Crescentic glomerulonephritis is a rapidly progressive form of glomerular inflammation resulting in end-stage renal disease. Histologically, it is characterised by glomerular cell proliferation and crescent formation, infiltration of glomerular capillaries by inflammatory cells (primarily activated macrophages), and fibrosis (scarring). These processes have been mechanistically linked with specific Th1 and Th2 cytokines and with macrophage-derived mediators of injury, a number of which can activate or regulate protein kinase C (PKC). PKC includes at least 12 isoforms that can be divided in three subgroups: classical PKCs (PKCα, PKCβ1, PKCβ2, and PKCγ), novel PKCs (PKCδ, PKCe, PKCε, and PKCθ), and atypical PKCs (PKCδ and PKCλ). PKC is the cellular receptor for the lipid second messenger diacylglycerol (DAG) and, therefore, a key enzyme in signaling mechanisms triggered by activation of receptors coupled to phospholipase C. The novel PKCs (δ, ε, θ, and η) are dependent on DAG but not Ca²⁺ whereas the atypical PKCs (ζ and λ) are independent of both Ca²⁺ and DAG. PKC isoforms display a distinct cell- and tissue-type expression pattern of localization while PKC activation is associated with membrane translocation of the enzyme.

The role of individual PKC isoforms in mediating cellular responses to injury such as proliferation, apoptosis, cytoskeleton rearrangement, cell motility and scarring is currently being elucidated. In experimental models of tissue injury/disease, recent evidence points to PKCε activation as a protective mechanism against fibrosis as shown in the myocardium, the lung, and the diabetic kidney. Activity and intracellular localization of PKCε is controlled by phosphorylation at highly conserved sites present in the catalytic kinase domain. These sites are Thr⁵⁶⁶ in the activation loop, Thr⁷¹⁰ in the turn motif, and Ser⁷²⁹ in the C-terminal hydrophobic motif. Phosphoinositide-dependent kinase-1 (PDK-1) is the upstream kinase that directly phosphorylates the activation loop residue Thr⁵⁶⁶. This provides a link with the phosphoinositide-3 kinase (PI3-kinase) pathway as the PI3-kinase products, PtdIns(3,4)P₂ and PtdIns(3,4,5)P₃, bind and recruit PDK-1 to membranes thus leading to phosphorylation of downstream substrates such as PKCε. Phosphorylation of Ser⁷²⁹ in the C-terminal hydrophobic motif depends on the internal catalytic activity of the kinase indicating that it occurs by autophosphorylation rather than an upstream kinase. Recent evidence indicates that Ser⁷²⁹ phosphorylation controls intracellular PKCε location and is required for the kinase to achieve mature conformation and to be primed for activation by co-factors. Further, PKCε phosphorylated at Ser⁷²⁹ accumulates in cells at quiescence.

Studies attempting to characterize localization of PKCε phosphorylated at Ser⁷²⁹, henceforth referred to as pPKCε, in renal disease models in which cell proliferation and scarring are prevalent features are scarce. In this work, we employed immunohistochemical methods to assess expression and localization of pPKCε in a rat model of immune-mediated renal inflammation resembling human rapidly progressive glomerulonephritis and characterised by proteinuria and formation of fibrocellular crescents in glomeruli. pPKCε localisation was examined in a non-inflammatory model of proteinuria resulting from direct, toxin-mediated, glomerular epithelial cell injury.

Materials and Methods

Models of rapidly progressive (crescentic) glomerulonephritis and puromycin aminonucleoside-induced glomerular epithelial cell injury

All animal experiments were performed according to the Institutional Animal Care and Use Committee (IACUC). Male Sprague-Dawley rats weighing 180-200 g were immunized intraperitoneally with 1 mg rabbit IgG emulsified in complete Freund’s adjuvant and given as a total volume of 0.5 mL. Five days after this immunization, animals were injected in the tail vein with a subnephritogenic dose of rabbit immune serum raised against rat particulate GBM as previously described. This dose of anti-rat GBM serum (0.15 mL/100 g body weight) was insufficient by itself to cause significant proteinuria when given to rats not preimmunized with rabbit IgG (subnephritogenic). The intravenous injection of the anti-rat GBM serum was repeated 24 h after the first injection. The rabbit anti-rat
Glomerular fibrosis was identified using the Masson-Goldner trichrome stain (Merck A.E., Athens, Greece). Briefly, tissue sections, deparaffinized and rehydrated as described above, were stained with Weigert’s iron hematoxylin (identifies cell nuclei) for 5 min, washed with tap water and decolorized with 1% (v/v) acetic acid. Sections were subsequently placed in a Azophostosphoric acid Orange G solution. Sections were finally air dried, dehydrated, and mounted. This method stains areas of scarring (collagen) as light green.

