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The Role of STAT3 Activation in Glomerulonephritis

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1. Introduction

Glomerulonephritis is a renal disease characterized by inflammation of the glomeruli, i.e., small blood vessels, in the kidneys. It may present with isolated hematuria and/or proteinuria or as nephritic syndrome, acute renal failure, or chronic renal failure. Glomerulonephritis has several different pathological patterns that can be broadly grouped into non-proliferative and proliferative types. Non-proliferative types include minimal change glomerulonephritis, focal segmental glomerulosclerosis, and membranous glomerulonephritis. Proliferative types include IgA nephropathy, post-infectious glomerulonephritis, membranoproliferative/mesangiocapillary glomerulonephritis, and rapidly progressive glomerulonephritis (Miller et al., 2010). Of the many factors involved in the inflammatory response, cytokines are the most important factors that bind to their receptors and activate signal transduction pathways. Progress in our understanding of inflammatory signaling pathways has led to the identification of the involvement of nuclear factor-κB (NF-κB), mitogen-activated protein kinases (MAPKs) such as p38, and Janus tyrosine kinase-signal transducer and activator of transcription (JAK-STAT) pathways (O'Neill, 2006). The NF-κB and p38 pathways are activated by the stimulation of interleukin-1 (IL-1) and tumor necrosis factor (TNF). The principal signaling pathways activated by IL-1 and TNF are the NF-κB and stress-activated MAPK pathways, whereas the JAK-STAT pathway is activated by many other cytokines.

2. STAT family

JAK-STAT is an important tyrosine kinase pathway activated by almost all cytokines (Ihle, 2001) that are well known for their role in the progression of renal diseases (Johnson, 1997). The STAT family consists of seven members (Table 1). The STAT proteins are unique transcription factors containing Src homology (SH) 2 and phosphotyrosine-binding domains. The SH2 domain interacts with sites of tyrosine phosphorylation to recruit STATs to receptor complexes. Following tyrosine phosphorylation of STATs, dimerization occurs between the SH2 domains. Tyrosine phosphorylation around amino acid position 700 (STAT1, tyrosine 701; STAT3 tyrosine 705) is essential for dimerization of STATs and the concomitant nuclear translocation of the dimer (Kaptein et al., 1996; Shuai et al., 1993). The basic model of cytokine pathways depends on tyrosine phosphorylation by JAK proteins non-covalently bound to specific receptors. The JAK family consists of four members: JAK1,

JAK2, JAK3, and Tyk2. In addition, the activity of the C-terminal transactivation domain of STATs is at least partially regulated by serine phosphorylation (serine 727 in STAT1 and STAT3) that does not involve the JAK protein (Wen et al., 1995). The kinase responsible for this serine phosphorylation depends on the signaling pathway and cellular context.

Family member	Chromosomal location		Activating cytokines	Phenotype of knockout mice
	Murine	Human		
STAT1	1	2q12–33	IFNs, IL-6	Viable, normal development, IFN functions eliminated, tumors increased, growth control impaired.
STAT2	10	12q13–14.1	IFNs	Viable, normal development, IFN functions affected.
STAT3	11	17q11.2–22	IL-6 family	Embryonic lethal, extraembryonic endoderm defects, cell survival impaired.
STAT4	1	2q12–33	IL-12	Viable, normal development, IL-12 functions eliminated, Th1 differentiation impaired.
STAT5A	11	17q11.2–22	Numerous	Viable, mammary gland deficiency, prolactin responsiveness eliminated.
STAT5B	11	17q11.2–22	Numerous	Viable, partial loss of growth hormone functions.
STAT6	10	12q13–14.1	IL-4, IL-13	Viable, normal development, IL-4 functions eliminated. Th2 differentiation impaired.

Table 1. Properties of STATs.

