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Role of TFEB in autophagic modulation of ischemia reperfusion injury in mice kidney and protection by urolithin A

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ABSTRACT

Kidney ischemia reperfusion injury (IRI) is an acute kidney injury associated with high number of mortality. We have examined the molecular mechanism and found that oxidative stress and hypoxia leads to induction of autophagy. In IRI induced autophagy, TFEB translocated to nucleus in response to IRI and induced a number of target genes of Coordinated Lysosomal Expression and Regulation (CLEAR) network. Real-time PCR analyses result showed IRI dependent increase in mRNA level to lysosomal hydrolases (Ctsa, Psap), lysosomal membranes (Lamp1), lysosomal acidification (Atp6ap1) non-lysosomal proteins involved in lysosomal biogenesis (M6pr, Nagpa) and autophagy (Becn1, VPS11). Overall, both lysosomal biogenesis and autophagy pathways were induced. Two key players of TFEB dependent proteins in autophagy, LAMP1 and BECN1 were verified by protein analyses. Pretreatment with urolithin A promoted autophagy and attenuated renal injury in kidney IRI and thus inverse relationship existed between TFEB–CLEAR pathway and kidney injury. Urolithin A also attenuated IRI induced pro-inflammatory cytokines TNFα, IL1β, MIP1α and MIP2 mRNA and associated kidney injury. Overall, our results explored the understanding of autophagy and CLEAR network to kidney IRI and those insights may help to develop new therapeutic strategies to protect against IRI.

1. Introduction

Acute kidney injury is caused by renal surgery, sepsis or nephrotoxicity and is one of the major incidences among hospitalized patients (Dellepiane et al., 2016; Weir et al., 2015). It can also develop chronic kidney disease (Venkatachalam et al., 2015). Ischemia-reperfusion injury (IRI) is the most common acute kidney injury animal model and demonstrated severe injury of renal tubular epithelial cell and vasculature, accompanied by a strong inflammatory response (Edwards, 2015). Thus IRI causes a rapid loss of renal function mainly due to tubular cell death. As a defense to these threats, tubular cells generate a series of protection mechanisms such as induction of stress response genes and cell cycle regulators. Autophagy also contributes to the defensive mechanism, but its reno-protective mechanism is not clear.

Autophagy is an evolutionarily conserved recycling mechanism of cellular macromolecules and organelle in response to stress. The pathogenesis of IRI in the kidney also involves various stresses including oxidative stress, hypoxia, and lack of nutrient or growth factors or limited energy supplies (Decuypere et al., 2015). Thus autophagy response to cellular stress is an adaptive and cytoprotective process in IRI of the kidney. Numerous studies with neurodegenerative disease, cardiovascular complication, and infectious diseases demonstrated the role of dysregulated autophagy in pathophysiology (Deretic et al., 2013; Giordano et al., 2014; Nishida et al., 2015). Similar studies are very limited to kidney diseases. Renal IRI induced autophagy in mice (Jiang et al., 2010). Detailed studies demonstrate that autophagy occurs in proximal tubules (Jiang et al., 2012). Autophagy demonstrated beneficial aspect in conditional kidney proximal tubule-specific ATG5 and ATG7 knock out mice (Kimura et al., 2011). It has been established that

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autophagy in tubules protects against injury and cell death in acute kidney injury (Chien et al., 2007; Kaushal, 2012). Pharmacological inhibition of autophagy is also used as a tool to understand the role of autophagy in kidney IRI injury (Zhang et al., 2015).