Immunohistochemistry

PKCe phosphorylated at Ser\(^{729}\) (pPKCe) was detected in paraffin-embedded tissues. Sections were deparaffinized by two consecutive treatments (5 min each) with xylene. Rehydration was performed with graded alcohols (90%, 80%, and 70%) for 4 min each. Endogenous peroxidase was blocked with 3% H\(_2\)O\(_2\) in methanol for 15 min at room temperature. Antigen retrieval was subsequently performed by boiling the sections with 1X Target Retrieval Solution (Dako Ltd., Athens, Greece) for 10 min, which progressively oxidizes existing tissue aldehydes to carboxylic acid resulting in a strong Schiff’s reaction. Following washing, sections were incubated with Schiff’s reagent (Sigma-Aldrich) for 15 min. Harris’ Haematoxylin for 2 min was used as counterstain. Sections were subsequently dehydrated, cleared in xylene for 5 min, and mounted.

In rats with CGN or PAN-induced GEC injury (n=4). P values were (n=4): 2.3±0.4 in control, 12.8±2.1 (n=6) in rats with CGN, and 15.3±2.0 in rats with PAN-induced GEC injury (n=4).

In glomeruli of animals with CGN, there was glomerular infiltration by macrophages, periglomerular infiltration by mononuclear
cells, and formation of fibrocellular crescents and scarring [Figure 1, panel B (nephritic glomerulus) vs panel A (control glomerulus)]. As expected, in glomeruli of animals that received PAN no apparent changes were detected by light microscopy (not shown). In glomerular cells of control kidneys, pPKC-ε phosphorylated at Ser729 (pPKC-ε) was barely detectable or undetectable (Figure 2A). In animals with CGN, pPKC-ε immunolocalized in glomerular epithelial cells (GEC) (Figure 2B). These cells were identified as GEC on the basis of their positivity for the GEC specific marker WT1 (Figure 2C). In glomeruli with prominent crescent formation, cells within crescents were also positive for pPKC-ε, as shown in Figure 2B. In glomeruli of rats that received PAN and developed proteinuria of comparable severity with that noted in CGN rats, there was no apparent pPKC-ε expression in GEC (Figure 2D).

In animals with CGN, pPKC-ε immunolocalized in glomerular epithelial cells (GEC) (Figure 2B). These cells were identified as GEC on the basis of their positivity for the GEC specific marker WT1 (Figure 2C). In glomeruli with prominent crescent formation, cells within crescents were also positive for pPKC-ε, as shown in Figure 2B. In glomeruli of rats that received PAN and developed proteinuria of comparable severity with that noted in CGN rats, there was no apparent pPKC-ε expression in GEC (Figure 2D).

Since the CGN model employed in this study is macrophage-dependent, we examined whether glomerular localization of infiltrating macrophages (identified as ED1+ cells) was similar to that of pPKC-ε+ cells. As shown in Figure 4, the localization pattern of these two cell types was quite disparate; whereas ED1+ cells distributed throughout the nephritic glomerulus, pPKC-ε+ expression was mainly restricted in GEC. pPKC-ε also immunolocalized in non-proximal tubules surrounding glomeruli (Figure 2 A,B). A number of these tubules were surrounded by inflammatory cell infiltrates and scarring (Figure 5). The identity of pPKC-ε positive tubules was further assessed using the biotinylated lectins Arachnis hypogaea (AH) and Tetragonolobus purpureas (TP). AH is specific for distal

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**Figure 1.** Trichrome stains of control (A) and nephritic glomerulus (B) with fibrocellular crescent. Scarring (collagen) stains as light green. Scale bar: 50 μm.

**Figure 2.** Immunolocalization of pPKC-ε in glomerulus of control (A), and nephritic animal (B); pPKC-ε is barely detectable or absent in intrinsic cells of the control glomerulus. pPKC-ε is intensely expressed in glomerular epithelial cells and within cellular crescent of the nephritic glomerulus (B); immunolocalization of the visceral epithelial cell marker, WT-1 in the nephritic glomerulus (C); lack of pPKC-ε staining in GEC of a PAN-treated rat (D). Scale bars: 50 μm.