3. STAT3

STAT3 is a member of the JAK-STAT signaling pathway (Zhong et al., 1995). Cytoplasmic STAT3 in unstimulated cells is activated by recruitment through the SH2 domain to phosphorylated motifs within complexes of cytokine receptors, growth factor receptors, and non-receptor tyrosine kinases. Determination of STAT3 functions based on knockout mice studies have been difficult because mouse embryos die early in embryogenesis, prior to gastrulation (Takeda et al., 1997). STAT3 is essential for the early development of mouse embryos. Recently, some studies have succeeded in isolating STAT3 from individual tissues by the Cre-loxP method (Akira, 2000), which circumvents the problem of embryonic lethality, and revealed the roles of STAT3 in a wide variety of tissues (Table 2). A surprising result from such studies has been the identification of a multitude of and sometimes contradictory roles of STAT3 in biological processes including cell growth, cell growth suppression and apoptosis, and cell motility. The phenotypes resulting from the loss of STAT3 in adult tissues include failure of cell survival, impaired apoptosis, loss of negative feedback regulation, and impaired cell migration and wound healing (Levy & Lee, 2002). Of great current interest is the persistently active STAT3, which occurs in a wide variety of human tumors (Bowman & Jove, 1999). Overexpression and/or elevated protein tyrosine kinase activity of the epidermal growth factor receptor (EGFR), Src, and other protein

kinases is associated with the progression of numerous human cancers. As a consequence, growing evidence indicates that abnormal STAT3 signaling in response to hyperactive protein tyrosine kinase activity is frequent in human tumors and is associated with the progression of oncogenesis (Garcia & Jove, 1998). Furthermore, STAT3 can be converted into an oncogene by experimental mutation (Bromberg et al., 1999). A persistently active protein is required because introduction of a dominant-negative form of STAT3 into head and neck cancer cells or multiple myeloma cells causes apoptosis of recipient cancer cells (Bowman et al., 2000). Persistent STAT3 activation in head and neck cancer is associated with mutations in EGFR or mutations that result in the production of excess ligands or normal receptors (Song & Grandis, 2000). In some multiple myelomas, excess production of IL-6 might be the underlying defect (Catlett-Falcone et al., 1999). IL-6-dependent accumulation of long-lived plasma cells occurs due to elevated levels of a key regulatory protein, Bcl-x_L, a member of the Bcl-2 family of proteins that prevent apoptosis. Constitutive activation of STAT3 signaling, an important component of the IL-6 pathway, directly contributes to the induction of Bcl-x_L gene expression. Thus, constitutive activation of STAT3 signaling in response to IL-6 promotes tumor cell survival and malignant progression of multiple myelomas by directly inducing expression of a key apoptosis regulatory protein. All these results suggest that STAT3 may be essential for many cell functions.

Target tissue	Phenotype
Skin	Impaired second hair cycle, wound repair and keratinocyte migration
Thymic epithelium	Age-dependent thymic hypoplasia, hypersensitivity to stress
T lymphocytes	Impaired IL-6-dependent survival and IL-2Rα expression
Monocytes/neutrophils	Enhanced inflammatory responses and Th1 differentiation, chronic colitis
Granulocytes	Enhanced proliferation owing to impaired negative feedback
Mammary epithelium	Defective apoptosis, delayed mammary involution
Liver	Impaired acute phase response
Neurons	Impaired cell survival

Table 2. Tissue-specific roles of STAT3 (Levy & Darnell, 2002).

4. STAT3 in gp130 cytokine signaling

Several cytokines including IL-6, IL-11, leukemia inhibitory factor, oncostatin M, ciliary neurotrophic factor, and cardiotrophin share a gp130 subunit that is required to activate JAKs and STATs (Stahl et al., 1994). These cytokines are competent to activate STAT3 and induce various pleiotrophic responses that include hematopoiesis regulation, immune response, and neuronal differentiation (Snick, 1990). gp130-associated kinases JAK1, JAK2, and Tyk2 become activated on stimulation, and the cytoplasmic tail of gp130 is phosphorylated (Heinrich et al., 1998). STAT3 is recruited to phosphorylated tyrosine residues in the YXXQ motif including the tyrosine residue Y705 of gp130, where it is activated and dimerized. It subsequently enters the nucleus and regulates gene expression (Hirano et al., 2000). STAT3 is essential for gp130-mediated cell survival and G1 to S cell cycle transition signals. Both *c-myc* and *pim* have been identified as target genes of STAT3 and together can compensate for STAT3 in cell survival and cell cycle transition. On the