The degradation of cellular compartments is regulated by a specific network known as CLEAR (Coordinated Lysosomal Expression and Regulation). These specific set of genes are the target of Transcription factor EB (TFEB). Those target genes are involved in vesicle formation, cargo recognition, lysosome fusion and cargo degradation (Settembre and Ballabio, 2011). The research on TFEB and the CLEAR pathway are limited until now. The CLEAR network plays a critical role in common neurodegenerative diseases such as Alzheimer's, Parkinson's and Huntington's (Palmieri et al., 2011). The importance of TFEB regulated CLEAR pathways in acute kidney injury including IRI is important to investigate due to the following reasons. After binding to target gene promoters TFEB regulates pathways such as glycosaminoglycan degradation, hemoglobin degradation, chitin degradation and sphingolipid degradation (Palmieri et al., 2011), which are crucial in acute kidney injury (Guebre-Egziabher et al., 2013; Gyebi et al., 2012). The complex targets of TFEB regulation include protein degradation, energy metabolism (glycolysis, TCA cycle), steroid biosynthesis, antigen processing and presentation, signaling pathways (Chemokine, p53, JAK-STAT, insulin *etc*.) and DNA metabolism (Palmieri et al., 2011), which are implicated in acute kidney injury (Kezic et al., 2016; Kinsey et al., 2008; Tang and Zhuang, 2015). One of the targets of TFEB is the pathways involved in the removal of the dead and injured cell and its processing (Palmieri et al., 2011). Such processes in kidney IRI is crucial to the recovery process and the role of TFEB regulated CLEAR network is thus an important aspect of kidney acute injury. Therefore, TFEB and associated CLEAR network will have significant potential to influence various molecular events in acute kidney injury. In addition to that IRI also involves significant oxidative stress, cell death, and inflammation. Autophagy and lysosomal degradations, both modulated by TFEB, protect against those damage associated in proximal tubular cells in IRI (Jiang et al., 2012; Sureshbabu et al., 2015). This study on the renoprotective effect of TFEB-CLEAR pathway in IRI is crucial to understand the molecular mechanism as well as to develop the new therapeutic intervention.

Dietary compounds can induce autophagy and protects against diseases based on animal model studies (Hasima and Ozpolat, 2014; Nunes et al., 2016). Urolithin A, the main metabolite from pomegranate juice, induced autophagy and also protects against kidney injury (Guada et al., 2017; Ren and Zhang, 2018; Ryu et al., 2016). Evaluation of urolithin A for safety is reported and genotoxicity is not observed (Heilman et al., 2017).

In this study, we demonstrated the distinct role of TFEB regulated CLEAR network in well-characterized kidney IRI model in mice. Urolithin A pretreatment enhanced TFEB level and reduced inflammatory responses and associated kidney injury.

2. Method

2.1. Mice experiments

Animals were housed in facilities according to international guidelines, and studies were approved by and conducted in accordance with the Institutional Animal Care and Use Committee. C57BL/6 male mice (6–8 week-old, 25–30 g, Shanghai Animal Center of Chinese Academy of Science, Shanghai, P.R.China) were housed eight per cage with free access to food and water, and were kept in a constant environment (22 ± 2 °C, 50 ± 5% humidity, 12 h light/dark cycle).

All protocols were approved by the Committee on the Ethics of Animal Experiments of First Affiliated Hospital, College of Medicine, Zhejiang University.

Mice were anesthetized with ketamine hydrochloride (100 mg/kg body weight, i.v.). After medial laparotomy, all renal arteries and veins were clamped by microaneurysm clamps for 35 min. After the renal clamps were removed, the kidneys were observed for a further 5 min to ensure blood flow then the incisions were sutured in two layers. All mice were kept at 37 °C during the procedure and allowed to recover. Mice were then returned to their cages and were allowed free access to food and water. Mice with delayed recovery from anesthesia or with signs of hemorrhage were excluded from the study. A separate set with 4 mice in each group with urolithin A (50 mg/kg, 3 days prior and 30 min before surgery) were performed. Each group was treated with either with vehicle or urolithin A.

