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Oxidative Stress and Chronic Allograft Nephropathy

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Oxidative stress defined as outbalanced generation of reactive oxygen species (ROS) than the existing antioxidative defense mechanisms plays an important role in tissue injury. Ischemia/reperfusion accompanied during organ transplantation is well- established oxidative stress-induced tissue injury. We hypothesized that oxidative stress may also play a role in the development and progression of chronic allograft nephropathy (CAN), since that ROS are major signaling molecules of growth factors and cytokines [platelet-derived growth factors, transforming growth factor-β1 (TGF-β1)] upregulated in the kidney of CAN, that ROS in turn upregulate TGF-β1, and that mycophenolic acid may inhibit features of CAN [proliferation and extracellular matrix (ECM) accumulation in vascular smooth muscle cells and glomerular mesangial cells] through inhibiting cellular ROS. Cellular ROS activate signal transduction cascade (protein kinase C, mitogen-activated protein kinases, and janus kinases) and transcription factors (nuclear factor-κB, activated protein-1, specificity protein 1, and signal transducers and activators of transcription) leading to regulation of genes and proteins involved in cellular proliferation, ECM remodeling, and apoptosis accompanied in CAN. This review is intended to provide an overview of oxidative stress in renal allograft nephropathy.

Key Words: Antioxidants, chronic allograft nephropathy, ischemia-reperfusion injury, nicotinamide adenosine dinucleotide phosphate (reduced form) oxidase, platelet-derived growth factor, reactive oxygen species, transforming growth factor-β1

INTRODUCTION

Oxidative stress is defined as a tissue injury induced by increase in reactive oxygen species (ROS) such as hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), and hydroxyl radical ($^{\cdot}OH$). ROS are continuously generated under normal physiology but effectively eliminated by existing antioxidative defense mechanisms such as antioxidative enzymes [superoxide dismutase (SOD), catalase, and glutathione peroxidase], vitamins C and E, and glutathione reduced form (GSH). However, when the generation of ROS outbalances the existing antioxidative defense mechanisms, ROS will react with and denature cellular macromolecules including carbohydrates, lipids, proteins, and nucleic acids. ROS thus have been considered cytotoxic to a given tissue or cell. However, recent evidence suggests that ROS may be an integral component of membrane receptor signaling in mammalian cells, as ROS fulfill the important prerequisites for intracellular messengers.[1] In this context, i) the production of ROS has been detected in various cells stimulated by cytokines, growth factors, seven transmembrane receptor agonists, and phorbol ester, ii) administration of ROS mimics the effects of given external stimuli (first messenger), iii) generation of ROS in response to external stimuli are related to the activation of other signal transduction molecules such as signal transduction cascade [protein kinase C (PKC), mitogen-activated protein kinases (MAPK), and janus kinases (JAK)] and transcription factors [nuclear factor-κB (NF-κB), activated protein-1 (AP-1), specificity protein 1 (Sp1), and signal transducers and activators of transcription (STAT)], iv) antioxidants effectively ameliorate altered cell physiology in response to external stimuli.

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ROS can be generated within the nephron segments like the glomeruli and segments 2 and 3 of the proximal tubule.[2] Ischemia/reperfusion (I/R) inevitably accompanied with organ transplantation is well-characterized oxidative stress-induced tissue injury immediately after kidney transplantation.[3-5] Injury initiated by the lack of oxygen during cold preservation is augmented by ROS during subsequent warm reperfusion of grafts through activation of inflammatory cascade. On the other hand, there are a few reports on the role of oxidative stress in chronic allograft nephropathy (CAN). CAN is the most common cause of graft loss after the first post-transplantation year[6,7] and no specific treatment available for CAN at present. It is, therefore, necessary to understand the mechanisms involved in the development and progression of CAN in order to provide a specific treatment for CAN. In this review, we propose the hypothesis that growth factor- and cytokine-induced ROS may act as integral signaling molecules in CAN.

OXIDATIVE STRESS AND RENAL INJURY

Chronic renal failure (CRF) is now viewed as a state of chronic inflammation[8,9] and the prevalence of atherosclerosis is strikingly higher in CRF than in normal population.[10] It is, therefore, reasonable to speculate that oxidative stress is increased in CRF. Indeed, surrogate markers of oxidative stress were found increased and antioxidative defense mechanisms decreased in CRF.[11] Recent experimental studies also suggest that CRF plays active role in inducing oxidative stress. Vaziri et al.[12] demonstrated that superoxide dismutase expression was decreased and nicotinamide adenosine dinucleoride phosphate reduced form oxidase (NADPH oxidase) expression increased in the kidneys of experimental CRF rats. Buzello et al.[13] reported that nitrotyrosine expression in atherosclerotic plaque was increased in uninephrectomized Apo E knock-out mice and further increased with subtotal nephrectomy.

