BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 28(3), 213-221 (2020)

Fyn Kinase: A Potential Therapeutic Target in Acute Kidney Injury

Md Jamal Uddin, Debra Dorotea, Eun Seon Pak and Hunjoo Ha*

Graduate School of Pharmaceutical Sciences, College of Pharmacy, Ewha Womans University, Seoul 03760, Korea

Abstract

Acute kidney injury (AKI) is a common disease with a complex pathophysiology which significantly contributes to the development of chronic kidney disease and end stage kidney failure. Preventing AKI can consequently reduce mortality, morbidity, and healthcare burden. However, there are no effective drugs in use for either prevention or treatment of AKI. Developing therapeutic agents with pleiotropic effects covering multiple pathophysiological pathways are likely to be more effective in attenuating AKI. Fyn, a non-receptor tyrosine kinase, has been acknowledged to integrate multiple injurious stimuli in the kidney. Limited studies have shown increased Fyn transcription level and activation under experimental AKI. Activated Fyn kinase propagates various downstream signaling pathways associated to the progression of AKI, such as oxidative stress, inflammation, endoplasmic reticulum stress, as well as autophagy dysfunction. The versatility of Fyn kinase in mediating various pathophysiological pathways suggests that its inhibition can be a potential strategy in attenuating AKI.

Key Words: Fyn kinase, Acute kidney injury, Inflammation, Oxidative stress, ER stress, Autophagy

INTRODUCTION

Acute kidney injury (AKI) occurs in 1-35% of patients in hospitals and is associated with high mortality (Bellomo *et al*., 2004). The incidence of AKI is on the rise in both high-income and low-income countries. Nearly 600,000 cases of AKI are reported each year in the United States (Rifkin *et al*., 2012). The conventional belief is that survivors of AKI are likely to fully recover kidney function. But, growing evidences suggest that patients who survive an episode of AKI might have a significant risk of developing progressive chronic kidney diseases (CKD) (Coca *et al*., 2012; Lewington *et al*., 2013). Thus, measures in preventing the progression of AKI can consequently reduce short- and long-term mortality, morbidity, and healthcare burden (McCaffrey *et al*., 2017).

AKI is commonly caused by ischemia reperfusion injury (IRI), sepsis, and drug toxicity. The new paradigm has emphasized that the pathophysiology of AKI is not solely attributed to the impairment of kidney perfusion. Various toxic or ischemic insults propagate tubular injury in AKI, which can be mediated by microvascular dysfunction, oxidative stress, inflammation, immune dysregulation, and gene-regulated cell death or senescence (Gallagher *et al*., 2017). Multiple pathophysiological pathways identified for each AKI etiology renders the complexity of plausible therapeutic approach against AKI. A number of agents have been tested in the clinical trials, including anti-inflammatory agents, antioxidants, vasodilators, apoptosis inhibitors, and repair agents as recently reviewed (Benoit and Devarajan, 2018), but there are currently no effective pharmacological agents used clinically for AKI. It is suggested that the panacea for preventing the progression of AKI should interlink these pathophysiological pathways and act to prevent cellular dysfunction in response to multiple insults (Chen and Busse, 2017).

Fyn is a 59 KDa non-receptor tyrosine kinase that belongs to the Src family kinases (SFK). Following its initial finding as a proto-oncogene, Fyn kinase has been demonstrated to regulate a diverse cellular functions, such as cell growth, survival, adhesion, cytoskeletal remodeling, motility, and T-cell receptor signaling (Sugie *et al*., 1991; Appleby *et al*., 1992; Calautti *et al*., 2002). The role of Fyn kinase has massively expanded to various pathological conditions since then (Yu *et al*., 2010; Yamada *et al*., 2012; Lee *et al*., 2013; Panicker *et al*., 2015; Shang *et al*., 2015; Cheng *et al*., 2016; Seo *et al*., 2016; Mkaddem *et al*., 2017), as shown in Table 1.

Considering the pathophysiological role of Fyn, this article reviews the current knowledge on Fyn kinase as a possible important mediator involved in the diverse pathological path-

Open Access https://doi.org/10.4062/biomolther.2019.214

Received Dec 17, 2019 **Revised** Apr 1, 2020 **Accepted** Apr 6, 2020
Published Online Apr 27, 2020

***Corresponding Author**
E-mail: hha@ewha.ac.kr
Tel: +82-2-3277-4075, Fax: +82-2-3277-2851

Table 1. Role of Fyn in various pathological conditions

Organs/cells	Models	Mechanisms	References
Organs			
Kidney	STZ-induced type 1 diabetes	Suppresses Nrf2 expression	Shang *et al*., 2015; Cheng *et al*., 2016
Kidney	Obstructive fibrosis	Mediates STAT3 activation	Seo *et al*., 2016
Kidney	Lupus nephritis	Mediates ITAM phosphorylation	Mkaddem *et al*., 2017
Liver	STZ-induced type 1 diabetes	Decreases GSK-3β phosphorylation	Zhang *et al*., 2012
Visceral adipose tissue	HFD-induced obesity	Increases M1/decreases M2 macrophages	Lee *et al*., 2013
Muscle	Fyn overexpression	Decreases Vep34/p150/Beclin1/Atg14 complexes	Yamada *et al*., 2012
Mid brain	Parkinson's disease	Increases proinflammatory cytokines	Panicker *et al*., 2015
Cells			
Podocytes	Apoptosis	Increases TRPC6 phosphorylation	Yu *et al*., 2010
Microglia	Parkinsonian neurotoxin	Mediates PKCδ>MAPK>NF-κB signaling	Panicker *et al*., 2015

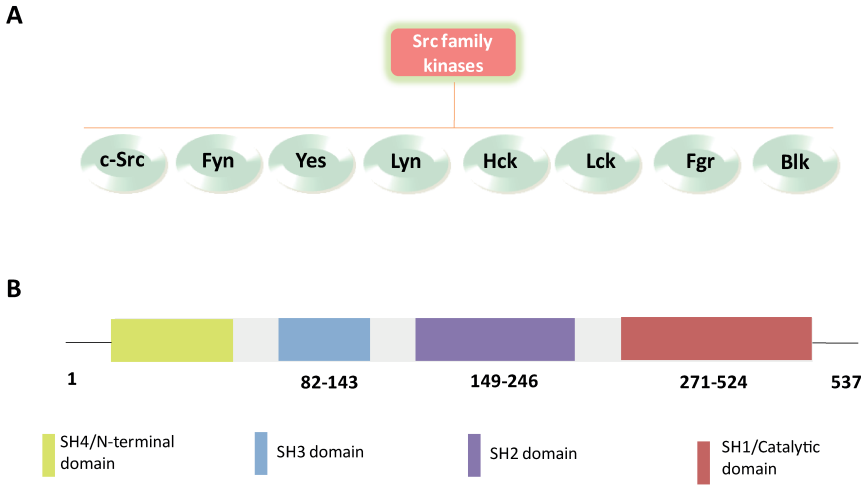

Fig. 1. (A) Src family kinase members and (B) their activation domain structure.

ways of AKI. A better understanding on Fyn kinase is important to propagate a further investigation on Fyn kinase as a novel therapeutic target against AKI.