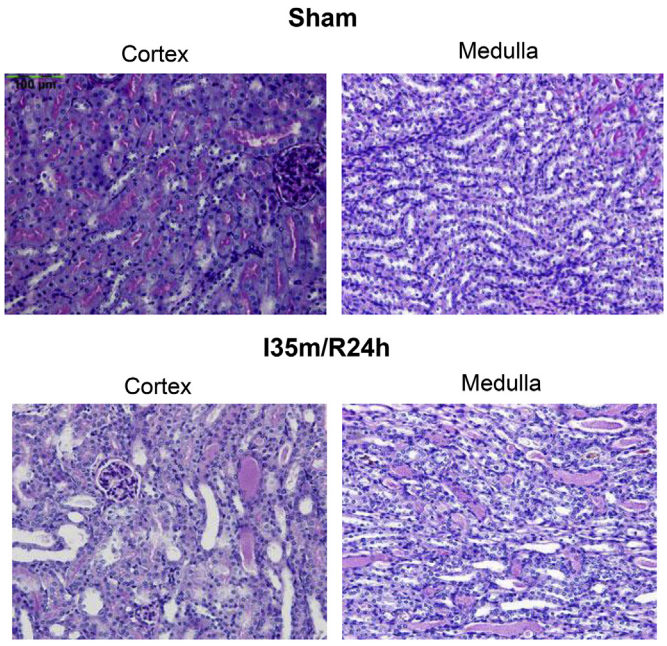

Fig. 1. IRI induces tubular cell damages Histopathological damage was evaluated by PAS staining. Desquamation of tubular cells, PAS-positive brush border, tubular cast, and tubular dilatations were observed. Representative images from cortex and medullar area of kidney were depicted.

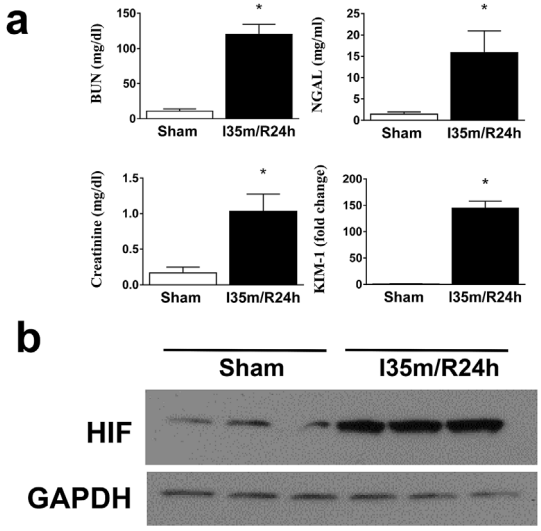

Fig. 2. IRI induces kidney dysfunction and induction of HIF1. (a) Kidney dysfunction was determined by serum analyses of BUN, Creatinine, NGAL and KIM-1 using analyzer and ELISA based assays. All four markers were increased significantly. *p < 0.05 versus sham-operated mice, n-6/group. (b) Western blot analyses demonstrated the induction of HIF 1 at protein level.

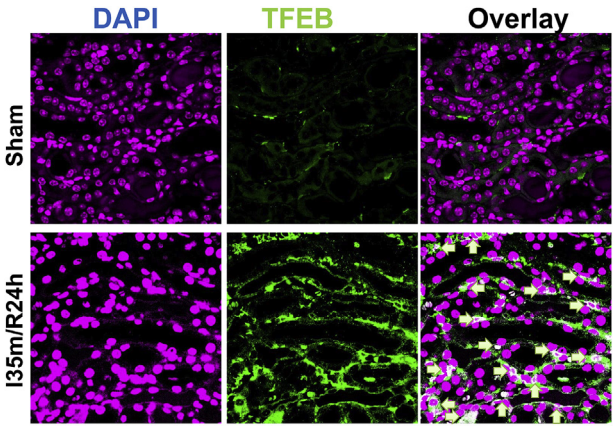

Fig. 3. IRI leads to nuclear localization of TFEB. Fluorescence imaging by confocal microscope demonstrated overlay of DAPI (magenta) nuclear staining and TFEB (green) in the damaged tubular cells. Images were with 40X oil objective lens. Co-localizations of TFEB and nuclear (white) were further pointed by the arrow. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

