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Renin-Angiotensin System Activation and Extracellular Signal-Regulated Kinases in Glomerulonephritis

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1. Introduction

Abnormal extracellular matrix (ECM) remodeling is a prominent biological feature of progressive glomerulonephritis (GN), and leads to glomerular dysfunction and sclerosis (Kagami et al., 2001; Prols et al., 1999). This condition is pathologically manifested in all the three major cells types of the glomerulus, and is characterized by the accumulation of fibronectin, laminin, and collagen in the diseased glomeruli (Kagami et al., 2004; Schnaper et al., 2003). Published genetic data (Boute et al., 2000; Kaplan et al., 2000; Patrakka et al., 2000) and the finding of podocyte abnormalities in transgenic mouse models of glomerulosclerosis (Shih et al., 1999) and patients with focal segmental glomerulosclerosis (Srivastava et al., 2001) suggest that the visceral epithelial cell plays a significant role. This assertion is supported by earlier data implicating potential epithelial cell stressors, such as glomerular hypertension, hyperfiltration, or hypertrophy in sclerosis (Brenner, 1985). Some models implicate the endothelial cells in the sclerotic process (Akaoka et al., 1995; Lee et al., 1995b). Still others suggest a role for the mesangial cells (MC) (Habib, 1973). As seen in human GN and experimental rat GN models, activated MCs acquire increased mitogenicity and migratory activity, and exhibit de novo synthesis of α-smooth muscle actin (α-SMA) and interstitial collagen (Hugo et al., 1996; Johnson, 1994). In addition, filtered macromolecules may be trapped in the mesangium, initiating an inflammatory response that could play a role in stimulating ECM synthesis. A unifying hypothesis that includes participation of all the cellular elements of the glomerulus can be constructed. Glomerular capillary hypertension, or a genetic or acquired abnormality in podocyte adhesion or structure, permits hyperfiltration of macromolecules. Paracrine signals from the injured podocyte stimulate endothelial cell expression of leukocyte adhesion molecules and impair endothelial cell fibrinolytic activity. Signals from epithelial or endothelial cells to the mesangium, or direct delivery of proinflammatory substances through the glomerular filtrate, initiates a process that culminates in the accumulation of ECM (Schnaper and Kopp, 2003). Mesangial expansion infringes on the capillary spaces, decreasing filtration surface area in the glomerular tuft. A major concept emerging from molecular cell biological studies is that pathological mesangial remodeling in progressive kidney disease is caused by

uncontrolled interactions between MCs, ECM, and growth factors (Rupprecht et al., 1996). Recent efforts have been directed towards modeling the cellular events regulating glomerular ECM turnover. Clarifying the molecular and cellular mechanisms responsible for pathological ECM remodeling may help to elucidate the pathogenesis of progressive glomerular sclerosis (Gruden et al., 2000; Krepinsky et al., 2003). A variety of physiological, pharmacological, and molecular approaches have been used to study how various mediators initiate or modify intracellular signaling pathways to cause mesangial cell matrix accumulation. These factors include transforming growth factor (TGF)-β (Border and Noble, 1997), basic fibroblast growth factor (bFGF) (Haseley et al., 1999), platelet-derived growth factor (PDGF) (Haseley et al., 1999), angiotensin II (Ang II) (Mezzano et al., 2001), connective tissue growth factor (CTGF) (Gupta et al., 2000), and various eicosanoids (Ledbetter et al., 1990).