**Figure 3.** E-cadherin immunohistochemical expression in glomerulus and non-proximal tubules of a control kidney (A) and in glomerulus of a kidney with CGN (B); there is loss of E-cadherin expression in the nephritic glomerulus. (C), crescentic glomerulus with evidence for epithelial-to-mesenchymal (E-to-M) transformation of GEC identified by strong expression of α-smooth muscle actin in cells populating the crescent. Black arrows point to visceral and parietal GEC with E-to-M transformation, and to the vascular pole of the glomerulus. Scale bar: A and B, 100 μm; C, 50 μm.
tubules and collecting ducts, while TP stains cells of the Henle’s loop. Certain pPKC positive tubules (Figure 6A) were also positive for the AH lectin (Figure 6B) indicating that they were either distal convoluted or collecting. Another population of pPKC positive tubules was also positive for the TP lectin as shown in Figure 7. In this figure, two 0.5 µm serial sections were stained for pPKC and the TP lectin. Shown are tubules that were strongly positive for pPKC (tubules demarcated by the black arrow heads in panel A), but negative for the TP lectin (same tubules demarcated by the black arrow heads in panel B), indicating they were non-proximal in origin. Also shown, are tubules that were weakly positive for pPKC (panel A, black arrows) and strongly positive for the TP lectin (panel B, black arrows) indicating their origin as thick segments of Henle’s loops.

In a population of non-proximal tubules that were strongly positive for pPKC, there was heterogeneity in staining of their epithelial cells with positively stained alternating with negatively stained cells (Figure 8 A,B). These tubules were AH lectin positive but TP lectin negative indicating that they were distal or collecting in origin. Further examination of histologic characteristics of these tubules revealed morphology compatible with that of collecting tubules; specifically, they were lined with cuboidal to columnar cells separated by clearly obvious margins and the nuclei of which were closer to the base than apex.

Discussion

In the glomerular inflammation model employed in this study, responses of intrinsic glomerular cells, including proliferation and apoptosis, to pro-inflammatory mediators released by infiltrating macrophages play a crucial role in determining severity of renal dysfunction and the likelihood of progression of inflammation to irreversible stages. In this regard, emphasis has been placed on GEC lesions believed to develop due to effects of pro-inflammatory mediators. GEC are the most vulnerable component of the glomerular filtration barrier owing to their terminally differentiated nature. Well characterized GEC lesions include crescent formation, scaring and transdifferentiation to a mesenchymal (myofibroblast-type) phenotype. Although studies on expression of classical PKCs (α, β, γ) and novel PKCs (δ, ε) isoen-
zymes in the normal kidney have been performed, observations on localization of fully active PKC isozenzymes in lesions such as those described above are scarce. The present study on localization of PKC phosphorylated at Ser229 in these lesions was prompted by evidence that phosphorylation of this residue is required for the enzyme to assume its mature conformation and to become primed for activation. This may facilitate PKCs dependent processes observed within these lesions. Such processes include: apoptosis, which PKC suppresses, cell growth, which PKC promotes, and myofibroblast formation associated with scarring, which PKC also promotes. Phosphorylation of PKCs at the activation loop, turn motif and hydrophobic site in the carboxyl terminal domain primes them for activation by cofactors. The earliest PKC translation product is an unphosphorylated (immature form) cytoskeleton-associated protein. The initial step for its maturation is a series of ordered phosphorylation steps that prepare the enzyme for catalysis. The first phosphorylation event occurs at the activation loop and at position Thr246 by phosphoinositide-dependent kinase 1 (PDK-1) and functions as a switch by unmasking the entrance of the substrate-binding cavity thus exposing the necessary residues for catalysis. This step is followed by a second rapid autophosphorylation event at the turn motif and at position Thr703. Phosphorylation in this position locks the enzyme in a thermally stable catalytic component and in a phosphatase-resistant conformation. The final and third phosphorylation event occurs at the C-terminal hydrophobic motif, which for PKC is on Ser229. This event can be the result of autophosphorylation of the enzyme or be phosphorylated by its own upstream kinase, particularly PDK-2. Once the C-terminal serine is phosphorylated, the enzyme assumes its mature conformation. At this point, dephosphorylation of the Ser229 abolishes kinase activity, suggesting that this residue is critical for PKC activation. It can, therefore, be proposed that identification of PKC phosphorylated at Ser229 within tissue lesions would indicate that the kinase has assumed its mature conformation and is primed for activation. Further, the phosphorylation state of Ser229 was shown to control intracellular localization of PKC in response to cell stimulation.