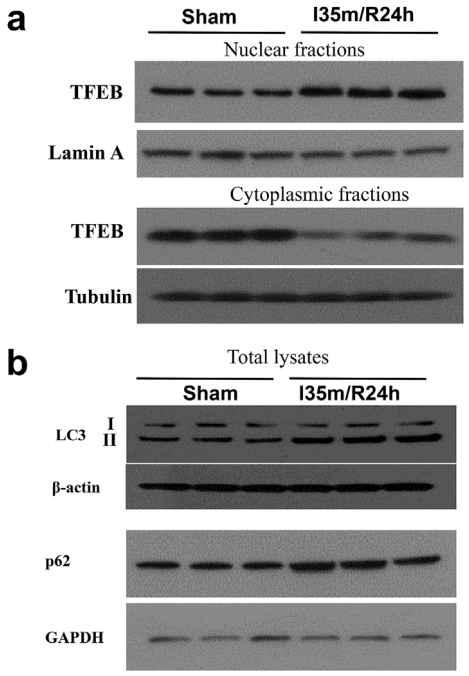

Fig. 4. IRI induces autophagy. (a) IRI induced translocation of TFEB to nuclear fraction and decrease in cytoplasmic fraction as evident from Western blot. Lamin A was used as a marker for nuclear fraction and tubulin was used as cytoplasmic fraction. (b) Increase in LC3 and LC3 II conversion along with induction of p62 was observed. GAPDH was used as a loading control in Western blot experiments. mRNA level of p62 was also determined by Real-time PCR and the level was increased.

2.2. Blood chemistry analyses

Serum creatinine (CREA) levels and blood urea nitrogen (BUN) were measured by Automated.

Chemical Analyzer (7600, Hitachi, Japan) as described earlier (Xia et al., 2011)

2.3. Determination of kidney injury by neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury Molecule-1 (KIM-1)

NGAL and KIM-1 were measured from serum using Mouse NGAL Quantikine ELISA Kit and Mouse KIM-1 Quantikine ELISA Kit (R&D Systems China Co. Ltd, Changning, China) according to the manufacturer's instruction.

2.4. Kidney histology

Histology was performed in paraffin-embedded tissue sections as described earlier (Pan et al., 2014). Two independent observers examined the slides by light microscopy in a blinded fashion.

2.5. Isolation of nuclear fraction from tissue

Nuclear fractions and cytoplasmic fractions were prepared using commercial nuclear fractionation kit (Pierce, IL, USA) and followed the manufacturer's instruction.

2.6. Protein estimation and Western blot

Tissues were homogenized and suspended in 600 µl of RIPA buffer (Sigma, Hong Kong, China), and protein concentration of lysate or nuclear fraction were determined by Bio-Rad protein assay kit (BioRad Laboratories, Shanghai, China). The values obtained were corrected for BSA.

An equal amount of protein was loaded on SDS-PAGE and transferred into a nitrocellulose membrane. The blots were probed with primary antibodies followed by HRP conjugated secondary antibodies. Primary antibodies were used as HIF 1, GAPDH, TFEB, Lamin A, LC3, p62, LAMP 1, Beclin 1, Tubulin and β-actin (Abcam, Shanghai, China.). Primary antibodies against TNFα and IL1β were obtained from R&D Systems China Co. Ltd, Changning, China.

2.7. Real-time PCR

Isolation of RNA and Real-time PCR was carried out as described earlier (Pan et al., 2014). The primer sets for TNFα, IL1β, MIP1α, MIP2,Ctsa (cathepsin A), Psap (prosaposin), Lamp1 (lysosomal-associated membrane protein 1), ATP6ap1 (ATPase, H+ transporting, lysosomal accessory protein 1), M6pr (mannose-6-phosphate receptor, cation dependent), Nagpa (N-acetylglucosamine-1-phosphodiester alpha-N-acetylglucosaminidase), Becn1 (beclin 1, autophagy related), Vps11 (vacuolar protein sorting-associated protein 11) and β-actin were purchased from Qiagen (Pudong, Shanghai, China).

2.8. Fluorescence microscopy

Tissue specimens were fixed in 10% buffered formalin for 24 h and embedded in paraffin. Ten-micron-thick tissue sections were incubated with antibody against TFEB (Abcam) which was detected with Alexa Fluor 488-conjugated secondary antibody. Nuclei were stained with DAPI.

2.9. Statistical analysis

All values are expressed as mean ± SD. Student's paired *t*-test was performed for comparison of data of paired samples and ANOVA was used for multiple group comparisons followed by Tukey's post hoc test. A probability (P) value < 0.05 was considered significant.