2. The renin-angiotensin system (RAS) in GN

The RAS plays an important role in fluid and electrolyte homeostasis, the development of hypertension, and the progression of renal disease (Anderson et al., 1986; Navar et al., 1999). Recently, the focus of interest on the RAS has shifted towards the role of the local RAS in specific tissues (Dzau and Re, 1994). The local RAS in the kidney has several pathophysiological functions not only in regulating blood pressure, but also in renal cell growth and production of glomerulosclerosis, which is induced during the development of renal fibrosis (Kagami et al., 1994; Ruiz-Ortega and Egido, 1997). Indeed, previous studies have shown that RAS blockades have beneficial effects in rats and humans with various renal diseases, and these effects are often considerably more significant than their suppressive effects on blood pressure (Horita et al., 2004; Ravid et al., 1998). Chronic GN, which results in substantial renal damage, is frequently characterized by relentless progression to end-stage renal disease. Renal Ang II, whose production is enhanced in chronic GN, can elevate the intraglomerular pressure, increase glomerular cell hypertrophy, and augment ECM accumulation (Brunner, 1992; Kohan, 1998). Ang II antagonists or synthesis inhibitors markedly decelerate, and can even prevent, renal deterioration in renal disease (Anderson et al., 1986; Brunner, 1992; Giatras et al., 1997; Lafayette et al., 1992). This may be a reflection of the relatively short-term nature and small sample size of these studies, but may also be an indication that factors other than Ang II play an important role in the progression of GN.

3. Mitogen-activated protein kinase (MAPK)

The MAPK signaling pathway is a highly conserved module involved in various cellular functions, including cell proliferation, survival, differentiation, and migration (Fig. 1). Extracellular stimuli, such as growth factors and environmental stress, induce sequential activation of the MAPK cascade. At least four members of the MAPK family have been identified: extracellular signal-regulated kinase 1/2 (ERK1/2), p38, c-Jun N-terminal kinase (JNK), and ERK5 (Nishimoto and Nishida, 2006). The cascade allows for signal amplification, modulation, and specificity in response to different stimuli (Ferrell, 1996; Rose et al., 2010). As with many signaling pathways, complex regulatory mechanisms are utilized to direct the functional outcome mediated by MAPKs. The prototypic ERK1/2 pathway is found to be mainly responsive to stimulation by growth factors (Ramos, 2008), while p38

and JNK are collectively called stress-activated MAPKs (SAPKs) due to their induction by physical, chemical, and physiological stressors (Kyriakis and Avruch, 2001). In addition, the ERK5 pathway is implicated in both growth and stress signaling (Hayashi et al., 2004). The specificity and efficiency of MAPK signaling pathways are often dictated by specific docking and bindings partners (Jacobs et al., 1999; Raman et al., 2007; Remenyi et al., 2005). These include positive and negative modulators and scaffolding proteins that help to bring upstream and downstream signaling components together (Dhanasekaran et al., 2007; Morrison and Davis, 2003; Pearson et al., 2001). Thus, MAPKs form complex signaling networks that can be induced by a large array of external stimuli, and can achieve highly specific cellular effects through multitudes of regulatory mechanisms (Rose et al., 2010).

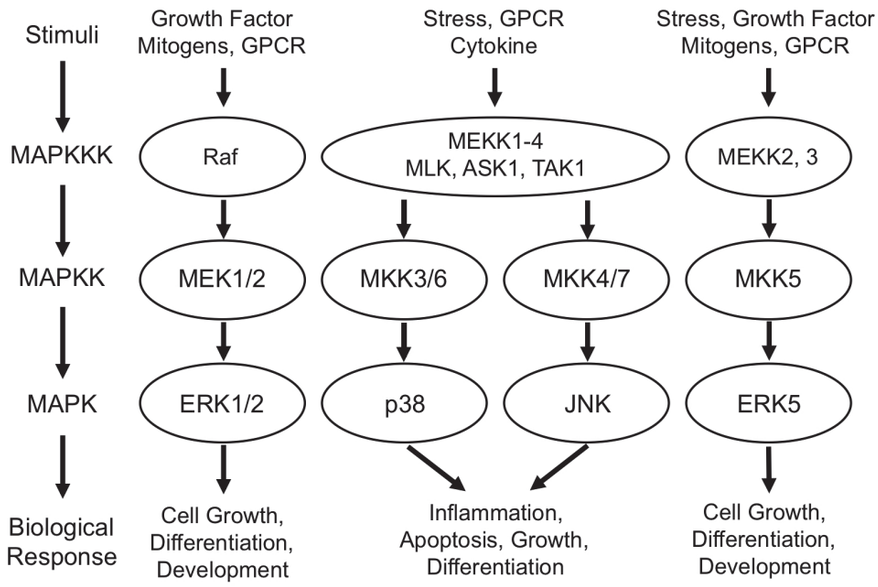

Fig. 1. Mitogen-activated protein kinase (MAPK) signaling. GPCR, G protein-coupled receptor; MLK, Mixed lineage kinase; TAK, TGF-β activated kinase; ASK, Apoptosis signal-regulating kinase.