other hand, the SH2 domain-bearing protein tyrosine phosphatase (SHP)-2 is recruited to the phosphorylated tyrosine residue Y759 in gp130, where it becomes activated and forms a complex with adaptor/docking proteins, Gab1 and Gab2, leading to activation of the Ras-MAPK pathway (Hibi & Hirano, 2000). Several *in vitro* experiments have shown that SHP-2- and STAT3-mediated signal transduction pathways initiated through gp130 are involved in growth, differentiation, and gene expression in various cell lines (Fukuda et al., 1996; Hirano et al., 2000; Nakajima et al., 1996). SHP-2-mediated ERK/MAPK activation has been suggested to play a negative role in STAT3-mediated biological responses (Jain et al., 1998; Sengupta et al., 1998). The tyrosine residue Y759 also provides the binding site for the suppressor of cytokine signaling 3 (SOCS3) protein that negatively regulates gp130 signals (Nicholson et al., 2000; Schmitz et al., 2000). To clarify the roles of SHP-2- and STAT3-mediated signal transduction pathways *in vivo*, a series of knock-in mouse lines was generated in which gp130-mediated STAT3 or SHP-2 signals were selectively disrupted. This disruption was achieved by mutating the tyrosine residues in all YXXQ motifs or the tyrosine residue Y759 to phenylalanine ($gp130^{FXXQ/FXXQ}$ and $gp130^{F759/F759}$ mice, respectively) (Ohtani et al., 2000). Analyses of these mice indicated that SHP-2-mediated or Y759-dependent signals negatively regulate the biological responses elicited by STAT3-mediated signals *in vivo* and that the balance of positive and negative signals generated through gp130 is skewed or shifted toward positive STAT3 signaling in $gp130^{F759/F759}$ mice (Fig. 1).

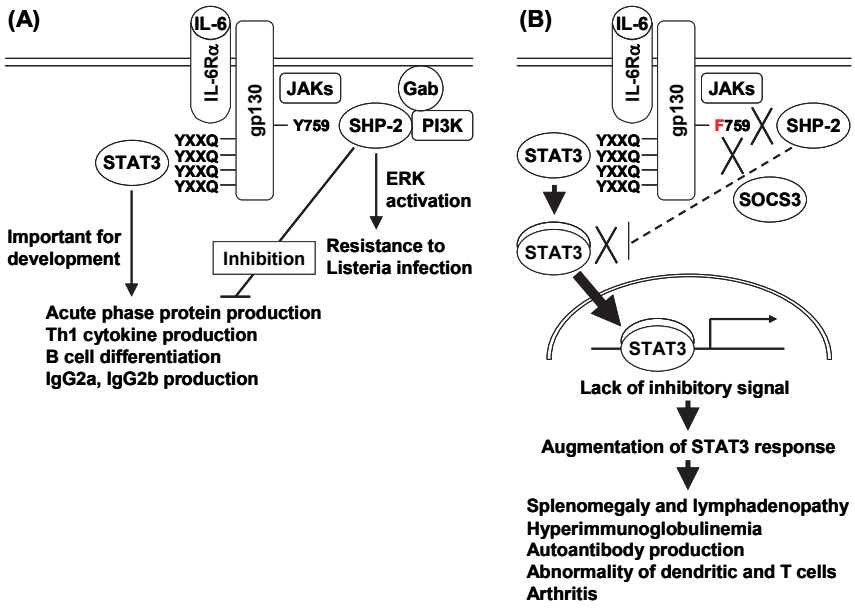

Fig. 1. The role of gp130 signals *in vivo*. A: STAT3/YXXQ and SHP-2/Y759 signals induce responses independent of each other. SHP-2/Y759 signals negatively regulate the biological responses elicited by STAT3-mediated signals. B: The balance of positive and negative signals generated through gp130 is skewed or shifted toward positive STAT3 signaling in $gp130^{F759/F759}$.

