Editorial Comment

Cytokines in the progression of renal disease

J. Floege

Department of Nephrology, Medizinische Hochschule Hannover, Germany

Both the glomerulosclerosis and the interstitial fibrosis that occur in progressive renal disease exhibit a number of common histological features which are largely independent of the primary underlying renal disease. Such features include an increase in the amount of extracellular matrix, cellular hypertrophy and hyperplasia, as well as the infiltration of the tissue by leukocytes, in particular macrophages. While the mechanisms that govern the development of glomerular sclerosis have been the subject of intense research, the factors involved in the pathogenesis of interstitial fibrosis are less well understood. However, given the number of common features of, for example, glomerular mesangial cells and interstitial fibroblasts [1], it appears reasonable to assume that glomerular and interstitial fibrosis may depend to a substantial degree on similar pathogenetic mechanisms. In the glomerulus it has been proposed that an initial loss of functioning nephrons will induce an increased local or circulating concentration of factors that can initiate cellular, in particular mesangial cell, growth and matrix overproduction in the remaining intact nephrons [2]. Cellular hyperplasia and/or hypertrophy as well as matrix accumulation in turn lead to glomerulosclerosis of these latter nephrons, thereby establishing a vicious circle [2].

Cell culture findings have established that polypeptide factors, and in particular cytokines, regulate the proliferation of glomerular cell types [3,4]. Insight into the regulation of mesangial cell proliferation in vivo has been derived from studies of the mesangio-proliferative glomerulonephritis that is induced in rats by injection of antibodies directed against the Thy 1.1 antigen on the mesangial cell surface [3]. Anti-Thy 1.1 nephritis is characterized by a rapid wave of mesangial cell proliferation, macrophage influx, and increased synthesis of extracellular matrix proteins [3]. Three growth factors, which may have important roles in this in-vivo proliferative response, are platelet-derived growth factor (PDGF), basic fibroblast growth factor (bFGF), and transforming growth factor-\(\beta\) (TGF-\(\beta\)). All three cytokine growth factors are present in various inflammatory cells, for example macrophages, as well as in mesangial cells themselves, thereby allowing these factors to exert either paracrine and/or autocrine pathways [3,4]. Based on currently available data we have proposed that bFGF may participate in the initiation, PDGF in the maintenance, and TGF-\(\beta\) in the resolution of the pathological mesangial cell proliferation in vivo [3]. In vivo experiments thus suggest that there may be phases during which certain cytokines may play a more prominent role than others, which may be important with respect to therapeutic intervention (see below). Further experimental data suggest that at least some of these factors may also be involved in the mesangial cell proliferation that occurs in chronic glomerular disease such as in the remnant kidney model in the rat as well as in the regulation of cell proliferation in the renal interstitium [3,4].

Not only cell proliferation but also their matrix production is regulated by cytokines [4]. Again, while a substantial amount of data based on cell culture studies exists, the factors involved in the regulation of matrix production in vivo have only recently begun to emerge. In the anti-Thy 1.1 nephritis model, mesangial cell proliferation is followed by a marked expansion of the mesangial extracellular matrix. Using neutralizing antibodies, both PDGF and TGF-\(\beta\) have been shown to be involved in the mesangial matrix expansion in this nephritis model [5,6]. In the remnant kidney model, both matrix expansion as well as the preceding overproduction of PDGF within the glomerulus have been shown [3,4], suggesting that processes similar to those present in the anti-Thy 1.1 nephritis may operate in this chronic model as well.

Given the evidence that cytokines are involved in the mediation of increased glomerular cell proliferation and overproduction of matrix, should a goal of therapeutic interventions be to block such cytokines? Clearly cytokines have important beneficial biological roles. Thus, PDGF appears to be involved in the embryogenesis of the glomerulus [7], and certainly its role in the early phase of anti-Thy 1.1 nephritis is a regenerative one following the initial mesangial cell injury [3]. It is therefore possible that PDGF does not have a pathological role in glomerular disease unless its expression is markedly upregulated or prolonged, such as in the later phases of anti-Thy 1.1 nephritis. Similarly, TGF-\(\beta\) has important, beneficial biological functions. For example, TGF-\(\beta\) by virtue of its antimitogenic activity is thought to play an important role in the prevention of the malignant transformation of cells [8]. Finally, mice congenitally deficient in TGF-\(\beta1\), despite having...
a normal fetal development, will die soon after birth
from a wasting syndrome with multifocal, mixed
inflammatory cell responses, tissue necrosis, and sub-
sequent widespread organ failure [9]. Thus there may
be risks in total and/or long-lasting inhibition of cyto-
kines such as PDGF and TGF-β. A challenge of future
research will therefore be to evaluate during which
phases of renal disease there is overproduction of
certain cytokines and whether any individual cytokine
may have a more central role during particular phases
of the disease. Only when these questions have been
clarified may anti-cytokine therapy of renal disease
become an option for clinicians.

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