Oxidative stress accompanied in CRF is significantly improved after successful renal transplantation but increases in CAN,[14,15] suggesting that oxidative stress may be a relevant pathophysiological factor for the development and progression of CAN. Oxidative stress-induced I/R injury in the kidney graft immediately after implantation is considered as one major deleterious factor of successful renal transplantation.[3-5] In addition that I/R injury causes an increased risk of delayed or primary non-function of transplanted grafts during the immediate post-transplant period, I/R has been identified as a key risk factor in predisposing earlier development of CAN and short graft life.[16,17]

OXIDATIVE STRESS AND CHRONIC ALLOGRAFT NEPHROPATHY

The major histological findings of CAN are gradual vascular obliteration, glomerulosclerosis, interstitial fibrosis with mononuclear cell infiltration, and tubular atrophy, while the clinical course of CAN is characterized by progressive loss of renal function, arterial hypertension, and proteinuria. These features are common in progressive renal injury in which oxidative stress has been proposed to play an important role.[11] Markers of oxidative stress, plasma lipid peroxides measured by malondialdehyde and carbonyl proteins, are increased and GSH decreased along with decreased SOD, glutathione peroxidase, and vitamin E in CAN[14,15,18,19] as in CRF.[11] We[20] recently observed that plasma malondialdehyde, IL-6, heat shock protein 70, and transforming growth facator-β1 (TGF-β1) were significantly increased in transplant recipients with serum creatinine between 1.5 and 5.0 mg% compared to healthy control and recipients with serum creatinine below 1.5 mg% at least 1 year after renal transplantation. Phorbol ester- and hydrogen peroxide-induced dichlorofluorescein-sensitive cellular ROS in PBMC was significantly higher in renal recipients with serum creatinine between 1.5 and 5.0 mg% than healthy control and recipients with serum creatinine below 1.5 mg%.[21] A preliminary study[19] suggest that supplementation of vitamin E may have protective effect on long-term graft function of renal transplantation. All these data suggest that oxidative stress is associated with CAN and may play a role in the development and progression of CAN. We propose the hypothesis

that growth factor- and cytokine-induced ROS may act as integral signaling molecules in CAN based on the following observations.

Platelet-derived growth factor (PDGF) and TGF-β1 play important roles in glomerulosclerosis characterized by mesangial cell proliferation and extracellular matrix (ECM) accumulation in the mesangium. The expression of both PDGF and TGF-β1 are upregulated in the kidneys undergoing CAN.[22] PDGF induces cell proliferation[23,24] and ECM accumulation[25] in vascular smooth muscle cells and glomerular mesangial cells through cellular ROS. ROS also mediate TGF-β1-induced plasminogen activator inhibitor-1 (PAI-1) in glomerular mesangial cells[26] and TGF-β1-induced epithelial-mesenchymal transition (EMT) and ECM accumulation in tubular epithelial cell.[27] PAI-1 suppresses generation of plasmin and activation of matrix metalloporteinases and thereby decreases ECM degradation. Antioxidants have been shown to effectively reduce PDGF-induced vascular smooth muscle cell proliferation[23,24] and TGF-β1-induced EMT and ECM accumulation in tubular epithelial cells[27] suggesting that ROS may act as major mediators in CAN. We[24] recently reported that mycophenolic acid, a selective inosine monophophate dehydrogenase inhibitor, inhibited PDGF-induced vascular smooth muscle cell proliferation through inhibiting cellular ROS and subsequent ERK1/2 and p38 MAPK activation. MPA inhibit PDGF-induced cellular ROS through inhibiting NADPH oxidase[28] and through directly scavenging hydrogen peroxide.[29]

On the other hand, exogenously administered hydrogen peroxide upregulates the expression of TGF-β1[30] in mesangial cells suggesting that TGF-β1-induced ROS may amplify TGF-β1 signaling involved in renal injury. Hydrogen peroxide upregulates fibronectin,[27,31] and PAI-1[26] in renal cells leading to ECM accumulation. Hydrogen peroxide also upregulates α-smooth muscle actin and downregulates E-cadherin expression through MAPK activation leading to tubulointerstitial fibrosis.[27]

The mechanisms involved in growth factor- and cytokine-induced cellular ROS are currently under active investigation. NADPH oxidase is considered as the major mechanism for cytokine-induced cellular ROS generation leading to tissue injury.[32] Considering that available antioxidants may act as not only antioxidants but also pro-oxidants depending on cellular redox state, it is important to understand the mechanisms involved in cellular ROS generation to provide effective treatment for oxidative tissue injury. ROS-regulated signaling pathways in vascular and renal cells leading to CAN also need to be completely understood in order to provide target molecules for the treatment of oxidative stress-induced CAN.

CONCLUSION

Data from cell culture studies demonstrate that growth factor- and cytokine-induced ROS may amplify cellular signaling through upregulating the secretion of growth factors, cytokines, and ECM proteins by vascular and renal cells. These observations suggest that strategies to inhibit ROS generation may reduce oxidative stress and allow better preservation of graft function. Large-scale clinical trials are required to verify the role of oxidative stress and the therapeutic effect of antioxidants in the structural and functional changes in the kidneys of CAN.

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