The SHP-2 signal-deficient mice (gp130$^{F759/F759}$) were born normally but displayed splenomegaly and lymphadenopathy and an enhanced acute phase reaction. In contrast, the STAT3 signal-deficient mice (gp130$^{FXXQ/FXXQ}$) died perinatally, similar to the gp130-deficient mice. The gp130$^{F759/F759}$ mice showed prolonged gp130-induced STAT3 activation. Importantly, these mice in a mixed background with 129 and C57BL/6 spontaneously develop a rheumatoid arthritis-like autoimmune disease in old age (Atsumi et al., 2002). The mice show severe immunological abnormalities, including autoantibody production, increased memory/activated T cells, impaired thymic negative selection, and peripheral clonal deletion. Development of a rheumatoid arthritis-like disease is entirely dependent on mature lymphocytes, but abnormally enhanced homeostatic proliferation of CD4 T cells is caused by augmented production of IL-7 by non-hematopoietic stromal cells through a STAT3-dependent process (Sawa et al., 2006). In mice showing hyperactivation of STAT1/STAT3, T cell recruitment and CCL5/RANTES expression is enhanced (McLoughlin et al., 2005). A recent study described an IL-17A-triggered positive-feedback loop of IL-6 signaling that involved activation of the transcription factors NF-κB and STAT3 in fibroblasts (Ogura et al., 2008). Although the underlying mechanisms by which STAT3 regulates tissue fibrosis are not fully understood, its activation is required for upregulation of transforming growth factor (TGF)-β signaling, activation/proliferation of myofibroblasts, and deposition of extracellular matrix proteins (Ma & Zhuang, 2011). All these results suggest that STAT3 plays an important role in the function of multiple cells.

5. STAT3 activation in renal cells

Various factors show STAT3 activation in glomerular mesangial and proximal tubule cells. High glucose activates the growth-promoting enzyme JAK2 and its latent STAT transcription factors (STAT1, STAT3, and STAT5) and increases TGF-β and fibronectin synthesis in mesangial cells (Wang et al., 2002). High glucose-induced tyrosine phosphorylation of JAK2, STAT1, and STAT3 as well as TGF-β and fibronectin synthesis are abolished by a specific JAK2 inhibitor, AG-490. However, antisense oligonucleotide studies have shown that STAT1 activation is more important than STAT3 activation for TGF-β and fibronectin synthesis. Angiotensin II induces phosphorylation of JAK2, STAT1, STAT3, STAT5A/STAT5B and SHP-2, and angiotensin II-induced phosphorylation is enhanced by high glucose levels (Amiri et al., 2002). Angiotensin II-induced growth and collagen IV synthesis are also increased under high glucose conditions. Transfection of glomerular mesangial cells with JAK2 antisense oligonucleotides blocks angiotensin II-induced growth and collagen IV synthesis under both normal and high glucose conditions.

In renal proximal tubule cells, IL-6 increases phosphorylation of STAT3, phosphoinositide-3 kinase (PI3K)/Akt, MAPKs, and NF-κB (Lee et al., 2007). IL-6 also stimulates α-methyl-D-[^{14}C]glucopyranoside uptake, which is indicative of active transport in renal proximal tubule cells. The increased uptake can be blocked by pretreatment with a STAT3 inhibitor, a PI3K inhibitor, an Akt inhibitor, MAPK inhibitors, and NF-κB inhibitors. High glucose also induces activation of Raf-1, p42/p44 MAPK, JAK2, STAT1, and STAT3 (but not STAT5) in renal tubular epithelial cells (Huang et al., 2007). Moreover, severe oxidative stress leads to tyrosine phosphorylation of STAT3 at Y705 (Arany et al., 2006). This event depends on the activation of EGFR and JAK2 and is directly linked to cell death because inhibition of STAT3 function enables cells to survive severe oxidative stress.

