Nitric oxide triggers the expression of proinflammatory and protective gene products in mesangial cells and the inflamed glomerulus

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Introduction

Nitric oxide (NO) is a double-edged sword. Synthesized in appropriate amounts by endothelial cells, neurons or macrophages it contributes to blood pressure regulation, neuronal communication and immune defence to name but a few important functions. On the other hand, excessive and uncontrolled production of NO by the inducible isoform of NO synthase (iNOS) is associated with several severe diseases like septic shock, stroke, neurodegeneration, diabetes, arthritis and other forms of chronic inflammation. The kidney does not escape from the impact of NO. I will highlight how increased understanding of the role of NO in renal pathophysiology has modified our way of thinking and the concepts of how to approach kidney diseases therapeutically.

Mesangial iNOS expression and the role of NO

We described previously that renal mesangial cells express iNOS upon exposure to inflammatory cytokines such as interleukin 1β (IL-1β) and tumour necrosis factor α (TNF-α) [1] and characterized the responsible enzyme as a so-called macrophage-type of NOS [2]. Indeed, this was the first description of iNOS expression in a non-immune cell. We hypothesized that it seems quite possible that the tremendous formation of NO under the influence of IL-1β and TNF-α may provide mesangial cells with properties that make them act partially as macrophages. Moreover, at the same time, NO causes relaxation of these contractile cells and, thus, leads to a state of glomerular hyperfiltration. These conditions seem to be important pathogenetic mechanisms for the development of glomerular sclerosis [3,4]. To summarize, NO had taken centre stage as a proinflammatory mediator in kidney diseases. In the following years, the expressional regulation of iNOS in mesangial cells was elucidated [5–7] and therapeutic strategies for the inhibition of iNOS which might provide the potential for a novel class of anti-inflammatory agents emerged [8].

Targets of NO action

More recently, NO itself has been increasingly implicated in the control of transcription factors and the general transcriptional machinery. In this way NO serves as an intracellular signalling molecule to modify gene expression [9–11]. One of the first genes identified as a target for transcriptional regulation by NO was iNOS itself, suggesting that NO modulates its own biosynthetic machinery [12]. This potent amplification mechanism may form the basis for the excessive formation of NO in acute and chronic inflammatory diseases. Moreover, other enzymes producing pro-inflammatory mediators, such as cyclooxygenase 2 and secretory phospholipase A2, are also transcriptionally affected by NO [for review see 10]. Other prime targets of NO-triggered gene regulation are chemokines. Release of chemokines is considered as a pivotal step in leukocyte recruitment necessary during initiation and maintenance of inflammatory responses. In this way, NO participates in the regulation of interleukin 8, macrophage inflammatory protein 1x, monocyte chemoattractant protein 1 and macrophage colony stimulating factor [10]. A most convincing demonstration, also in mechanistic terms, was reported recently for the CXC chemokine MIP-2 [13]. The authors reported on a NO- and IL-1β-dependent increase in MIP-2 mRNA and protein levels in renal mesangial cells. Furthermore, inhibition of IL-1β-induced endogenous NO formation markedly attenuated MIP-2 protein expression. Transfection of a 770-bp MIP-2 promoter–luciferase reporter gene construct into mesangial cells combined with deletion and mutational analysis identified critical nuclear factor NFκB and NF-IL-6 binding sites required for the NO-dependent effect.
regulation of MIP-2. In vivo, the inhibition of NO synthesis in the Thy-1.1 model of mesangio-proliferative glomerulonephritis by a specific iNOS inhibitor resulted in a marked reduction of MIP-2 expression. Strikingly, infiltration of neutrophils into the glomerulus was attenuated by more than 90% in rats treated with iNOS inhibitor. Down-regulation of MIP-2 may partly explain the beneficial effect of NOS inhibitors observed in early phases of glomerulonephritis.

Other groups of target genes for NO action are the matrix metalloproteinases and plasminogen activators and their endogenous inhibitors [11,14–16]. In the kidney, accumulation of extracellular matrix is often a hallmark of chronic disease, eventually leading to the development of glomerulosclerosis. In this context, the coordinate expression of proteases and their inhibitors by inflammatory cytokines and NO will allow the fine-tuned regulation of tissue proteolysis and protect against overwhelming tissue destruction.

Induction of cellular defence or cell death?

Furthermore, the changes associated with the exposure of cells to exogenous NO or to endogenously produced NO lead to activation of genes encoding a heterogeneous panel of protective antioxidant defence enzymes, including copper/zinc superoxide dismutase [17], haem oxygenase 1 [18], and members of the inhibitor of apoptosis protein (IAP) family [19].

We believe that the NO-induced upregulation of these proteins can be envisaged as a defence mechanism that serves to protect cells and tissues that simultaneously produce NO and superoxide, as do mesangial cells, against the imbalanced formation of cytotoxic mediators in conditions associated with local or systemic inflammation. Whether the net effect of NO is either beneficial or deleterious will be determined by the amount and duration of NO production and the microenvironment of a cell, especially the generation of reactive oxygen species and the antioxidant capacity. It seems quite obvious that ongoing analysis of NO signalling and gene regulation will provide therapeutically valuable information, while it broadens and enriches our understanding of the inflammatory response in kidney diseases.

References


