin, and stromal cell-derived factor-1 (SDF-1), as well as by placental growth factor, granulocyte- and granulocyte-macrophage colony-stimulating factors (68–72). A number of investigators have addressed the question whether EPCs can be efficiently delivered to areas of tissue ischemia to preserve or restore end organ function by participating in vasculogenesis. In a model of myocardial infarction in bone marrow transplanted mice, histological analysis showed donor-derived endothelial cells in areas of neovascularization at the border zone of the infarct (73). Recently, the degree of myocardial neovascularization and the level of protection against ischemia-induced cardiomyocyte apoptosis in rats have been shown to depend on the absolute numbers of injected angioblasts (74). These experimental data have been strongly supported by clinical observations. Adams and colleagues (75) found increased levels of circulating EPC in patients with coronary artery disease (CAD) after exercise-induced myocardial ischemia. Lambiase and colleagues (76) showed an inverse correlation between the density of coronary collaterals and numbers of peripheral EPC in CAD.

Comparatively less data has been published on EPCs and endothelial regeneration in the kidney. Rookmaaker and colleagues (77) observed a more than 4-fold increase in the number of bone marrow-derived glomerular endothelial cells by day 7 after anti-Thy-1.1 injection to bone marrow transplanted rats. The participation of donor-derived cells in glomerular endothelial cell turnover has also been shown in bone marrow transplanted rats with unilateral nephrectomy and anti-Thy-1.1 injection (78). In patients with chronic renal insufficiency numbers of circulating EPC are almost 30% lower than in healthy controls (79).

Pharmacologic mobilization of EPC can be achieved using statins (80), VEGF (81), erythropoietin (82), ACE inhibitors (83), and estrogens (84). Each of these medications has side-effects and some are precluded in ischemic AKI. Therefore, the search for endogenous signaling pathways leading to mobilization of EPC is so critically important.

Endothelial cell transplantation experiments were performed in our laboratory (85). Injections of HUVECs to athymic nude rats subjected to renal artery clamping dramatically improved renal function. Chimeric cells expressing endothelial nitric oxide synthase, thus mimicking one of the functions of endothelial cells, were also partially protective, although less than the mature endothelial cells. These studies were extended to stem cells derived from skeletal muscle of Tie-2/GFP mice, ex vivo expanded and differentiated to EPC, and injected to mice with acute renal ischemia. This procedure was associated with a significant functional and structural preservation (86).

Stem and progenitor cell competence may be compromised, especially in the course of chronic systemic diseases and metabolic disturbances. The existence of dysfunctional EPCs originating from BM has been documented in atherosclerosis (87,88), essential hypertension (89,90), preeclampsia (91), hyperglycemia (92), smoking (93) and type I and type II diabetes patients

(94–96). It has recently been shown that diabetic state promotes aging of cardiac stem cells, a tissue resident stem cell population, and contribute to the heart failure (97). Therefore, development of therapeutic strategies directed to restore stem cell competence represents the issue of highest priority. In this vein, Sasaki et al (104) obtained promising results by ex vivo treatment of dysfunctional bone marrow mononuclear cells obtained from patients with ischemic cardiomyopathy to restore the competence to EPC population.

In summary (see Fig 1), similar sets of mediators may be involved in pro-inflammatory or proregeneration processes. The progression along either of these pathways is by and large dependent on the biological context and ambient microenvironmental conditions. Learning how to manipulate those processes may open exciting new venues for therapy of renal disease.

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Figure 1.

A brief summary of mediators and potential outcomes in renal disease progression or regression.