3.1 ERK1/2

ERK1 and ERK2 are isoforms of the classical MAPK. Both ERK1 and ERK2 are activated by MAP/ERK kinase 1 (MEK1) and MEK2, which are members of the MAPKK family (Nishimoto and Nishida, 2006). After stimulation by a variety of mitogens, including peptide growth factors, MEK1/2 is activated by MAPKKK-mediated phosphorylation. These MAPKKKs include Raf and Mos. MEK1/2 then phosphorylates threonine and tyrosine residues in the Thr-Glu-Tyr (TEY) sequence of ERK1/2, thereby activating it. Activated ERK1/2 phosphorylates many substrates, including transcription factors, such as Elk1 and c-Myc, and protein kinases, such as ribosomal S6 kinase (RSK). Subsequently, immediate early genes, such as c-Fos, are induced. At the cellular level, ERK1/2 regulates cell cycle progression, proliferation, cytokinesis, transcription, differentiation, senescence, cell death, migration, GAP junction formation, actin and microtubule networks, and cell adhesion (Ramos, 2008). Owing to its role in cellular biology, ERK1/2 is a prominent player in physiological settings, influencing the immune system and heart development and

participating in the cellular response to many hormones, growth factors, and insulin. The ERK1/2 pathway is activated not only by growth factors, serum, and phorbol esters, but also by G protein-coupled receptors (GPCR), cytokines, microtubule disorganization, and other stimuli (Goldsmith and Dhanasekaran, 2007; McKay and Morrison, 2007; Raman et al., 2007). Prototypically, binding of growth factors (such as FGF) to their respective receptor tyrosine kinases (RTK) activates Ras, which recruits and activates Raf (MAP3K) at the plasma membrane. Once activated, Raf phosphorylates and activates MEK1/2. MEK1/2, in turn, activates ERK1/2 by phosphorylation of the Thr and Tyr residues in the conserved TEY motif within its regulatory loop. Activated ERK1/2 can phosphorylate downstream proteins, including many transcription factors, in the cytoplasm or nucleus.

3.2 ERK5

ERK5, also known as big MAP kinase 1 (BMK1), is twice the size of the other MAPKs (Lee et al., 1995a; Zhou et al., 1995). Since it is activated by oxidative stress and hyperosmolarity, ERK5 was initially documented as a MAPK family member activated by stress stimuli (Abe et al., 1996). Subsequently, ERK5 was also shown to be activated in response to serum, one of the well-known activators of ERK1/2 (Kato et al., 1997). Once activated, ERK5 exerts its kinase activity on a number of other protein kinases and transcription factors in both the cytosol and the nucleus. Furthermore, unlike other MAPKs, ERK5 has been shown to function directly as a transcriptional activator (Akaike et al., 2004; Kasler et al., 2000). Diverse biological roles of ERK5, including cell survival, differentiation, proliferation, and growth, have also been identified. ERK5 is reported to play a physiological role in neuronal survival, endothelial cell response to sheer stress, prostate and breast cancer, cardiac hypertrophy, and atherosclerosis (Hayashi and Lee, 2004; Nishimoto and Nishida, 2006; Wang and Tournier, 2006). Nerve growth factor, Ang II, high glucose, and other stimulators of ERK1/2 can also increase ERK5 activity (Kamakura et al., 1999). Similar to the ERK1/2 pathway, the MEK-ERK5 pathway is blocked by MEK inhibitors (Kamakura et al., 1999). Thus, there are similarities between the activation modes and functions of the ERK5 and ERK1/2 pathways. However, recent studies have also identified some distinctive features of the ERK5 and ERK1/2 pathway (Mulloy et al., 2003; Squires et al., 2002).