6. STAT3 activation in an animal model of glomerulonephritis

In an animal model of mesangial proliferative glomerulonephritis induced by the injection of anti-Thy1.1 antibody, STAT3 is phosphorylated in mesangial cells (Yanagita et al., 2001a). STAT3 phosphorylation peaks 8 days after the anti-Thy1.1 injection. Inhibition of growth arrest-specific gene 6 by the extracellular domain of its receptor Axl or warfarin abolishes STAT3 phosphorylation (Yanagita et al., 2001a) and inhibits mesangial cell proliferation (Yanagita et al., 2001b) *in vivo*. STAT3 can be expressed and activated in the kidneys of rats with immune complex glomerulonephritis using BSA as an antigen (Zhang et al., 2005). These rats also have increased macrophage infiltration (detected by a surface marker for monocytes/macrophages, ED-1), with some cells showing simultaneous expression of p-STAT3 and ED-1; this may contribute to inflammatory proliferation in the glomeruli and accumulation of extracellular matrix proteins. Inhibition of angiotensin-converting enzyme (ACE) with fosinopril downregulates STAT3 activation and ED-1 influx, and these effects may attenuate renal damage in this model. Hyperglycemia induces activation of JAK2 and STATs, including STAT3, *in vivo* (Banes et al., 2004). Phosphorylation of JAK2, STAT1, STAT3, and STAT5 in the glomeruli by streptozotocin (STZ) injection is reduced in rats treated with the ACE inhibitor captopril, angiotensin II type 1 receptor antagonist candesartan, or AG-490. Furthermore, both candesartan and AG-490 inhibit STZ-induced increases in urinary protein excretion. Knockdown of STAT3 activity *in vivo* prevents diabetic glomerulopathy (Lu et al., 2009). While the number of glomeruli does not differ between diabetic STAT3 knockdown and reference mice, the diabetic STAT3 knockdown mice exhibit significantly less proteinuria, mesangial expansion, glomerular cell proliferation, and macrophage infiltration than the diabetic reference mice. Reduction in STAT3 activity abrogates the stimulation of inflammatory markers, including IL-6, intercellular adhesion molecule-1, and monocyte chemotactic protein (MCP)-1, and blocks nuclear translocation of NF-κB. JAK2-STAT3 proteins may be involved in the early kidney damage associated with diabetes. AG490 also ameliorates adriamycin-induced nephritic syndrome in mice (Li et al., 2007). JAK-STAT signaling is activated in adriamycin nephropathy. Phosphorylation of JAK2, STAT1, and STAT3 is significantly inhibited by AG490. Proteinuria, glomerulosclerosis, tubulointerstitial lesions, and renal α-smooth muscle actin expression are significantly suppressed by AG490 treatment. In addition, AG490 inhibits MCP-1 mRNA expression accompanied by reduced interstitial infiltration of macrophages and T cells. Activation of JAK-STAT signaling is involved in the progression of glomerular diseases with proteinuria. While AG490 inhibits phosphorylation of STAT1 and STAT3, a novel selective inhibitor of STAT3, S3I-201, has been synthesized. S3I-201 preferentially inhibits STAT3 DNA-binding activity and diminishes tyrosine phosphorylation of STAT3 (Siddiquee et al., 2007). In a mouse model of renal interstitial fibrosis induced by unilateral ureteral obstruction, STAT3 was activated and administration of S3I-201 attenuated both STAT3 activation and extracellular matrix protein deposition following injury (Pang et al., 2010). S3I-201 reduced infiltration of the injured kidney by inflammatory cells and suppressed injury-induced expression of fibronectin, α-smooth muscle actin, and collagen type 1 proteins, as well as expression of multiple cytokines. Furthermore, S3I-201 inhibited proliferation and preferentially induced apoptosis in renal interstitial fibroblasts of the obstructed kidney. Inhibition of STAT3 signaling may hold therapeutic potential for fibrotic kidney diseases. IL-6 expression is increased in S-(1,2 dichlorovinyl)-L-cysteine-induced acute renal tubule necrosis (Vaidya et al., 2003) and renal ischemia-reperfusion injury (Lemay et al., 2000) in mice. IL-6-deficient mice are resistant to