STRUCTURE AND FUNCTION OF FYN

SFK is a family of proto-oncogenic, non-receptor tyrosine kinases. Eight members of SFK including c-Src, Fyn, Yes, Blk, Fgr, Hck, Lck, and Lyn have been identified up to now. All the members of SFK share a similar structure, having Src homology domains SH1, SH2, SH3, and SH4 (Fig. 1) (Roskoski, 2015; Liu *et al*., 2016). SH4 domain is important for membrane localization, while SH3 domain is essential for protein-protein interactions. SH2 domains acts protein motifs binding to phosphorylated tyrosine sites. Meanwhile, SH1 domain is the catalytic kinase domain where Src can be activated by auto-phosphorylation at Tyr416, which is induced upon activation of a wide variety of transmembrane receptor proteins that include the receptor tyrosine kinases, G protein-coupled receptors, integrins, and cytokine receptors (Moran *et al*., 1990; Jelic *et al*., 2007).

There are three variants of Fyn such as FynT, FynB, and FynC, which arise from alternative splicing of exon 7 of the Fyn gene. Biological effects of FynC has not been reported yet (Goldsmith *et al*., 2002). Although FynT and FynB have been reported to have some biological functions in T cells, hematopoietic cells, brain, and muscle (Cooke and Perlmutter, 1989; Davidson *et al*., 1992, 1994; Resh, 1998; Goldsmith *et al*., 2002; Yamada *et al*., 2012), their distinct and detailed biological functions in kidney have not been explored yet.

INVOLVEMENT OF FYN IN AKI

While evidences indicate that patients who have history of AKI may develop to progressive CKD (Coca *et al*., 2012; Lewington *et al*., 2013), increased Src kinase activity has also been reported during the progression of CKD such as in streptozotocin (STZ)-induced type-1 diabetes (Taniguchi *et*

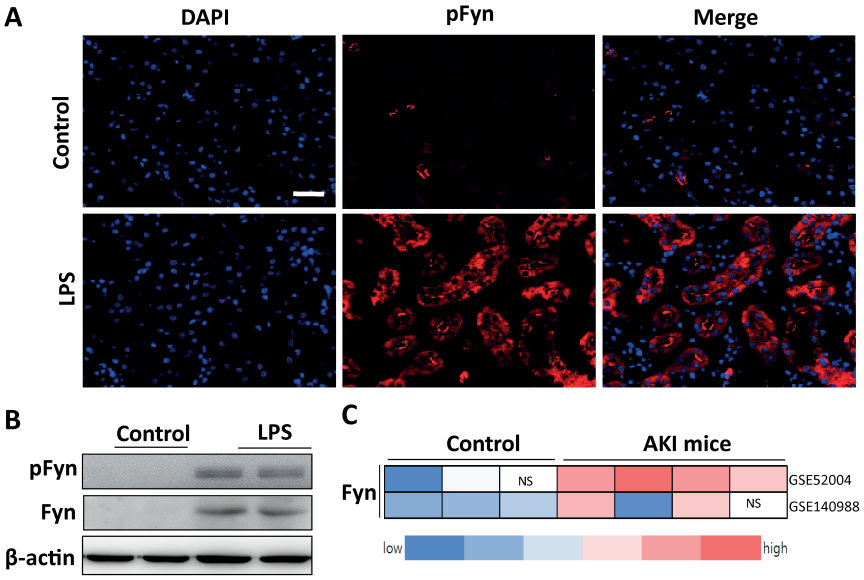

Fig. 2. Fyn is increased in AKI. (A, B) AKI was induced by LPS (15 mg/kg, i.p). (A) Paraffin-embedded kidney sections were subjected to immunofluorescence staining using an anti-pFyn antibody (1:100; Santa Cruz Biotechnology, Inc., Santa Cruz, CA, USA) and anti-rabbit Alexa Fluor 588 (1:1,000; A11036; Life Technologies, Carlsbad, CA, USA). Nuclei were stained with DAPI. Images were taken using a Zeiss ApoTome Axiovert 200 M microscope (Carl Zeiss Microscopy GmbH, Jena, Germany). Scale bar indicates 50 μm. (B) pFyn and Fyn protein expression was detected by western blotting. Representative images are shown. (C) Transcription level of Fyn gene in IRI-induced AKI mice were analyzed using GEO database. Upper panel GSE52004; control (n=2), AKI (n=4) and lower panel GSE140988; control (n=3), AKI (n=3). NS, no sample.

al., 2013), db/db type-2 diabetes (Wu *et al*., 2015), as well as unilateral ureteral obstruction (UUO)-induced tubulointerstital fibrosis (Yan *et al*., 2016).

The involvement of Src kinase in the development of AKI has recently been suggested (Xiong *et al*., 2017). IRI-induced kidney dysfunction, inflammation, tubular epithelial cell apoptosis, and fibrosis are attenuated by PP1, a non-selective Src kinases inhibitor (Xiong *et al*., 2017). Our preliminary results showed an increased total as well as phosphorylated Fyn in the kidney of lipopolysaccharides (LPS)-treated mice, a model of sepsis-associated AKI (Fig. 2A, 2B). LPS-induced inflammation, oxidative stress, and tubulointerstitial injury were suppressed by PP2, a non-selective Src kinases inhibitor (data not shown). Furthermore, the gene expression omnibus database (GEO), a public functional genomics repository analysis (https://www.ncbi.nlm.nih.gov/geo/) shows increased transcription of Fyn in the kidney under IRI-induced AKI in mice (Fig. 2C).

Fyn mediates disorganization of the F-actin cytoskeleton leading to podocyte dysfunction *in vitro*, and Fyn deficiency ameliorates high glucose-induced Fyn activation and F-actin remodeling (Lv *et al*., 2016). On the contrary, a few reports show that basal Fyn is involved in the regulation of cytoskeletal architecture (Saito *et al*., 2010) and maintenance of kidney morphology via nephrin phosphorylation in podocytes (Verma *et al*., 2003; Li *et al*., 2004). In addition, Fyn deficiency contributes to proteinuria in mice (Yu *et al*., 2001).

THE PATHOPHYSIOLOGICAL ROLE OF FYN KINASE IN THE AKI

The precise mechanism how Fyn kinase mediates kidney injury has not been clearly understood. This section summarizes the current knowledge on Fyn kinase in mediating the oxidative stress, inflammation, ER stress, and autophagy dysfunction, all of which have been proposed to play important roles in AKI.

Oxidative stress

Reactive oxygen species (ROS) (Li *et al*., 2009; Mittwede *et al*., 2015) play important roles in AKI. The expression of Fyn is upregulated via ROS-mediated oxidative stress in response to diverse stimuli (Anuranjani and Bala, 2014; Rizvi *et al*., 2014; Santosa *et al*., 2015). Oxidative stress promotes to generation of specific CD36 ligands such as microparticles (MP) and oxidized LDL (oxLDL). Attachment of these ligands by CD36 activates Fyn kinase (Li *et al*., 2010).

On the other hand, Fyn translocation into nuclei exports nuclear Nrf2 to cytosol, where it binds to Keap1 for proteosomal degradation (Jain and Jaiswal, 2007; Koo *et al*., 2012). Nrf2 is a well-known transcription factor that regulates anti-oxidative response by increasing transcription of genes such as heme oxygenase-1 (HO-1) and NAD(P)H: quinone oxidoreductase 1 (NQO1) (Li *et al*., 2012; Miyata *et al*., 2013). Fenofibrate activates the Nrf2 expression in the nuclei by activation of phosphoinositide 3-kinases (PI3K)/protein kinase B (PKB/Akt)/glycogen synthase kinase-3β (GSK-3β) -dependent inhibition of Fyn nuclear translocation, resulting in attenuation of oxidative stress in type-1 diabetic kidney injury (Cheng *et al*., 2016).