4. MAPKs in GN

A number of former studies have reported that the MAPK pathway plays a crucial role in the development of renal diseases. Bokemeyer et al. reported that ERK1/2 activation occurs in the rat Thy-1 model of mesangioproliferative nephritis, and that inhibition of the ERK1/2 pathway results in a significant reduction in mesangial cell proliferation in this model (Bokemeyer et al., 2000; Bokemeyer et al., 2002). The glomerular ERK1/2 was maximally activated on day 6 and represents a putative mediator of the proliferative response in mesangioproliferative GN. In addition, ERK1/2 activation in human glomerulopathies is associated with cell proliferation, histological lesions, and renal dysfunction (Masaki et al., 2004). Thus, these studies showing ERK activation in damaged glomeruli raise the possibility that ERK1/2 is an important signal molecule for acute inflammation-induced cellular proliferation in GN.

ERK5 was originally shown to be activated by stress stimuli or serum (Kamakura et al., 1999; Kato et al., 1997). Other stimuli, such as oxidative stress, Ang II, and high glucose, can also activate ERK5 in various cell types (Kato et al., 2000). Previous reports have

demonstrated that ERK5 is activated in the glomeruli of diabetic nephropathy rat models, but not in normal control rats. High glucose also induces ERK5 activation in cultured MCs in vitro (Suzaki et al., 2004). It was suggested that ERK5 might be involved in glomerular injury during the pathogenesis of diabetic nephropathy.

4.1 Animal experiments

We have established a progressive model of mesangioproliferative GN, as previously described (Nakamura et al., 1999). Briefly, rats (n = 36) were uninephrectomized, and, 1 week later, administered with a single intravenous injection of 2 mg of nephritogenic anti-Thy-1 monoclonal antibody 1-22-3. This monoclonal antibody recognizes a critical epitope of the Thy-1.1 molecule on the mesangial cell surface. Upon binding to its epitope, the antibody induces severe complement-dependent mesangial cell injury. The injection of monoclonal antibody 1-22-3 into uninephrectomized rats induced chronic progressive glomerulosclerosis with marked proteinuria. Control rats (n = 6) only received a vehicle. Six rats were sacrificed at each time point (days 3, 7, 14, 28, and 56 after the monoclonal antibody injection). In addition, 6 rats were sacrificed as baseline controls (0 h) prior to the injection of monoclonal antibody 1-22-3, and 5 rats (Nx group) were injected with PBS one week post-uninephrectomy and sacrificed on day 56 after the injection.

The right kidney of each rat was removed, immediately fixed in 10% buffered-formalin, embedded in paraffin, cut into 4-μm sections, and stained with periodic acid-Schiff (PAS) reagent. The mean glomerular cell number, which was based on the total glomerular cell count per glomerular cross section after PAS staining, was calculated for 30 glomeruli/kidney. A pathologist, who was blinded to the other findings, semi-quantitatively analyzed the glomerulosclerosis score. The percentage of each glomerulus occupied by the mesangial matrix was estimated and assigned a code, according to the following system: 0, 0%; 0.5, 1-5%; 1, 5-25%; 2, 25-50%; 3, 50-75%; and 4, >75%. Frozen sections (3 μm) were fixed in acetone, incubated with a rabbit anti-phospho-ERK5 antibody at 4°C overnight, and then incubated with a FITC-conjugated donkey anti-rabbit IgG antibody. To evaluate the level of glomerular staining with each antibody, we performed a semi-quantitative analysis, according to the following scoring system: 0, diffuse, very weak or no mesangial staining; 1+, 1-25% of glomerular tufts exhibit focal increases in mesangial staining; 2+, 25-50% of glomerular tufts exhibit strong mesangial staining; 3+, 50-75% of glomerular tufts exhibit strong mesangial staining; and 4+, >75% of glomerular tufts exhibit strong mesangial staining. For each kidney section, 30 glomeruli were selected at random and evaluated in a blinded fashion by the same pathologist. The mean value per section was then calculated. Formalin-fixed tissue sections (3 μm) were deparaffinized with xylene and rehydrated through a graded series of ethanol. Endogenous peroxidase was blocked by incubation with hydrogen peroxide, and the samples were heated at 121°C for 15 minutes in 0.01 mol/L citrate buffer (pH 6.0) for antigen retrieval. Next, the sections were incubated at 4°C for 24 hours with an anti-phospho-ERK1/2 antibody diluted in PBS containing 1% BSA. After washing with PBS, the sections were incubated with a biotinylated secondary antibody and avidin-biotin-peroxidase complex (ABC Elite; Vector Laboratories, Burlingame, CA), and developed with 3,3′-diaminobenzidine. Each section was counterstained with Mayer's hematoxylin, dehydrated, and coverslipped. The phospho-ERK1/2-positive cells in 30 full-size glomeruli were counted, and the mean value was calculated.

