The complex role of osteopontin in renal disease

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Introduction

Osteopontin is a multifunctional protein which is produced not only in bone and cartilage as its name implies, but also in the kidney, hence its alternative name uropontin [1,2]. Osteopontin is encoded by a single gene which contains seven exons and six introns, and it maps to human chromosome 4q22 and mouse chromosome 5. Several splice variants have been described. The 5′-flanking region of the osteopontin gene contains numerous consensus sequences for transcription factors, including a vitamin D-response element (VDRE), a glucocorticoid response element (GRE), a ras-responsive element (RRE) and several AP-1 (c-jun–c-fos heterodimer) binding sites [3]. These transcription factor recognition sites explain the complex regulation of osteopontin expression by vitamin D, growth factors, cytokines and phorbol esters. Transcription of the osteopontin gene results in a protein with ~300 amino acids in most species. Osteopontin is a secreted phosphoprotein which contains two calcium- and two heparin-binding sites, and an Arg–Gly–Asp (RGD) cell adhesion motif. The RGD sequence is required for binding of osteopontin to integrin receptors. The principal integrin which binds osteopontin is the vitronectin receptor z4β1. Additional receptors include the integrins z5β1 and z5β3 and the hyaluronan receptor CD44 [4,5].

Osteopontin expression in cells and in the normal kidney

Osteopontin is expressed by many cell types in vivo and in vitro, including epithelial and mesenchymal cells and cells of haemopoietic origin such as T cells and macrophages. Cultured renal tubular epithelial and mesangial cells have been shown to produce osteopontin in vitro, particularly when stimulated with growth factors, cytokines or 1,25(OH)2-vitamin D [6–8]. In the normal kidney osteopontin is constitutively expressed by segments of the loop of Henle, the distal tubule and by the papillary and pelvic epithelium of the renal fornix, with some differences in mouse, rat and human [9–12]. Being secreted by these distal nephron segments and the urethelium, osteopontin is also found in the urine [13].

The diverse roles of osteopontin

Osteopontin is a calcium-binding protein and plays an essential role in regulating bone mineralization [1]. Osteopontin inhibits calcium oxalate and hydroxyapatite growth in vitro and acts as an inhibitor of stone formation [14,15]. Calcium oxalate crystals can bind directly to kidney tubular epithelial cells and stimulate osteopontin synthesis, thereby possibly limiting further crystallization [16,17]. Being present in the urine, osteopontin could act as an inhibitor of kidney stone formation in vivo [13,18,19]. Indeed, osteopontin has been found in calcium oxalate kidney stones.

It has been suggested that osteopontin could also be an inhibitor of tissue calcification through its ability to bind calcium at high capacity and low affinity [2]. Osteopontin is found at sites of calcification in atherosclerotic plaques and calcified aortic valves where it possibly could limit further calcium deposition. Osteopontin has also been found to be associated with intrarenal calcifications, for example in a rat nephrolithiasis model (ethylene glycol intoxication) [20].

Apart from playing an important role as an inhibitor of stone formation, it has been demonstrated that osteopontin is important in cell adhesion and migration. In vitro studies have shown that osteopontin is capable of stimulating macrophage chemotaxis [5,21] and vascular smooth muscle cell (VSMC) migration [22]. Macrophage recruitment in tubulointerstitial...
renal disease has been linked to chemotaxis by osteopontin [23], and VSMC migration in response to osteopontin could be important in the pathogenesis of atherosclerotic plaque formation [2]. Subcutaneous injection of purified osteopontin results in a macrophage-rich infiltrate [24,25]. Furthermore, osteopontin is found abundantly in granulomatous lesions such as tuberculosis and silicosis, which also suggests a role for osteopontin in macrophage infiltration and granuloma formation [26].

Recent studies have pointed to yet another role for osteopontin, namely its antagonism of nitric oxide (NO) synthesis. In studies examining inducible NO synthase (iNOS) expression in mouse and human kidney tubular epithelial cells, osteopontin was found to inhibit iNOS and subsequent NO production [27,28]. Osteopontin could thereby influence the various functions of NO in the kidney, including the regulation of vascular tone, glomerular haemodynamics and salt and water balance. Osteopontin is also capable of suppressing NO production by macrophages, suggesting a role in antagonizing the NO-mediated cytotoxic action of macrophages [29].

Osteopontin in experimental renal disease states

Osteopontin has been examined in various experimental models of renal injury. In contrast, much less information is available regarding osteopontin in human renal disease states. Using immunofluorescence staining and in situ hybridization, we found a marked up-regulation of osteopontin mRNA and protein in the proximal tubules of CBA/CaH-kdkd mice with interstitial renal disease and also in MRL-Faslpr mice with lupus nephritis [30,31]. In the rat, several renal injury models have been examined for osteopontin expression, including renal ischaemia [32–34], ureteral obstruction [35,36], protein overload proteinuria [37], angiotensin II-induced tubulointerstitial nephritis [38], cyclosporin nephropathy [39,40], pyruvomycin nephrosis [41,42], anti-Thy-1 nephritis [41], passive Heymann nephritis [41] and anti-GBM nephritis [43,44]. The common pattern in these renal disease models is that osteopontin is markedly induced and overexpressed by proximal tubules, both at the mRNA and protein level. The factors that promote the expression of osteopontin at these sites have not been determined but could involve cytokines and growth factors. In most of the studies, a correlation exists between the magnitude of osteopontin expression in areas of tubulointerstitial injury and the infiltration with mononuclear cells, suggesting that osteopontin could participate directly in the renal macrophage infiltration in vivo.

Direct evidence that osteopontin plays a role in renal interstitial macrophage infiltration comes from a study in a rat model of anti-GBM nephritis where an anti-osteopontin antibody led to a significant reduction in glomerular injury and recovery of renal function [44]. Using an osteopontin knockout (KO) mouse, it was shown in a preliminary report that the early macrophage influx after unilateral ureteral obstruction was significantly reduced in the osteopontin KO mice compared with control mice [45]. Osteopontin is certainly not the only chemotactic protein involved in macrophage accumulation, and additional proteins such as the chemokines do play a significant role as well. Whether osteopontin is important in human tubulointerstitial inflammation and whether it functions as a macrophage chemoattractant in man will need to be determined in future studies.

References


The antiproliferative effect of glucocorticoids: is it related to induction of TGF-β?

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Introduction

Glucocorticoids (GCs) are used in treating disorders of heightened immunity such as transplant rejection, owing to their capacity to prevent T cell activation by a multitude of mechanisms, including induction of the expression of the immunosuppressive cytokine, transforming growth factor (TGF-β). Similar to GCs, TGF-β is a pleiotropic mediator that modulates several aspects of the inflammatory response, and is a potent suppressor of T cell activation and cytokine expression. Because of their similar scope of action, it is of interest to examine the available evidence to resolve the issue

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