Inflammation

Inflammation is a key contributor to AKI (Andrade-Oliveira *et al*., 2019; Patschan *et al*., 2019). It also plays an important role in AKI-CKD transition (Matsushita *et al*., 2019; Ogbadu *et al*., 2019). AKI is tightly associated with tubulointerstitial inflammation in response to hypoxia and reperfusion (Bonventre and Zuk, 2004). Hypoxia induces endothelial and tubular epithelial cells damage in the initial phase, and subsequent leukocyte recruitments are responsible for the apoptosis and necrosis of endothelial and tubular epithelial cells (Rana *et al*., 2001). The widespread inflammation in kidney tissue is recognized by toll-like receptors (TLRs), which activate several kinases and nuclear factor kappa B (NF-κB) (Jang and Rabb, 2009), leading to apoptosis of cells.

The contribution of SFKs in immune responses are well recognized (Abram and Lowell, 2008; Chen *et al*., 2014). Fyn kinase regulates antigen-specific activation of T cells, and its deficiency rigorously suppressed T cell responses (Sugie *et al*., 2004). Fyn also increases pro-inflammatory cytokines in mast cells, macrophages, basophils, as well as natural killer cells (Rajasekaran *et al*., 2013). The pro-inflammatory effects resulted from Fyn activation has been demonstrated in various tissues including the kidney (Table 1). Fyn kinase enhances microglial neuro-inflammatory responses via Cδ (PKCδ)>mitogen-activated protein kinase (MAPK)>NF-κB pathway, which is associated to the pathogenesis of Parkinson's disease (Panicker *et al*., 2015). Fyn kinase is directly or indirectly associated with the inflammation in liver (Zhang *et al*., 2012; Zhao *et al*., 2018). Fyn kinase mediates visceral adipose tissues inflammation through increasing M1 macrophages and decreasing M2 macrophages. Fyn deficiency promotes a preferential increase in subcutaneous adipose tissue mass and decreases visceral adipose tissue inflammation (Lee *et al*., 2013). Role of signal transducer and activator of transcription 3 (STAT3) in mediating inflammation and fibrosis is well known. Fyn kinase induces STAT3 activation leading to fibrosis in obstructive nephropathy in mice (Seo *et al*., 2016).

Fyn-activating signature is found in patients with lupus nephritis. Autoimmune and inflammatory disease has been recognized as a result from dysregulation and chronic stimulation of immunoreceptor tyrosine-based activation motif (ITAM)-containing immunoreceptor. Fyn can phosphorylate ITAM contained in the aggregated immunoreceptors. Under chronic stimulation, this immunoreceptor signaling activation aggravates inflammatory and immune diseases (Mkaddem *et al*., 2017).

ER stress and apoptosis

Endoplasmic reticulum (ER) stress (Bailly-Maitre *et al*., 2006; Gao *et al*., 2012; Xu *et al*., 2016; Fan *et al*., 2017; Uddin *et al*., 2018) and apoptosis (Linkermann *et al*., 2014) play important roles in the pathogenesis of AKI. There are three sensors in ER stress such as RNA-dependent protein kinase-like ER kinase (PERK), activating transcription factor 6 (ATF6), and inositol-requiring enzyme 1α (IRE1α) (Zheng *et al*., 2013). The activated IRE1 cleaves XBP1 to generate spliced XBP1 (sXBP1) (Calfon *et al*., 2002) and activates JNK (Urano *et al*., 2000). The sXBP1 increases the expression of unfolded protein response (UPR)/UPR target genes and stimulates the production of inflammatory cytokine genes (Kim *et al*., 2015).

In the kidney, mechanistic target of rapamycin complex 1 (mTORC1) mediates IRE1α-JNK pathway leading to cell death (Kato *et al*., 2012). Fyn overexpression increases mTORC1 activation leading to activation of IRE1α-JNK signaling, which potentiates the ER stress-induced cell death in skeletal muscle and in HEK293T cells. Synergic effect of Fyn and thapsigargin (ER stress inducer) accelerates IRE1α-induced cell death. Rapamycin inhibits mTORC1 activation and suppresses IRE1α expression and JNK phosphorylation, which protects cells against Fyn- and thapsigargin-induced cell death (Wang *et al*., 2015). Activated Src kinase is also associated with kidney tubular epithelial cell apoptosis in diabetic db/db mice, which is attenuated by PP2 treatment (Wu *et al*., 2015). PP2 also inhibits high glucose-induced cell death in cultured HK-2 cells and shear stress-induced podocyte apoptosis (Huang *et al*., 2012). The Fyn-mediated cell death is also evident in other tissues such as neurons. Fyn kinase involved in the amyloid-mediated apoptosis in cortical neurons (Lambert *et al*., 1998), and pro-apoptotic Fyn/PKCδ-mediated signaling pathway contributes to oxidative stress-induced cell death in dopaminergic neurons (Saminathan *et al*., 2011).

Autophagy

Autophagy is generally a cytoprotective mechanism that eliminates damaged macromolecules and organelles during various stress (Kroemer *et al*., 2010). Although Suzuki *et al*. (2008) have shown the harmful effects of autophagy, various studies have suggested protective role of autophagy in AKI (Yang *et al*., 2008; Jiang *et al*., 2010; Hsiao *et al*., 2012). Nutrient sensors, i.e. AMP-activated protein kinase (AMPK) and mTORC1 play important roles in regulation of autophagy in AKI (Sengupta *et al*., 2010; Kim *et al*., 2011; Alers *et al*., 2012), and several studies have suggested the involvement of Fyn kinase in these metabolic signaling (Fig. 3).

A crosstalk between Fyn kinase and the AMPK pathway has been reported through Fyn-dependent regulation of liver kinase B1 (LKB1), an AMPK upstream activator. Fyn null mice exhibits increased insulin sensitivity in adipose and skeletal muscle, which are associated with increment of fatty acid oxidation, AMPK activation, and acetyl-CoA carboxylase inhibition (Bastie *et al*., 2007). Fyn kinase directly phosphorylates LKB1 on Y261 and Y365, resulting in decreased AMPK phosphorylation (Bastie *et al*., 2007; Yamada *et al*., 2010). Fyn also inhibits AMPK enzymatic activity via phosphorylation on the α-subunit of AMPK on Y436, without altering the assembly state of the AMPK heterotrimeric complex. A treatment with pro-inflammatory cytokine, TNFα enhances Fyn-dependent AMPKα Y436 phosphorylation and inhibits autophagy, which is abolished in response to Y436 mutation of AMPKα (Yamada *et al*., 2016).