$HgCl_2$-induced acute kidney injury compared with wild-type mice (Nechemia-Arbely et al., 2008). IL-6 expression and STAT3 activation in renal tubular epithelial cells is significantly increased during the development of injury, suggesting active IL-6 signaling. Activation of the JAK-STAT pathway in renal and non-renal cells in kidney diseases is shown in Fig. 2.

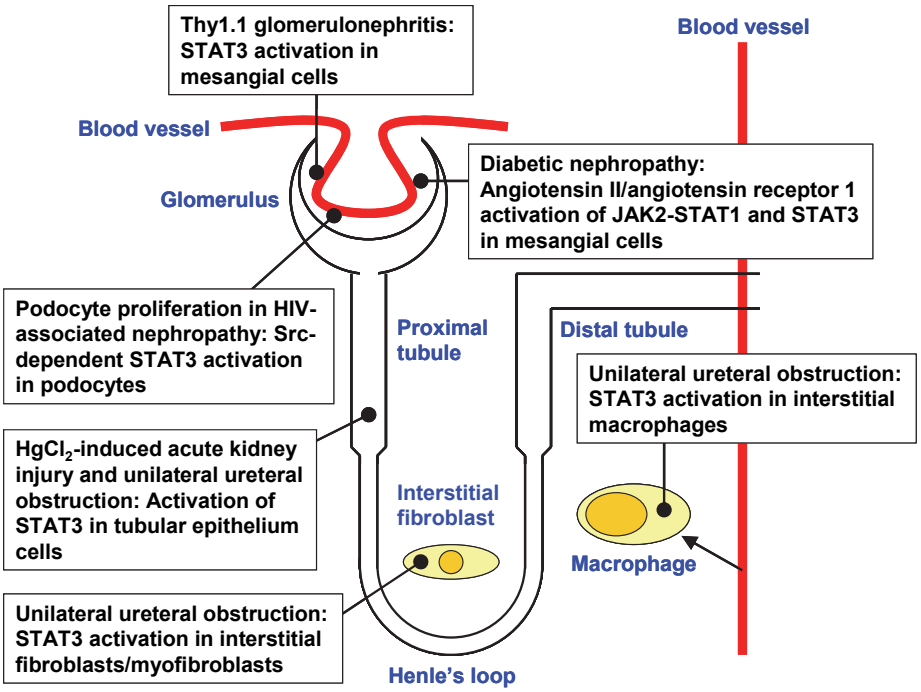

Fig. 2. Activation of the JAK-STAT pathway in renal and non-renal cells in kidney diseases (Chuang & He, 2010).

We have generated a series of knock-in mouse lines with several genetic backgrounds in which gp130-mediated STAT3 or SHP-2 signals are selectively disrupted. gp130 is a shared receptor of the IL-6 cytokine family (Ohtani et al., 2000). We found that characteristic abnormalities in C57BL/6 background $gp130^{F759/F759}$ mice included not only spontaneous polyarthritis but also glomerulonephritis (Fig. 3, only in females) (Tsuji et al., 2009). However, spontaneous glomerulonephritis did not develop in DBA/1J background mice, indicating that genetic background may affect the development of disease.

