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; Mkademed 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-
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 Perlmuter, 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.

IN VolvEMENT 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

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**Table 1.** Role of Fyn in various pathological conditions

| Organs/cells | Models | Mechanisms | References |
|-------------|--------|------------|------------|
| 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/Bclin1/Atg14 complexes | Yamada et al., 2012 |
| Mid brain   | Parkinson’s disease        | Increases proinflammatory cytokines | Panicker et al., 2015 |
| Cells       | Podocytes                  | Increases TRPC6 phosphorylation | Yu et al., 2010 |
| Cells       | Microglia                  | Mediates PKCδ>MAPK>NF-κB signaling | Panicker et al., 2015 |

**Fig. 1.** (A) Src family kinase members and (B) their activation domain structure.
al., 2013), db/db type-2 diabetes (Wu et al., 2015), as well as unilateral ureteral obstruction (UUO)-induced tubulointerstitial 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 is well recognized (Afram and Lowell, 2008; Chen et al., 2014). Fyn kinase regulates antigen-specific activation of T cells, and its deficiency rigorously suppressed T cell responses (Surje 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 microgial neuro-inflammatory responses via Cö (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 tissue 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 (Uruno 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 acetetyl-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 heterotrimetric 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
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 downregulation 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

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**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.
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 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.

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