AMPK suppresses mTORC1 activation through phosphorylation of raptor and tuberous sclerosis complex (TSC1/2) (Sanchez *et al*., 2012). Overexpression of Fyn inhibits LKB1-AMPK pathway, which subsequently promotes mTORC1 activation (Yamada *et al*., 2010, 2012). Although Fyn-induced activation of mTORC1 signaling complex is evident (Yamada *et al*., 2012), study showing inhibition of autophagy via Fyn/mTOR signaling axis is lacking. However, Src kinase-regulated mTOR signaling has been shown to inhibit autophagy. NADPH oxidase 2 (Nox2)-induced oxidative stress induces persistent Src kinase activation, resulting in activation of mTOR via PI3K/Akt phosphorylation in mice model of Duchenne muscular dystrophy. Inhibition of either Nox2 or Src kinase abrogates defective autophagy and attenuates the progression of disease (Pal

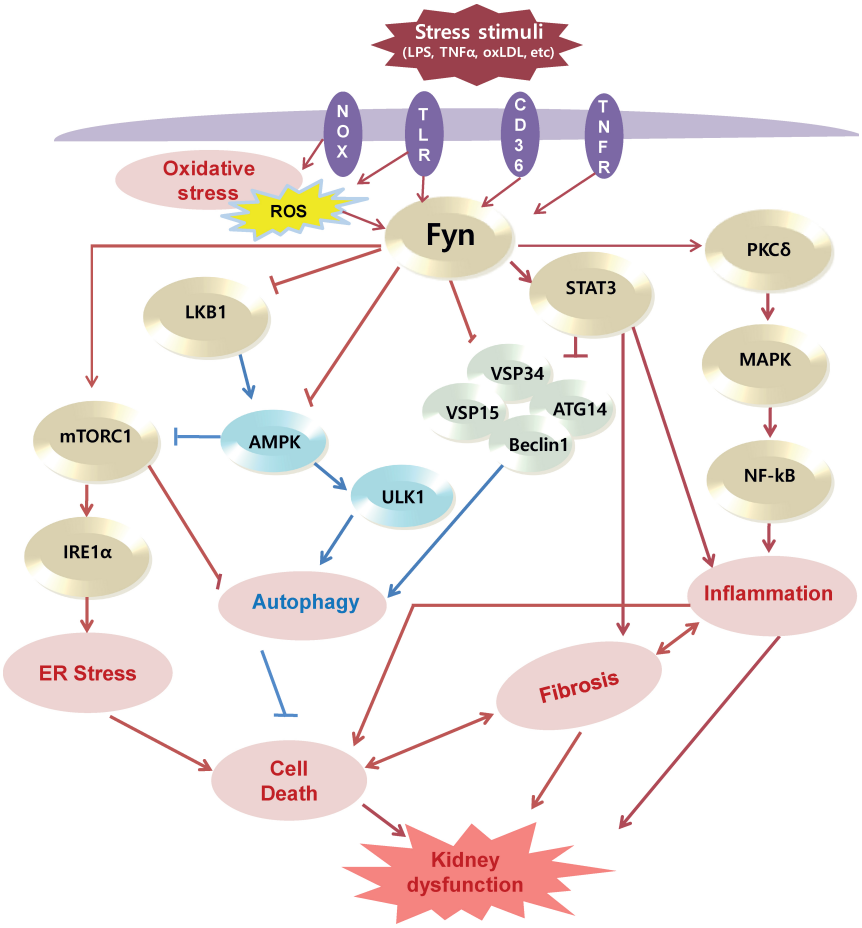

Fig. 3. Fyn signaling pathway. Activation of NOX, TLR, CD36, and TNFR may increase Fyn with or without ROS-mediated oxidative stress. Activated Fyn may i) suppress LKB1-AMPK and thus increases mTORC1-ER stress pathway and ii) activate STAT3 signaling which inhibits macroautophagy through suppression of VSP34, activates inflammation signaling, and mediates fibrosis. Additionally, Fyn also activates inflammation signaling (PKCδ>MAPK>NF-κB). All of these ultimately may contribute to kidney dysfunction. TNFR, tumor necrosis factor receptor.

et al., 2014). Src kinase is also critical for amino acid-induced mTORC1 activation via Rag GTPase-mediated GATOR1 and Rags dissociation. Src kinase induces mTORC1 recruitment and activation at the lysosomal surface, which leads to down-regulation of autophagy (Pal *et al*., 2018).

In addition, Fyn-dependent STAT3 activation decreases Vps34 protein level, leading to inhibition of Vps34/p150/Beclin1/Atg14 complex assembly. Muscle specific FynB or FynT over-expressing animals exhibits muscle wasting associated with inhibited macroautophagy (Yamada *et al*., 2012).

FYN, A POSSIBLE MEDIATOR OF AKI TO CKD TRANSITION

Patients who have history of AKI may develop to progressive CKD (Coca *et al*., 2012; Lewington *et al*., 2013). Kidney fibrosis is a histological hallmark of CKD (Ardura *et al*., 2010). AKI promotes progressive tubulointerstitial fibrosis in humans (Basile *et al*., 2012) and pet animals (Keegan and Webb, 2010; Lawson *et al*., 2015). Following severe AKI, the proximal tubule cellular repair process can lead to fibrosis. Increased synthesis of native and foreign hepatocyte growth factor (HGF) in damaged tubular epithelial cells during the initial stage of AKI, leads to the generation of pro-fibrotic factors including cytokines, growth factors, and matrix proteins (Yang *et al*., 2011). Consequently, AKI can result in proliferation of fibroblasts and excessive deposition of extracellular matrix (Yang *et al*., 2011; Du *et al*., 2013).

The activation of Src kinase is strongly associated with the progressive kidney fibrosis in various models, such as STZ-induced diabetes (Taniguchi *et al*., 2013), db/db diabetes (Wu *et al*., 2015), and obstructed fibrosis (Yan *et al*., 2016), and Fyn kinase is elevated in the STZ-induced diabetic kidney (Cheng *et al*., 2016). Administration of non-selective Src kinase inhibitors attenuates the development of kidney fibrosis. Furthermore, Fyn deficiency attenuates kidney fibrosis through inhibition of STAT3 activation in UUO mice. STAT3 siRNA in Fyn-deficient proximal tubular cells suppresses α-SMA expression, whereas a STAT3 activator partially restores plasminogen activator inhibitor-1 expression (Seo *et al*., 2016). It remains to be determined whether inhibition of Fyn at early

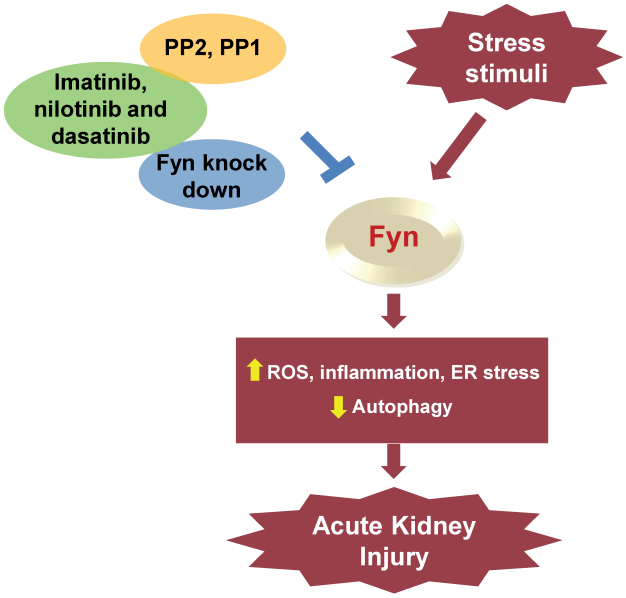

Fig. 4. Schematic diagram of Fyn involvement in AKI. Stress stimuli increases Fyn activation leading to ER stress, inflammation, and cell death. These events ultimately lead the cells to die, and AKI is started to develop. Using pharmacological or genetic approach to inhibit Fyn may attenuate Fyn-mediated AKI.

stage of AKI may prevent AKI-associated CKD.

