Gremlin: an example of the re-emergence of developmental programmes in diabetic nephropathy

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Abstract

The past two decades have yielded major advances in our understanding of the pathogenetic mechanisms that cause diabetic nephropathy. Of particular interest is the emerging paradigm of the recapitulation of developmental programmes within the diabetic kidney. Recently we have used the complementary techniques of suppression subtractive hybridization and Affymetrix GeneChips to assess changes in gene expression in human mesangial cells subjected to high ambient glucose concentrations and cyclic mechanical strain in vitro, the latter being models of hyperglycaemia and glomerular hypertension, respectively. In this review, we will focus on the potential role of one such differentially expressed gene, namely gremlin, in the pathogenesis of diabetic nephropathy. In the context of developmental nephrology, gremlin warrants special mention. Gremlin is a 184 amino acid protein and a member of the cysteine knot superfamily. The protein is highly conserved during evolution and is present in soluble and cell-associated forms. It belongs to a novel family of bone morphogenetic protein (BMP) antagonists that includes the head-inducing factor Cerberus and the tumour suppressor DAN. These proteins play important roles in limb development and neural crest cell differentiation. Evidence will be presented that mesangial cell gremlin expression is up-regulated by high ambient glucose, cyclic mechanical strain and transforming growth factor-β (TGF-β) and that gremlin may be an important modulator of mesangial cell proliferation and epithelial–mesenchymal transdifferentiation in a diabetic milieu.

Keywords: bone morphogenetic proteins; mesangial cells; transdifferentiation; transforming growth factor-β; tubule epithelial cells

Diabetic nephropathy is a complex disorder characterized histologically by mesangial expansion and sclerosis, glomerular basement membrane thickening and the subsequent development of tubulointerstitial fibrosis. Hyperglycaemia is the major driving force for renal injury in this setting. Mechanisms through which hyperglycaemia perturbs renal function include: dysregulation of protein kinase C activity [1], generation and activity of advanced glycation end-products [2], increased metabolism of glucose by aldose reductase [3], glomerular hypertension [4] and alteration of the intracellular redox potential [5]. The molecules downstream of these events, which influence renal cell turnover, matrix metabolism and scarring, are still being defined. Much attention has focused on the pivotal role of transforming growth factor-β (TGF-β) [6]; however, because of its pleiotropic actions, TGF-β may not be an ideal therapeutic target. The recent identification of increased expression of a number of genes which play roles in development [e.g. connective tissue growth factor, bone morphogenetic proteins (BMPs), vascular endothelial growth factor, drm/gremlin] in the context of diabetic nephropathy has focused interest on the role of ontogenic recapitulation in this disease [7–10]. In this short review, we will focus on the expression of drm/gremlin in diabetic nephropathy to highlight this emerging paradigm.

Reactivation of the ontogenic process in disease

Arrangement and order are central themes in the development of all mammalian organs. Organogenesis is encoded by harmonious interplay of many different growth factors, differentiation factors and their suppressors, and of adhesion molecules and their receptors, all functioning in concert to regulate cell proliferation, differentiation and death. Co-ordinated behaviour of these complex biological layers ensures that the ability to produce careful copies of discrete organs is conserved between generations. Many embryologically expressed genes regulate...
morphogenesis and then become quiescent. It is being appreciated increasingly that some developmental genes are reactivated in the adult in diseased tissues. In many cases, this re-emergence of developmental genes appears to be linked to tissue repair. Indeed, the therapeutic opportunities that exist within this system have been emphasized by recent research showing that the exogenous addition of the products of some developmental genes accelerates wound healing in simple, surgical models of injury [11].

Unfortunately, however, the poetic rhythm of the developmental programme does not always appear to resonate with the same harmony in the adult form. The ontogenic process is not always slavishly mirrored ex utero. Key elements may lack co-ordination or, indeed, be missing. Healing is embodied phenotypically as a starved form of the original, the fibrous scar. The repair process looks to have been subverted by the primal evolutionary demands for survival, and manifests itself as a poor abstraction of the embryonic reality. The conflation of developmental and inflammatory signals has resulted in the repair process as a form of chance. The challenge before us is to identify the pivotal developmental genes that are expressed in (or indeed that are absent from) this inflammatory milieu so that their energies might be harnessed and re-focused towards a more ordered system of resolution, repair and regeneration.

Gremlin in development and disease

The recent description of gremlin expression in the diabetic glomerulus serves to illustrate the complexities and opportunities posed by this emerging paradigm [8]. Gremlin, a member of a novel family of BMP antagonists which includes the tumour suppressor DAN and the head inducer Cerberus, was first isolated during a differential screen of transformed rat fibroblasts and their flat revertant [12]. Expression of gremlin has also been demonstrated in developing Xenopus pronephric duct [13] and in various human disease models [7,8]. Gremlin influences diverse processes in growth, differentiation and development by heterodimerization with BMPs, thereby inhibiting the ability of these ligands to bind to their receptors [13,14]. For example, gremlin plays an important role in limb bud development [14,15]. Vertebrate limb outgrowth and patterning depend on reciprocal interactions between sonic hedgehog (SHH) signalling from the posterior mesenchyme (polarizing region) and fibroblast growth factor (FGF) signalling from a specialized ectodermal structure, the apical ectodermal ridge (AER). Recent studies have shown that gremlin is an important modulator of the FGF/SHH feedback loop, by antagonizing BMP repression of FGF signalling [16].

In keeping with the general theme of the re-appearance of developmental genes in adult disease, increased expression of gremlin and BMPs has been identified recently in experimental models of diabetic nephropathy [8]. First identified as Induced in High Glucose 2 (IHG-2) in mesangial cells exposed to high extra-cellular glucose in vitro, subsequent in silico cloning revealed IHG-2 to be human gremlin [7,8]. Of parallel interest was the associated up-regulation of BMP2 and CTGF (a putative downstream mediator of TGF-β activity) in the same model system [7,8]. Increased gremlin expression has also been demonstrated in human mesangial cells exposed to cyclic mechanical strain in vitro and, in both streptozotocin-induced diabetic nephropathy and the 5/6 nephrectomy model of glomerular hypertension in vivo [8]. TGF-β, when added to serum-restricted human mesangial cells, augmented gremlin expression, while the stimulatory effect of high glucose on gremlin expression was attenuated by the addition of anti-TGF-β antibody [8]. This evidence suggests that gremlin is induced by TGF-β in the diabetic setting. Intriguingly, initial studies suggest that gremlin overexpression contributes to transdifferentiation of cultured tubular epithelial cells to a more fibroblast-like phenotype [17]. These data suggest a pathogenetic role for gremlin in diabetic nephropathy and identify gremlin as a potential therapeutic target.

The further exploration of these re-appearing developmental programmes may suggest novel approaches by which we can impose developmental order, as encoded in early life, to the reparative process in common acquired diseases with a view to effecting resolution with return of normal tissue architecture and function.

References