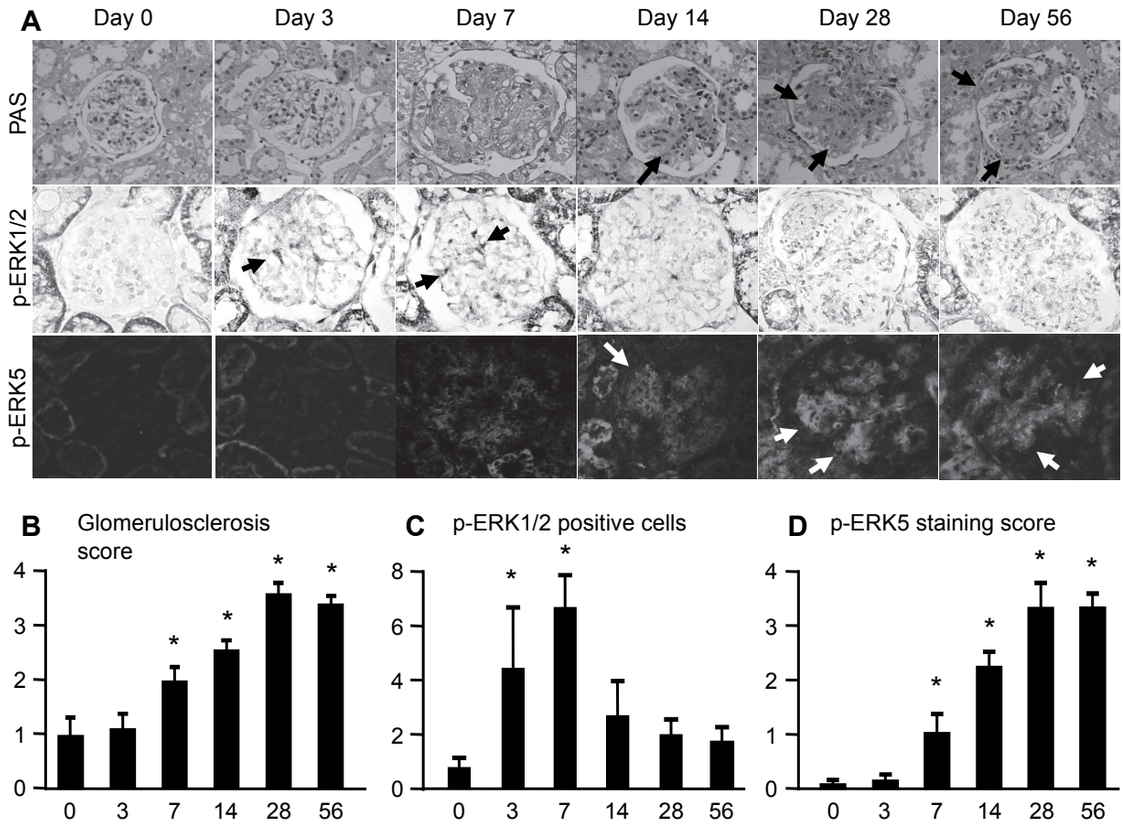

Fig. 2. Time course studies in glomerular histology and expression of phospho-ERK1/2 (p-ERK1/2) and phospho-ERK5 (p-ERK5) in normal and glomerulonephritis (GN) rats. A: analysis of glomerular histology on periodic acid-Schiff (PAS)-stained sections and sections immunostained with anti-p-ERK1/2 or anti-p-ERK5 antibody. Magnification, ×200. B: semi-quantitative assessment of glomerular ECM accumulation in normal and GN rats. C: semi-quantitative assessment of glomerular p-ERK1/2 expression. D: semi-quantitative assessment of glomerular p-ERK5 expression. Values are mean +/- SD. *P < 0.05 vs rats at day 0.