FURTHER DIRECTION AND CONCLUSION

Fyn kinase, a classic proto-oncogene, has been proposed to be activated and involved in the pathogenesis of AKI. The therapeutic effects of non-selective SFK inhibitors have been confirmed in the preclinical studies of CKD. Although the detailed mechanism by which Fyn kinase mediated AKI remains elusive, studies in both kidney and other tissues have suggested the important role of Fyn kinase in modulating various pathogenic pathways in AKI (Fig. 4). Activated Fyn kinase exacerbates inflammation, oxidative stress, and fibrosis development. The crosstalk between Fyn kinase and metabolic signaling, i.e. AMPK and mTOR also contributes to regulation of autophagy and ER stress.

There are a number of SFK inhibitors including imatinib, nilotinib, and dasatinib either approved for the treatment of malignancies or aimed at clinical trials in brain disorders (Schenone *et al*., 2011). None of these inhibitors targets one specific member of the SFKs, making it difficult to clarify the role of individual SFKs in a given disease. Thus, future studies should be conducted to clarify the role of Fyn by utilizing highly selective inhibitors and genetic manipulation. In addition, analyzing the expression profile of SFKs in kidney biopsies will also help to elucidate the role of individual SFKs in different kidney diseases. Considering the pathological roles of Fyn in various diseases including AKI, it would be worthwhile to develop an inhibitor targeting Fyn to treat the AKI patients.

CONFLICT OF INTEREST

All the authors declared no competing interests.

ACKNOWLEDGMENTS

This work was supported by a National Research Foundation grant (No. 2017R1D1A1B03028835) and Korean Health Technology R&D project through Korea Health Industry Development Institute (No. HI18C0695), Republic of Korea. Dr. Md Jamal Uddin is supported by the Korean Research Fellowship Program (No. 2015H1D3A1062189) and RP-Grant 2020 of Ewha Womans University, Republic of Korea.

REFERENCES

Abram, C. L. and Lowell, C. A. (2008) The diverse functions of Src family kinases in macrophages. *Front. Biosci.* **13**, 4426-4450.
Alers, S., Loffler, A. S., Wesselborg, S. and Stork, B. (2012) Role of AMPK-mTOR-Ulk1/2 in the regulation of autophagy: cross talk, shortcuts, and feedbacks. *Mol. Cell. Biol.* **32**, 2-11.
Andrade-Oliveira, V., Foresto-Neto, O., Watanabe, I. K. M., Zatz, R. and Camara, N. O. S. (2019) Inflammation in renal diseases: new and old players. *Front. Pharmacol.* **10**, 1192.
Anuranjani and Bala, M. (2014) Concerted action of Nrf2-ARE pathway, MRN complex, HMGB1 and inflammatory cytokines - implication in modification of radiation damage. *Redox Biol.* **2**, 832-846.
Appleby, M. W., Gross, J. A., Cooke, M. P., Levin, S. D., Qian, X. and Perlmutter, R. M. (1992) Defective T cell receptor signaling in mice lacking the thymic isoform of p59fyn. *Cell* **70**, 751-763.
Ardura, J. A., Rayego-Mateos, S., Rámila, D., Ruiz-Ortega, M. and Esbrit, P. (2010) Parathyroid hormone-related protein promotes epithelial-mesenchymal transition. *J. Am. Soc. Nephrol.* **21**, 237-248.
Bailly-Maitre, B., Fondevila, C., Kaldas, F., Droin, N., Luciano, F., Ricci, J. E., Croxton, R., Krajewska, M., Zapata, J. M., Kupiec-Weglinski, J. W., Farmer, D. and Reed, J. C. (2006) Cytoprotective gene bi-1 is required for intrinsic protection from endoplasmic reticulum stress and ischemia-reperfusion injury. *Proc. Natl. Acad. Sci. U.S.A.* **103**, 2809-2814.
Basile, D. P., Anderson, M. D. and Sutton, T. A. (2012) Pathophysiology of acute kidney injury. *Compr. Physiol.* **2**, 1303-1353.
Bastie, C. C., Zong, H., Xu, J., Busa, B., Judex, S., Kurland, I. J. and Pessin, J. E. (2007) Integrative metabolic regulation of peripheral tissue fatty acid oxidation by the SRC kinase family member Fyn. *Cell Metab.* **5**, 371-381.
Bellomo, R., Ronco, C., Kellum, J. A., Mehta, R. L. and Palevsky, P. (2004) Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit. Care* **8**, 204-212.
Benoit, S. W. and Devarajan, P. (2018) Acute kidney injury: emerging pharmacotherapies in current clinical trials. *Pediatr. Nephrol.* **33**, 779-787.
Bonventre, J. V. and Zuk, A. (2004) Ischemic acute renal failure: an inflammatory disease? *Kidney Int.* **66**, 480-485.
Calautti, E., Grossi, M., Mammucari, C., Aoyama, Y., Pirro, M., Ono, Y., Li, J. and Dotto, G. P. (2002) Fyn tyrosine kinase is a downstream mediator of Rho/PRK2 function in keratinocyte cell-cell adhesion. *J. Cell Biol.* **156**, 137-148.
Calfon, M., Zeng, H., Urano, F., Till, J. H., Hubbard, S. R., Harding, H. P., Clark, S. G. and Ron, D. (2002) IRE1 couples endoplasmic reticulum load to secretory capacity by processing the XBP-1 mRNA. *Nature* **415**, 92-96.
Chen, H. and Busse, L. W. (2017) Novel therapies for acute kidney injury. *Kidney Int. Rep.* **2**, 785-799.
Chen, J., Elfiky, A., Han, M., Chen, C. and Saif, M. W. (2014) The role of Src in colon cancer and its therapeutic implications. *Clin.*