3. Results

3.1. IRI induces kidney dysfunction, tubular cell damage and induction of hypoxia-inducible factor (HIF)

We examined the extent of IRI damage by PAS histology markers such as tubular structure, tubular dilatation, loss of tubular cells, swelling and necrosis and protein cast formation in cortex and medulla

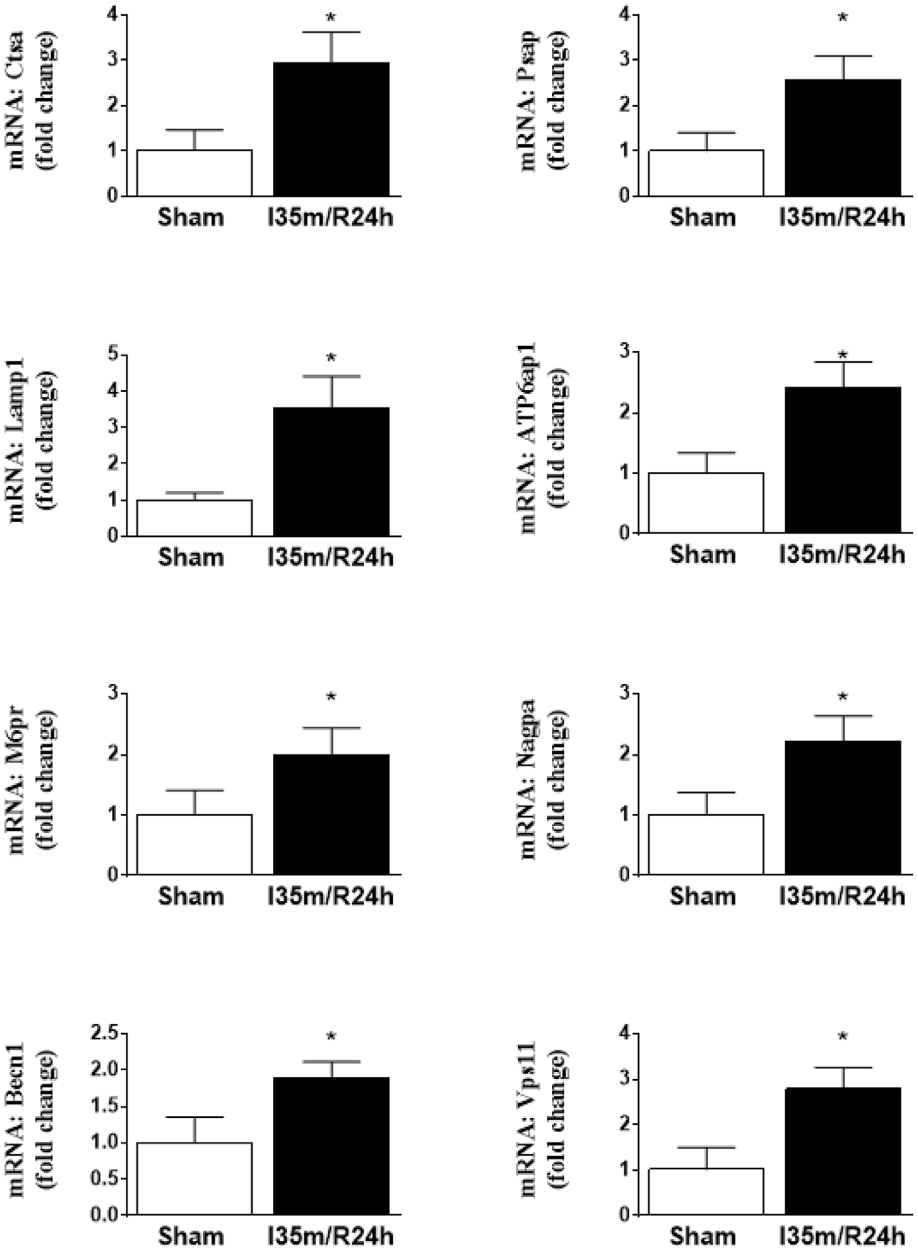

Fig. 5. IRI induces CLEAR network. Real-time PCR analyses demonstrated an increase of mRNA levels of CLEAR network genes namely Ctsa, Psap, Lamp1, ATP6ap1, M6pr, Nagpa, Becn1 and Vps11 in response to IRI. *p $<$ 0.05 versus sham-operated mice, n = 6/group.

(Fig. 1) at 24 h after a 35 min ischemic period, suggesting that tubular injury was significant.