4.2 ERK1/2 and ERK5 expression in rat models of progressive GN

Early induction of ERK1/2 phosphorylation was detected on days 3 and 7 of GN. A significant increase in phosphorylated ERK1/2 was not seen in the late phase of GN. In contrast to the time course of glomerular ERK1/2 phosphorylation, glomerular phospho-ERK5 expression was very weak on day 3. However, the level of this expression increased in the expanded mesangial area by day 7, and dramatically increased in a typical mesangial pattern by days 28 and 56 (Fig. 2). The level of glomerular phospho-ERK5 expression closely paralleled the glomerulosclerosis score during the course of chronic anti-Thy-1-induced GN ($P < 0.05$). Treatment of GN rats with an Ang II type 1 receptor blocker (ARB) resulted in a significant decrease in phospho-ERK5 expression, accompanied by remarkable histological improvement. We have also previously reported that increased ERK5 phosphorylation is associated with MC proliferation and ECM accumulation in the glomeruli of 52-week-old OLETE rats, a model of type 2 diabetic mellitus (DM) (Suzaki et al., 2004). Bokemeyer et al. demonstrated that glomerular ERK1/2 is maximally activated on day 6 and that blocking

the ERK1/2 pathway using a specific inhibitor results in a significant reduction in mesangial cell proliferation in mesangioproliferative GN (Bokemeyer et al., 2000; Bokemeyer et al., 2002). Thus, these studies demonstrating ERK activation in damaged glomeruli suggest the possibility that ERK1/2 is an important signal molecule for acute inflammation-induced cellular proliferation, and that ERK5 may participate in the development of chronic glomerular lesions in GN.

5. MAPK in glomerular cells

Ang II stimulates ERK1/2 activation via NADPH oxidase-dependent reactive oxygen species (ROS) production in cultured rat MCs (Gorin et al., 2004). Therefore, we examined whether oxidative stress mediates the effects of Ang II on ERK5 phosphorylation in MCs. Cultured rat MCs were established from intact glomeruli of Sprague-Dawley rats. MCs were pretreated with ARB or diphenylene iodonium (DPI) before stimulation with Ang II or H_2O_2. MCs were serum-starved for 48 hours in serum-free RPMI 1640 medium, prior to stimulation with H_2O_2 and/or Ang II in the presence or absence of reagents. Ang II-induced ERK5 phosphorylation in MCs was blocked by the pretreatment with ARB but not DPI, indicating that Ang II-induced ERK5 phosphorylation was mediated by the Ang II type 1 receptor and not by the Ang II-induced NAD(P)H oxidase-dependent ROS production (Urushihara et al., 2010). Furthermore, the costimulation of MCs with Ang II and H_2O_2 resulted in a synergistic increase in ERK5 phosphorylation, compared to the stimulation of MCs with either Ang II or H_2O_2 (Urushihara et al., 2010). These findings suggest that Ang II directly induces ERK5 phosphorylation via NADPH in an oxidase-independent manner, and that ROS and Ang II could each induce ERK5 phosphorylation in MCs through different signaling pathways.

5.1 ERK5-specific knockdown in cultured rat mesangial cells (MC)

To examine the endogenous function of ERK5 in MCs, we used the small interfering (si) RNA technique for ERK5 gene silencing. MCs were transiently transfected with a mixture of three ERK5-specific siRNAs, using the lipofection method. After incubation in a low-serum-containing medium (5% FBS) for 18 hours, the serum concentration was adjusted to that of complete medium and the cells were cultured further. A non-silencing siRNA that did not target any known mammalian genes was used as a negative control. The transfection efficiency, determined under the same experimental conditions by counting the number of fluorescently labeled siRNA-transfected cells using a fluorescence microscope, was ~80%. Inhibition of ERK5 expression was verified by quantitative real-time PCR and western blot analysis. Further, we evaluated the viability of siRNA-transfected cells cultured for 24 hours in serum-free medium using the WST-1 assay for determining cell survival rate. The WST-1 assay was performed using a cell counting kit, according to the manufacturer's protocol. Briefly, siRNA-transfected cells grown in 96-well plates were washed with PBS, and 10 μL of the WST-1 reagent was added to 100 μL of cell culture medium in each well. After incubation for 8 hours, the absorbance of the samples was measured at 450 nm (test) and 690 nm (reference) with a microplate reader. Additionally, we measured the soluble collagen levels in culture supernatants after 24 hours of incubation in serum-free medium using a Sircol collagen assay. This assay measures the total collagen secreted from cultured cells. Briefly, cells were cultured for 24 hours with or without treatment, and supernatants were collected. One milliliter of Sirius red, an anionic dye that specifically reacts with basic side chain groups of collagens, was added to 200 μL of the supernatant and incubated with