Colorectal Cancer **13**, 5-13.
Cheng, Y., Zhang, J., Guo, W., Li, F., Sun, W., Chen, J., Zhang, C., Lu, X., Tan, Y., Feng, W., Fu, Y., Liu, G. C., Xu, Z. and Cai, L. (2016) Up-regulation of Nrf2 is involved in FGF21-mediated fenofibrate protection against type 1 diabetic nephropathy. *Free Radic. Biol. Med.* **93**, 94-109.
Coca, S. G., Singanamala, S. and Parikh, C. R. (2012) Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int.* **81**, 442-448.
Cooke, M. P. and Perlmutter, R. M. (1989) Expression of a novel form of the fyn proto-oncogene in hematopoietic cells. *New Biol.* **1**, 66-74.
Davidson, D., Chow, L. M., Fournel, M. and Veillette, A. (1992) Differential regulation of T cell antigen responsiveness by isoforms of the src-related tyrosine protein kinase p59fyn. *J. Exp. Med.* **175**, 1483-1492.
Davidson, D., Viallet, J. and Veillette, A. (1994) Unique catalytic properties dictate the enhanced function of p59fynT, the hemopoietic cell-specific isoform of the Fyn tyrosine protein kinase, in T cells. *Mol. Cell. Biol.* **14**, 4554-4564.
Du, T., Zou, X., Cheng, J., Wu, S., Zhong, L., Ju, G., Zhu, J., Liu, G., Zhu, Y. and Xia, S. (2013) Human Wharton's jelly-derived mesenchymal stromal cells reduce renal fibrosis through induction of native and foreign hepatocyte growth factor synthesis in injured tubular epithelial cells. *Stem Cell Res. Ther.* **4**, 59.
Fan, Y., Xiao, W., Lee, K., Salem, F., Wen, J., He, L., Zhang, J., Fei, Y., Cheng, D., Bao, H., Liu, Y., Lin, F., Jiang, G., Guo, Z., Wang, N. and He, J. C. (2017) Inhibition of reticulon-1a-mediated endoplasmic reticulum stress in early aki attenuates renal fibrosis development. *J. Am. Soc. Nephrol.* **28**, 2007-2021.
Gallagher, K. M., O'Neill, S., Harrison, E. M., Ross, J. A., Wigmore, S. J. and Hughes, J. (2017) Recent early clinical drug development for acute kidney injury. *Expert Opin. Investig. Drugs* **26**, 141-154.
Gao, X., Fu, L., Xiao, M., Xu, C., Sun, L., Zhang, T., Zheng, F. and Mei, C. (2012) The nephroprotective effect of tauroursodeoxycholic acid on ischaemia/reperfusion-induced acute kidney injury by inhibiting endoplasmic reticulum stress. *Basic Clin. Pharmacol. Toxicol.* **111**, 14-23.
Goldsmith, J. F., Hall, C. G. and Atkinson, T. P. (2002) Identification of an alternatively spliced isoform of the fyn tyrosine kinase. *Biochem. Biophys. Res.Commun.* **298**, 501-504.
Hsiao, H. W., Tsai, K. L., Wang, L. F., Chen, Y. H., Chiang, P. C., Chuang, S. M. and Hsu, C. (2012) The decline of autophagy contributes to proximal tubular dysfunction during sepsis. *Shock* **37**, 289-296.
Huang, C., Bruggeman, L. A., Hydo, L. M. and Miller, R. T. (2012) Shear stress induces cell apoptosis via a c-Src-phospholipase D-mTOR signaling pathway in cultured podocytes. *Exp. Cell Res.* **318**, 1075-1085.
Jain, A. K. and Jaiswal, A. K. (2007) GSK-3beta acts upstream of Fyn kinase in regulation of nuclear export and degradation of NF-E2 related factor 2. *J. Biol. Chem.* **282**, 16502-16510.
Jang, H. R. and Rabb, H. (2009) The innate immune response in ischemic acute kidney injury. *Clin. Immunol.* **130**, 41-50.
Jelic, D., Mildner, B., Kostrun, S., Nujic, K., Verbanac, D., Culic, O., Antolovic, R. and Brandt, W. (2007) Homology modeling of human Fyn kinase structure: discovery of rosmarinic acid as a new Fyn kinase inhibitor and in silico study of its possible binding modes. *J. Med. Chem.* **50**, 1090-1100.
Jiang, M., Liu, K., Luo, J. and Dong, Z. (2010) Autophagy is a renoprotective mechanism during *in vitro* hypoxia and *in vivo* ischemia-reperfusion injury. *Am. J. Pathol.* **176**, 1181-1192.
Kato, H., Nakajima, S., Saito, Y., Takahashi, S., Katoh, R. and Kitamura, M. (2012) mTORC1 serves ER stress-triggered apoptosis via selective activation of the IRE1-JNK pathway. *Cell Death Differ.* **19**, 310-320.
Keegan, R. F. and Webb, C. B. (2010) Oxidative stress and neutrophil function in cats with chronic renal failure. *J. Vet. Intern. Med.* **24**, 514-519.
Kim, J., Kundu, M., Viollet, B. and Guan, K. L. (2011) AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nat. Cell Biol.* **13**, 132-141.
Kim, S., Joe, Y., Kim, H. J., Kim, Y. S., Jeong, S. O., Pae, H. O., Ryter, S. W., Surh, Y. J. and Chung, H. T. (2015) Endoplasmic reticulum stress-induced IRE1alpha activation mediates cross-talk of GSK-3beta and XBP-1 to regulate inflammatory cytokine production. *J. Immunol.* **194**, 4498-4506.
Koo, J. H., Lee, W. H., Lee, C. G. and Kim, S. G. (2012) Fyn inhibition by cycloalkane-fused **1**,2-dithiole-3-thiones enhances antioxidant capacity and protects mitochondria from oxidative injury. *Mol. Pharmacol.* **82**, 27-36.
Kroemer, G., Marino, G. and Levine, B. (2010) Autophagy and the integrated stress response. *Mol. Cell* **40**, 280-293.
Lambert, M. P., Barlow, A. K., Chromy, B. A., Edwards, C., Freed, R., Liosatos, M., Morgan, T. E., Rozovsky, I., Trommer, B., Viola, K. L., Wals, P., Zhang, C., Finch, C. E., Krafft, G. A. and Klein, W. L. (1998) Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc. Natl. Acad. Sci. U.S.A.* **95**, 6448-6453.
Lawson, J., Elliott, J., Wheeler-Jones, C., Syme, H. and Jepson, R. (2015) Renal fibrosis in feline chronic kidney disease: known mediators and mechanisms of injury. *Vet. J.* **203**, 18-26.
Lee, T. W., Kwon, H., Zong, H., Yamada, E., Vatish, M., Pessin, J. E. and Bastie, C. C. (2013) Fyn deficiency promotes a preferential increase in subcutaneous adipose tissue mass and decreased visceral adipose tissue inflammation. *Diabetes* **62**, 1537-1546.
Lewington, A. J., Cerda, J. and Mehta, R. L. (2013) Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int.* **84**, 457-467.
Li, B., Liu, S., Miao, L. and Cai, L. (2012) Prevention of diabetic complications by activation of Nrf2: diabetic cardiomyopathy and nephropathy. *Exp. Diabetes Res.* **2012**, 216512.
Li, H., Lemay, S., Aoudjit, L., Kawachi, H. and Takano, T. (2004) SRC-family kinase Fyn phosphorylates the cytoplasmic domain of nephrin and modulates its interaction with podocin. *J. Am. Soc. Nephrol.* **15**, 3006-3015.
Li, X., Hassoun, H. T., Santora, R. and Rabb, H. (2009) Organ crosstalk: the role of the kidney. *Curr. Opin. Crit. Care* **15**, 481-487.
Li, W., Febbraio, M., Reddy, S. P., Yu, D. Y., Yamamoto, M. and Silverstein, R. L. (2010) CD36 participates in a signaling pathway that regulates ROS formation in murine VSMCs. *J. Clin. Invest.* **120**, 3996-4006.
Linkermann, A., Chen, G., Dong, G., Kunzendorf, U., Krautwald, S. and Dong, Z. (2014) Regulated cell death in AKI. *J. Am. Soc. Nephrol.* **25**, 2689-2701.
Liu, D., Zhang, X., Hu, B. and Ander, B. P. (2016) Src family kinases in brain edema after acute brain injury. *Acta Neurochir. Suppl.* **121**, 185-190.
Lv, Z., Hu, M., Ren, X., Fan, M., Zhen, J., Chen, L., Lin, J., Ding, N., Wang, Q. and Wang, R. (2016) Fyn mediates high glucose-induced actin cytoskeleton reorganization of podocytes via promoting ROCK activation *in vitro*. *J. Diabetes Res.* **2016**, 5671803.
Matsushita, K., Saritas, T., Eiwaz, M. B., McClellan, N., Coe, I., Zhu, W., Ferdaus, M. Z., Sakai, L. Y., McCormick, J. A. and Hutchens, M. P. (2019) The acute kidney injury to chronic kidney disease transition in a mouse model of acute cardiorenal syndrome emphasizes the role of inflammation. *Kidney Int.* **19**, 30774-30784.
McCaffrey, J., Dhakal, A. K., Milford, D. V., Webb, N. J. and Lennon, R. (2017) Recent developments in the detection and management of acute kidney injury. *Arch. Dis. Child.* **102**, 91-96.
Mittwede, P. N., Xiang, L., Lu, S., Clemmer, J. S. and Hester, R. L. (2015) Oxidative stress contributes to orthopedic trauma-induced acute kidney injury in obese rats. *Am. J. Physiol. Renal Physiol.* **308**, 157-163.
Miyata, T., Suzuki, N. and van Ypersele de Strihou, C. (2013) Diabetic nephropathy: are there new and potentially promising therapies targeting oxygen biology? *Kidney Int.* **84**, 693-702.
Mkaddem, S. B., Murua, A., Flament, H., Titeca-Beauport, D., Bounaix, C., Danelli, L., Launay, P., Benhamou, M., Blank, U., Daugas, E., Charles, N. and Monteiro, R. C. (2017) Lyn and Fyn function as molecular switches that control immunoreceptors to direct homeostasis or inflammation. *Nat. Commun.* **8**, 246.
Moran, M. F., Koch, C. A., Anderson, D., Ellis, C., England, L., Martin, G. S. and Pawson, T. (1990) Src homology region 2 domains direct