We investigated IRI induced renal dysfunction by measuring serum Creatinine and BUN levels were determined. Compared to sham-operated animals, mice that underwent renal IRI exhibited a significant increase in BUN concentration (10.8 ± 3.06 mg/dl vs.120.2 ± 14.2 mg/dl) and Creatinine (0.17 ± 0.08 mg/dl vs.1.033 ± 0.24 mg/dl), suggesting a modest degree of glomerular dysfunction (Fig. 2a). We also measured two additional markers for acute kidney damage such as NGAL and KIM-1 as described earlier (Bolignano et al., 2008). Mice with renal IRI exhibited a significant increase in NGAL (1.43 ± 0.56 mg/ml vs.15.83 ± 5.5 mg/ml) and KIM-1 (144.3 ± 13.54 fold change).

HIF-1 is induced by hypoxia and is known for its role for tubular cell survival (Conde et al., 2012). In our IRI model, HIF-1 was significantly induced as evident from Western blot analyses where GAPDH were used as a loading control (Fig. 2b).

3.2. IRI leads to nuclear localization of TFEB and induction of autophagy

Previous time course studies demonstrated that 24 h reperfusion after ischemia demonstrates marked an increase in renal dysfunction markers and autophagy markers (Bylander et al., 2008; Chandrika et al., 2015; Reeves et al., 2008). The earlier report demonstrated that increase in autophagy in the tubular epithelial cells of IRI mouse models but detailed mechanisms were not studied (Liu et al., 2012). TFEB is involved in linking autophagy to lysosomal biogenesis and plays a lead role in degradation mechanism (David, 2011). We examined the role of TFEB and found that TBEB translocated to the nucleus in response to IRI injury in mice (Fig. 3).To verify further, we analyzed both nuclear and cytoplasmic fractions of TFEB. TFEB level was significantly increased in nuclear fraction whereas its level in the cytoplasmic fraction was decreased (Fig. 4a). TFEB translocated to the nucleus of tubular cells as evident by fluorescence microscopy and Western blot experiments. In a similar pattern, autophagy markers LC3II and p62 (Sequestosome-1)