gentle rotation for 30 minutes at room temperature. After centrifugation, the collagen-bound dye was resolublized in 1 mL of 0.5 M NaOH, and the absorbance at 540 nm was measured.

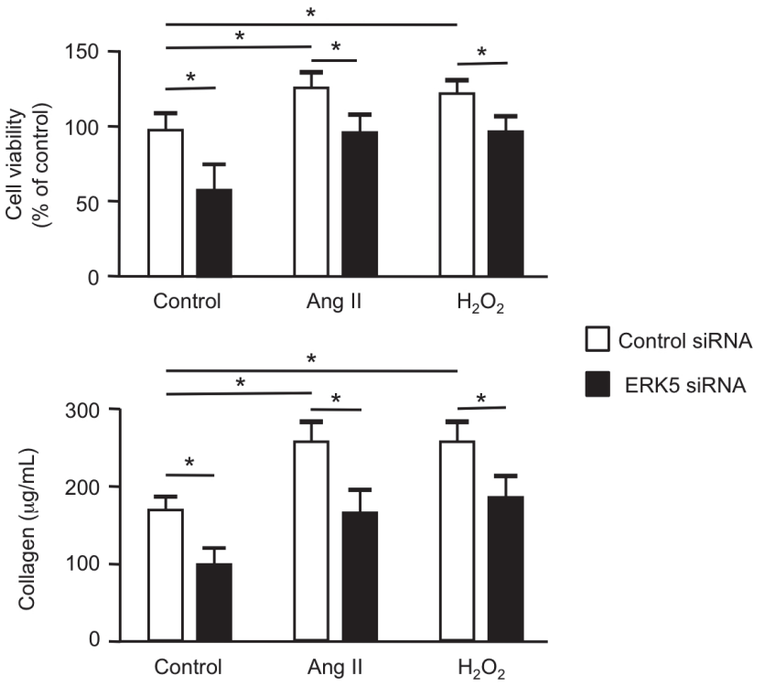

Fig. 3. Effects of Angiotensin II (Ang II) or H_2O_2 on cell viability and collagen secretion in ERK5 siRNA-transfected MCs. MCs were transfected with non-silencing siRNA (control siRNA) or ERK5-specific siRNA (ERK5 siRNA) and stimulated with Ang II (100 nM) or H_2O_2 (50 μM) after incubation in serum-free medium for 24 hours. Cell viability was evaluated using the WST-1 assay (8 hours; top), and collagen secretion in culture supernatants was evaluated by the Sircol assay (24 hours; bottom). Values are mean +/- SD. *P < 0.05 between groups as indicated.

5.2 Cell viability and collagen secretion

Using the WST-1 and Sircol assays, significant concentration-dependent decreases in both cell viability and soluble collagen secretion were observed in ERK5 siRNA-transfected, but not control siRNA-transfected MCs. Next, the effect of oxidative stress and Ang II on ECM accumulation and cell viability, and the involvement of ERK5 in these processes were examined. As seen in Fig. 3, Ang II and H_2O_2 significantly increased both cell viability and soluble collagen secretion in control siRNA-transfected MCs ($P < 0.05$). Transfection of ERK5 siRNA significantly reduced Ang II- or H_2O_2-induced increases in MC viability and collagen secretion compared to control siRNA transfection ($P < 0.05$).