7. STAT3 activation in human glomerulonephritis

In vitro and animal studies have shown that an increase in STAT3 activity may play a critical role in the development of glomerulonephritis. Few studies have investigated the role of STAT3 activation in human renal diseases, but one study has identified STAT3 activation in the normal human kidney and a marked increase in this activation in many forms of glomerulonephritis (Arakawa et al., 2008). The correlation of STAT3 activation with clinical and histological parameters suggests that this pathway plays an important role in the

pathogenesis of kidney diseases. In addition, mesangial expansion and podocyte loss in the glomeruli are important early features of diabetic nephropathy. JAK1, JAK2, and JAK3 as well as STAT1 and STAT3 are expressed at higher levels in patients with diabetic nephropathy than in control subjects (Berthier et al., 2009). Immunohistochemistry showed strong JAK2 staining in glomerular and tubulointerstitial compartments of patients with diabetic nephropathy compared with control subjects. These data suggest a direct relationship between tubulointerstitial JAK-STAT expression and the progression of kidney failure in patients with type 2 diabetic nephropathy and can be used to distinguish progressive human diabetic nephropathy. Further studies are needed to clarify the role of STAT3 activation in human glomerulonephritis.

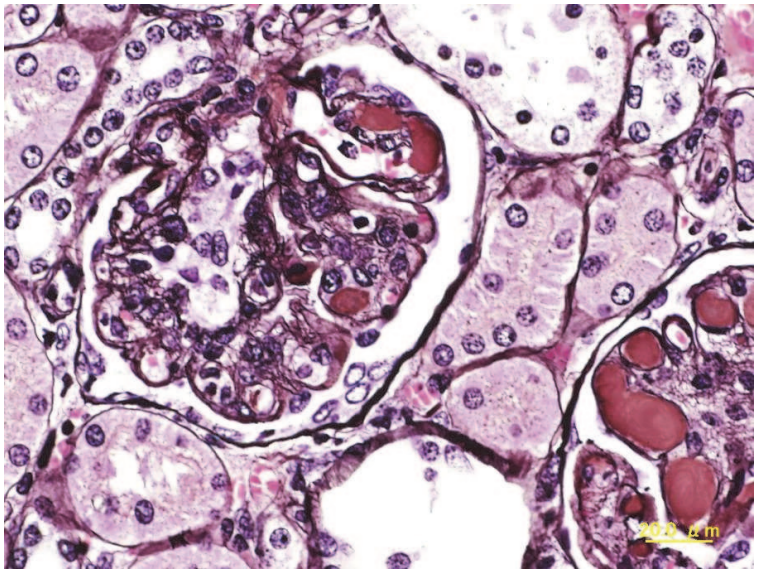

Fig. 3. Glomerulonephritis in a gp130$^{F759/F759}$ mouse (female, 12 months). Deposition of hyaline droplets in the subendothelial zone is shown.

8. Conclusions

The JAK-STAT pathway is a pleiotropic cascade essential to cytokine and growth hormone receptor signaling. Signaling through the JAK-STAT pathway is important for the kidney's response to injury in disease. STAT3 activation is observed in an animal model of glomerulonephritis and human glomerulonephritis, and the STAT3 pathway inhibition ameliorates the renal conditions in some animal models. Further studies are needed to clarify the role of STAT3 activation in human glomerulonephritis, but the STAT3 pathway inhibition may be one of the potential therapeutic approaches for renal diseases.

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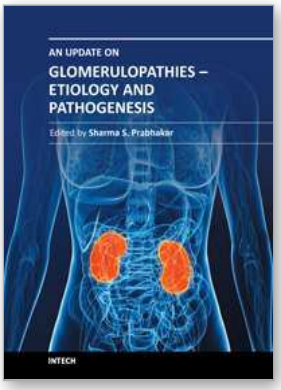

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The book has fourteen chapters which are grouped under different sections: Immune System and Glomerulonephritis, Animal Models of Glomerulonephritis, Cytokines and Signalling Pathways, Role of Cells and Organelles in Glomerulonephritis and Miscellaneous. While the purpose of this volume is to serve as an update on recent advances in the etio-pathogenesis of glomerulopathies, the book offers the current and broad based knowledge in the field to readers of all levels in the nephrology community.

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