Using an antibody against PKC phosphorylated at Ser229 (pPKC), the present study demonstrates a robust expression in glomerular epithelial cells (GEC) of animals with crescentic glomerulonephritis and was particularly prominent in cells within crescents. These had characteristics of an epithelial-to-mesenchymal cell transition process. Epithelial to mesenchymal transition (EMT) is typically defined by the acquisition of spindle cell morphology in combination with loss of E-cadherin and upregulation of mesenchymal markers. Consistent with these observations, cells in nephritic glomeruli had lost E-cadherin expression (Figure 7D) and acquired a mesenchymal phenotype recognized by expression of α-smooth muscle actin (Figure 6). Interestingly, glomerular localization of activated infiltrating macrophages, a prominent feature of the GN model employed, was quite different from that of pPKC expressing cells (Figure 4). This indicates that infiltrating macrophages is an unlikely cell type in which PKC phosphorylation at Ser229 occurred. The lack of a robust pPKC expression in GEC of animals given the GEC-specific toxin PAN and developing comparable degree of proteinuria indicates that effectors of PKC phosphorylation at Ser229 are at play in immune- but not in non-immune-mediated GEC injury. There are a number of factors that could promote generation of mature (fully phosphorylated) PKC in GEC and within fibrocellular crescents in immune-mediated glomerular injury. These include several second messengers including DAG and phosphatidylinositol 3,4,5-trisphosphate (PIP3) as well as specific fatty acids. In nephritic glomeruli, these messengers are generated by the increased production of cytokines that bind to tyrosine kinase receptors, which transmit signals by recruiting a variety of SH2-domain-containing proteins to multiple phosphorylated tyrosine residues. Key

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**Figure 7.** Serial sections of tubules strongly positive for pPKC (demarcated by the arrow heads in A) but negative for the TP lectin (demarcated by the arrow heads in B). Also shown, are tubules weakly positive for pPKC (A, black arrows). The same tubules are strongly positive for the TP lectin (B, black arrows). Scale bar: 50 μm.

**Figure 8.** Strongly pPKC positive tubules in which there is heterogeneity of pPKC staining amongst epithelial cells (positively alternating with negatively stained cells pointed by black arrows in A and B). These tubules were AH lectin positive and TP lectin negative. Scale bar: 50 μm.
among such cytokines is the platelet-derived growth factor (PDGF) which, in the model of glomerulonephritis employed, immunolocalizes along with its receptor within crescents. In this regard, it was shown that PDGF translocates PKCε from the cytosol to the cell membrane by activating PI3K and PLCγ2. Reactive oxygen and nitrogen species, shown to be overproduced in the CGN model, could also serve as effectors that can activate fully phosphorylated PKC-ε. In this regard, NOX1/NAPDH oxidase-derived reactive oxygen species were shown to accelerate translocation of PKCε, while hydrogen peroxide (H2O2) and nitric oxide (NO) also activate this kinase. Further, NO facilitates PKCε interaction with the specific anchoring protein, RACK2 (receptor for activated C kinase 2), and promotes PKCε translocation and activation.

Attempts to elucidate the role of PKCε in fibrosis occurring following tissue injury have yielded conflicting results. In PKCε deficient mice, tubulointerstitial fibrosis (fibronectin, RANK2 (receptor for activated C kinase 2), and promotes PKCε translocation and activation.20,46

In our study, pPKCε localization in collecting ducts was heterogeneous with pPKCε positive cells alternating with negative ones (Figure 8). It is likely that the pPKCε positive cells in collecting ducts are of the intercalated type since it was previously shown that such cells express both PKCε and the anion exchanger.22

In summary, the present study identifies the glomerular epithelial cell and fibrocellular crescents as a key site where pPKCε is expressed in experimental crescentic glomerulonephritis. Factors released as a result of the immune/inflammatory process apparently play a role since pPKCε was undetectable in non-immune mediated GEC injury. Whether the preferential expression of pPKCε in GEC and crescentic lesions facilitates PKCε-dependent processes remains to be determined.

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