Many studies have demonstrated that the ERK5 pathway controls cellular processes, such as proliferation, survival, differentiation, and ECM metabolism in pathophysiological conditions (Chang and Karin, 2001; Kyriakis and Avruch, 2001; Nishimoto and Nishida, 2006). We investigated the involvement of MC ERK5 expression in chronic progressive GN using in vitro and in vivo studies. We found that both cell viability and soluble collagen secretion were induced by Ang II or H_2O_2 in control MCs. These changes were significantly

inhibited in ERK5 siRNA-transfected MCs, suggesting a possible role for ERK5 expression in the sustained MC proliferation and pathological ECM accumulation observed in progressive GN. Furthermore, the data obtained from the treatment of GN rats with ARB indicate that Ang II is an inducer of MC ERK5 phosphorylation in vivo, and support the involvement of Ang II-induced ERK5 phosphorylation in progressive glomerular lesions. In general, the repair of proliferative GN-induced damage requires the regression of the proliferated glomerular cells by apoptosis and the appropriate removal of the accumulated pathological ECM (Shimizu et al., 1995). Based on our results, the activation of an ERK5 signal may not only induce prolonged MC survival, but also enhance the secretion of pathological collagen I within damaged glomeruli, thereby contributing to the development of progressive GN.

6. Conclusion

The present study has revealed that phospho-ERK1/2 and phospho-ERK5 expression in the glomeruli are markedly increased in an experimental model of progressive GN. Glomerular ERK1/2 activation seems to play an important role in acute inflammation-induced cellular proliferation in the development of GN. Furthermore, the enhancement of ERK5 phosphorylation by Ang II appears to be linked to the increased MC viability and pathological ECM accumulation in the chronic glomerular lesions in GN (Fig. 4). We, therefore, propose that the controlled regulation of glomerular ERK1/2 and ERK5 activation could provide the basis for an effective therapeutic strategy for preventing the progression of GN.

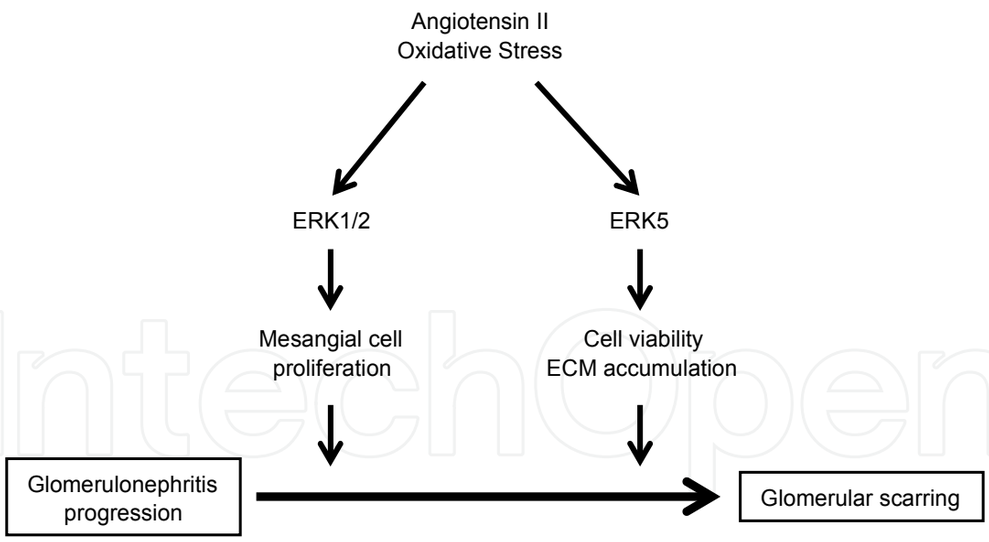

Fig. 4. ERK1/2 and ERK5 signaling during the course of progressive GN.

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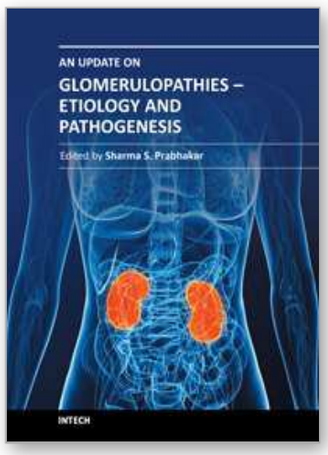

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