protein-protein interactions in signal transduction. *Proc. Natl. Acad. Sci. U.S.A.* **87**, 8622-8626.
Ogbadu, J., Singh, G. and Aggarwal, D. (2019) Factors affecting the transition of acute kidney injury to chronic kidney disease: Potential mechanisms and future perspectives. *Eur. J. Pharmacol.* **865**, 172711.
Pal, R., Palmieri, M., Chaudhury, A., Klisch, T. J., di Ronza, A., Neilson, J. R., Rodney, G. G. and Sardiello, M. (2018) Src regulates amino acid-mediated mTORC1 activation by disrupting GATOR1-Rag GTPase interaction. *Nat. Commun.* **9**, 4351.
Pal, R., Palmieri, M., Loehr, J. A., Li, S., Abo-Zahrah, R., Monroe, T. O., Thakur, P. B., Sardiello, M. and Rodney, G. G. (2014) Src-dependent impairment of autophagy by oxidative stress in a mouse model of Duchenne muscular dystrophy. *Nat. Commun.* **5**, 4425.
Panicker, N., Saminathan, H., Jin, H., Neal, M., Harischandra, D. S., Gordon, R., Kanthasamy, K., Lawana, V., Sarkar, S., Luo, J., Anantharam, V., Kanthasamy, A. G. and Kanthasamy, A. (2015) Fyn kinase regulates microglial neuroinflammatory responses in cell culture and animal models of parkinson's disease. *J. Neurosci.* **35**, 10058-10077.
Patschan, D., Schwarze, K., Henze, E., Hoffmann, J. C., Patschan, S., Ritter, O. and Muller, G. A. (2019) Acute kidney injury-associated systemic inflammation is aggravated in insulin-dependent diabetes mellitus. *J. Clin. Med. Res.* **11**, 720-723.
Rajasekaran, K., Kumar, P., Schuldt, K. M., Peterson, E. J., Vanhaesebroeck, B., Dixit, V., Thakar, M. S. and Malarkannan, S. (2013) Signaling by Fyn-ADAP via the Carma1-Bcl-10-MAP3K7 signalosome exclusively regulates inflammatory cytokine production in NK cells. *Nat. Immunol.* **14**, 1127-1136.
Rana, A., Sathyanarayana, P. and Lieberthal, W. (2001) Role of apoptosis of renal tubular cells in acute renal failure: therapeutic implications. *Apoptosis* **6**, 83-102.
Resh, M. D. (1998) Fyn, a Src family tyrosine kinase. *Int. J. Biochem. Cell Biol.* **30**, 1159-1162.
Rifkin, D. E., Coca, S. G. and Kalantar-Zadeh, K. (2012) Does AKI truly lead to CKD? *J. Am. Soc. Nephrol.* **23**, 979-984.
Rizvi, F., Shukla, S. and Kakkar, P. (2014) Essential role of PH domain and leucine-rich repeat protein phosphatase 2 in Nrf2 suppression via modulation of Akt/GSK3beta/Fyn kinase axis during oxidative hepatocellular toxicity. *Cell Death Dis.* **5**, e1153.
Roskoski, R., Jr. (2015) Src protein-tyrosine kinase structure, mechanism, and small molecule inhibitors. *Pharmacol. Res.* **94**, 9-25.
Saito, Y. D., Jensen, A. R., Salgia, R. and Posadas, E. M. (2010) Fyn: a novel molecular target in cancer. *Cancer* **116**, 1629-1637.
Saminathan, H., Asaithambi, A., Anantharam, V., Kanthasamy, A. G. and Kanthasamy, A. (2011) Environmental neurotoxic pesticide dieldrin activates a non receptor tyrosine kinase to promote PKCdelta-mediated dopaminergic apoptosis in a dopaminergic neuronal cell model. *Neurotoxicology* **32**, 567-577.
Sanchez, A. M., Candau, R. B., Csibi, A., Pagano, A. F., Raibon, A. and Bernardi, H. (2012) The role of AMP-activated protein kinase in the coordination of skeletal muscle turnover and energy homeostasis. *Am. J. Physiol. Cell Physiol.* **303**, 475-485.
Santosa, D., Castoldi, M., Paluschinski, M., Sommerfeld, A. and Haussinger, D. (2015) Hyperosmotic stress activates the expression of members of the miR-15/107 family and induces downregulation of anti-apoptotic genes in rat liver. *Sci. Rep.* **5**, 12292.
Schenone, S., Brullo, C., Musumeci, F., Biava, M., Falchi, F. and Botta, M. (2011) Fyn kinase in brain diseases and cancer: the search for inhibitors. *Curr. Med. Chem.* **18**, 2921-2942.
Sengupta, S., Peterson, T. R. and Sabatini, D. M. (2010) Regulation of the mTOR complex 1 pathway by nutrients, growth factors, and stress. *Mol. Cell* **40**, 310-322.
Seo, H. Y., Jeon, J. H., Jung, Y. A., Jung, G. S., Lee, E. J., Choi, Y. K., Park, K. G., Choe, M. S., Jang, B. K., Kim, M. K. and Lee, I. K. (2016) Fyn deficiency attenuates renal fibrosis by inhibition of phospho-STAT3. *Kidney Int.* **90**, 1285-1297.
Shang, G., Tang, X., Gao, P., Guo, F., Liu, H., Zhao, Z., Chen, Q., Jiang, T., Zhang, N. and Li, H. (2015) Sulforaphane attenuation of experimental diabetic nephropathy involves GSK-3 beta/Fyn/Nrf2 signaling pathway. *J. Nutr. Biochem.* **26**, 596-606.
Sugie, K., Jeon, M. S. and Grey, H. M. (2004) Activation of naive CD4 T cells by anti-CD3 reveals an important role for Fyn in Lck-mediated signaling. *Proc. Natl. Acad. Sci. U.S.A.* **101**, 14859-14864.
Sugie, K., Kawakami, T., Maeda, Y., Kawabe, T., Uchida, A. and Yodoi, J. (1991) Fyn tyrosine kinase associated with Fc epsilon RII/CD23: possible multiple roles in lymphocyte activation. *Proc. Natl. Acad. Sci. U.S.A.* **88**, 9132-9135.
Suzuki, C., Isaka, Y., Takabatake, Y., Tanaka, H., Koike, M., Shibata, M., Uchiyama, Y., Takahara, S. and Imai, E. (2008) Participation of autophagy in renal ischemia/reperfusion injury. *Biochem. Biophys. Res. Commun.* **368**, 100-106.
Taniguchi, K., Xia, L., Goldberg, H. J., Lee, K. W., Shah, A., Stavar, L., Masson, E. A., Momen, A., Shikatani, E. A., John, R., Husain, M. and Fantus, I. G. (2013) Inhibition of Src kinase blocks high glucose-induced EGFR transactivation and collagen synthesis in mesangial cells and prevents diabetic nephropathy in mice. *Diabetes* **62**, 3874-3886.
Uddin, M. J., Pak, E. S. and Ha, H. (2018) Carbon monoxide releasing molecule-2 protects mice against acute kidney injury through inhibition of ER stress. *Korean J. Physiol. Pharmacol.* **22**, 567-575.
Urano, F., Wang, X., Bertolotti, A., Zhang, Y., Chung, P., Harding, H. P. and Ron, D. (2000) Coupling of stress in the ER to activation of JNK protein kinases by transmembrane protein kinase IRE1. *Science* **287**, 664-666.
Verma, R., Wharram, B., Kovari, I., Kunkel, R., Nihalani, D., Wary, K. K., Wiggins, R. C., Killen, P. and Holzman, L. B. (2003) Fyn binds to and phosphorylates the kidney slit diaphragm component Nephrin. *J. Biol. Chem.* **278**, 20716-20723.
Wang, Y., Yamada, E., Zong, H. and Pessin, J. E. (2015) Fyn activation of mTORC1 stimulates the IRE1alpha-JNK pathway, leading to cell death. *J. Biol. Chem.* **290**, 24772-24783.
Wu, H., Shi, Y., Deng, X., Su, Y., Du, C., Wei, J., Ren, Y., Wu, M., Hou, Y. and Duan, H. (2015) Inhibition of c-Src/p38 MAPK pathway ameliorates renal tubular epithelial cells apoptosis in db/db mice. *Mol. Cell. Endocrinol.* **417**, 27-35.
Xiong, C., Zang, X., Zhou, X., Liu, L., Masucci, M. V., Tang, J., Li, X., Liu, N., Bayliss, G., Zhao, T. C. and Zhuang, S. (2017) Pharmacological inhibition of Src kinase protects against acute kidney injury in a murine model of renal ischemia/reperfusion. *Oncotarget* **8**, 31238-31253.
Xu, Y., Guo, M., Jiang, W., Dong, H., Han, Y., An, X. F. and Zhang, J. (2016) Endoplasmic reticulum stress and its effects on renal tubular cells apoptosis in ischemic acute kidney injury. *Ren. Fail.* **38**, 831-837.
Yamada, E., Bastie, C. C., Koga, H., Wang, Y., Cuervo, A. M. and Pessin, J. E. (2012) Mouse skeletal muscle fiber-type-specific macroautophagy and muscle wasting are regulated by a Fyn/STAT3/Vps34 signaling pathway. *Cell Rep.* **1**, 557-569.
Yamada, E., Okada, S., Bastie, C. C., Vatish, M., Nakajima, Y., Shibusawa, R., Ozawa, A., Pessin, J. E. and Yamada, M. (2016) Fyn phosphorylates AMPK to inhibit AMPK activity and AMP-dependent activation of autophagy. *Oncotarget* **7**, 74612-74629.
Yamada, E., Pessin, J. E., Kurland, I. J., Schwartz, G. J. and Bastie, C. C. (2010) Fyn-dependent regulation of energy expenditure and body weight is mediated by tyrosine phosphorylation of LKB1. *Cell Metab.* **11**, 113-124.
Yan, Y., Ma, L., Zhou, X., Ponnusamy, M., Tang, J., Zhuang, M.A., Tolbert, E., Bayliss, G., Bai, J. and Zhuang, S. (2016) Src inhibition blocks renal interstitial fibroblast activation and ameliorates renal fibrosis. *Kidney Int.* **89**, 68-81.
Yang, C., Kaushal, V., Shah, S. V. and Kaushal, G. P. (2008) Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. *Am. J. Physiol. Renal Physiol.* **294**, 777-787.
Yang, L., Humphreys, B. D. and Bonventre, J. V. (2011) Pathophysiology of acute kidney injury to chronic kidney disease: maladaptive repair. *Contrib. Nephrol.* **174**, 149-155.
Yu, C. C., Yen, T. S., Lowell, C. A. and DeFranco, A. L. (2001) Lupus-like kidney disease in mice deficient in the Src family tyrosine kinases Lyn and Fyn. *Curr. Biol.* **11**, 34-38.
Yu, L., Lin, Q., Liao, H., Feng, J., Dong, X. and Ye, J. (2010) TGF-beta1 induces podocyte injury through Smad3-ERK-NF-kappaB pathway and Fyn-dependent TRPC6 phosphorylation. *Cell Physiol. Biochem.* **26**, 869-878.

Zhang, C., Lu, X., Tan, Y., Li, B., Miao, X., Jin, L., Shi, X., Zhang, X., Miao, L., Li, X. and Cai, L. (2012) Diabetes-induced hepatic pathogenic damage, inflammation, oxidative stress, and insulin resistance was exacerbated in zinc deficient mouse model. *PLoS ONE* **7**, e49257.

Zhao, L., Zhang, C., Luo, X., Wang, P., Zhou, W., Zhong, S., Xie, Y., Jiang, Y., Yang, P., Tang, R., Pan, Q., Hall, A. R., Luong, T. V., Fan, J., Varghese, Z., Moorhead, J. F., Pinzani, M., Chen, Y. and Ruan, X. Z. (2018) CD36 palmitoylation disrupts free fatty acid metabolism and promotes tissue inflammation in non-alcoholic steatohepatitis. *J. Hepatol.* **69**, 705-717.

Zheng, M., Zhang, Q., Joe, Y., Kim, S. K., Uddin, M. J., Rhew, H., Kim, T., Ryter, S. W. and Chung, H. T. (2013) Carbon monoxide-releasing molecules reverse leptin resistance induced by endoplasmic reticulum stress. *Am. J. Physiol. Endocrinol. Metab.* **304**, 780-788.