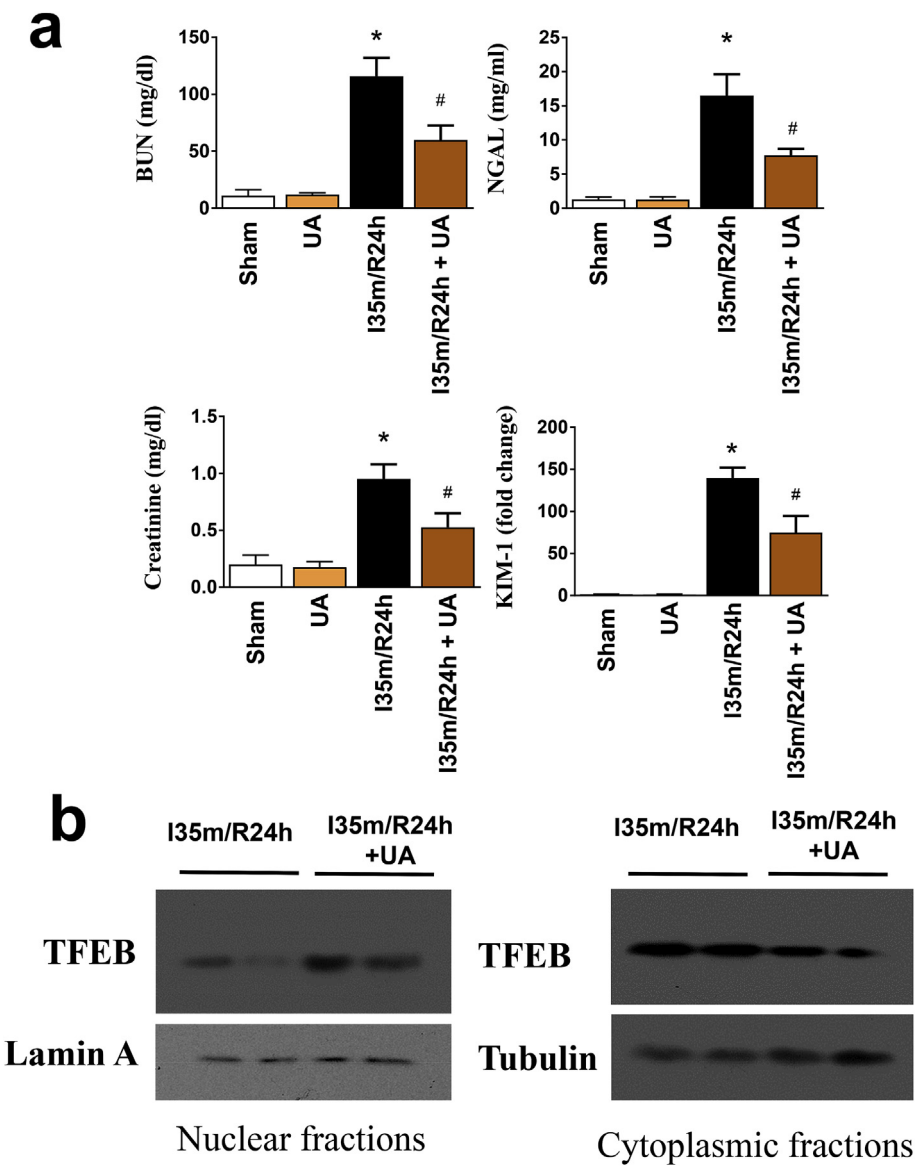

Fig. 6. Urolithin A pretreatment attenuated kidney dysfunction in IRI. (a) Urolithin A pretreatment significantly increased kidney dysfunction serum markers namely BUN, NGAL, Creatinine, and KIM-1. *p < 0.05 versus sham-operated mice, #p < 0.05 versus IRI mice, n = 4/group. (b) MA attenuated IRI induced translocation of TFEB to nuclear fraction and decrease in cytoplasmic fraction as evident from Western blot. Lamin A was used as a marker for nuclear fraction and tubulin was used as cytoplasmic fraction.

also increased in IRI kidney lysates as demonstrated by Western blot analyses (Fig. 4b). Measuring the processing of endogenous LC3 along with p62 by Western blot is used to detect increased autophagy in cells (Li et al., 2016). Lamin A, Tubulin and GAPDH were used as nuclear, cytoplasmic and total lysate loading controls respectively in the above experiments.

3.3. IRI induces TFEB-mediated CLEAR network

Lysosomal compartments require the coordinated expression of various proteins modulating hydrolases, acidification, and membrane molecules in response to autophagy and the process are regulated by the master regulator TFEB. All those genes have an E box motif in the promoter and thus lead to the discovery of the CLEAR network (Settembre and Medina, 2015). TFEB also regulate non-lysosomal proteins and autophagy (Palmieri et al., 2011). We examined mRNA levels of eight direct target genes of TFEB by real-time PCR which are involved in lysosomal hydrolases (Ctsa, Psap), lysosomal membranes (Lamp1), lysosomal acidification (Atp6ap1) non-lysosomal proteins involved in lysosomal biogenesis (M6pr, Nagpa) and autophagy (Becn1, VPS11). All target genes demonstrated significantly elevated mRNA level in response to IRI (Fig. 5). Quantitative Real-time PCR showed that mRNA level of genes Ctsa, Psap, Lamp1, Atp6ap1, M6pr, Nagpa, Becn1 and VPS11 were increased to 2.93 ± 0.68, 2.56 ± 0.53, 3.52 ± 0.88, 2.42 ± 0.41,2.0 ± 0.43, 2.22 ± 0.41, 1.9 ± 0.21and 2.78 ± 0.47 fold respectively. Lamp1 and Becn1 are instrumental in lysosomal biogenesis and degradation (Cao and Klionsky, 2007; Wang et al., 2013). Thus our data demonstrated significant upregulation of CLEAR genes in response to IRI in the kidney.

3.4. Urolithin A protects against IRI induced renal injury and attenuates against IRI induced an inflammatory response in kidney

Urolithin A protects against IRI induced kidney injuries as evident by injury markers BUN, NGAL, Creatinine, and KIM-1 (Fig. 6a). We observed a significant induction of TFEB nuclear localization with IRI plus urolithin A pretreatment compared to IRI plus vehicle (Fig. 6b).

Kidney IRI injury leads to oxidative damage and cell death, which

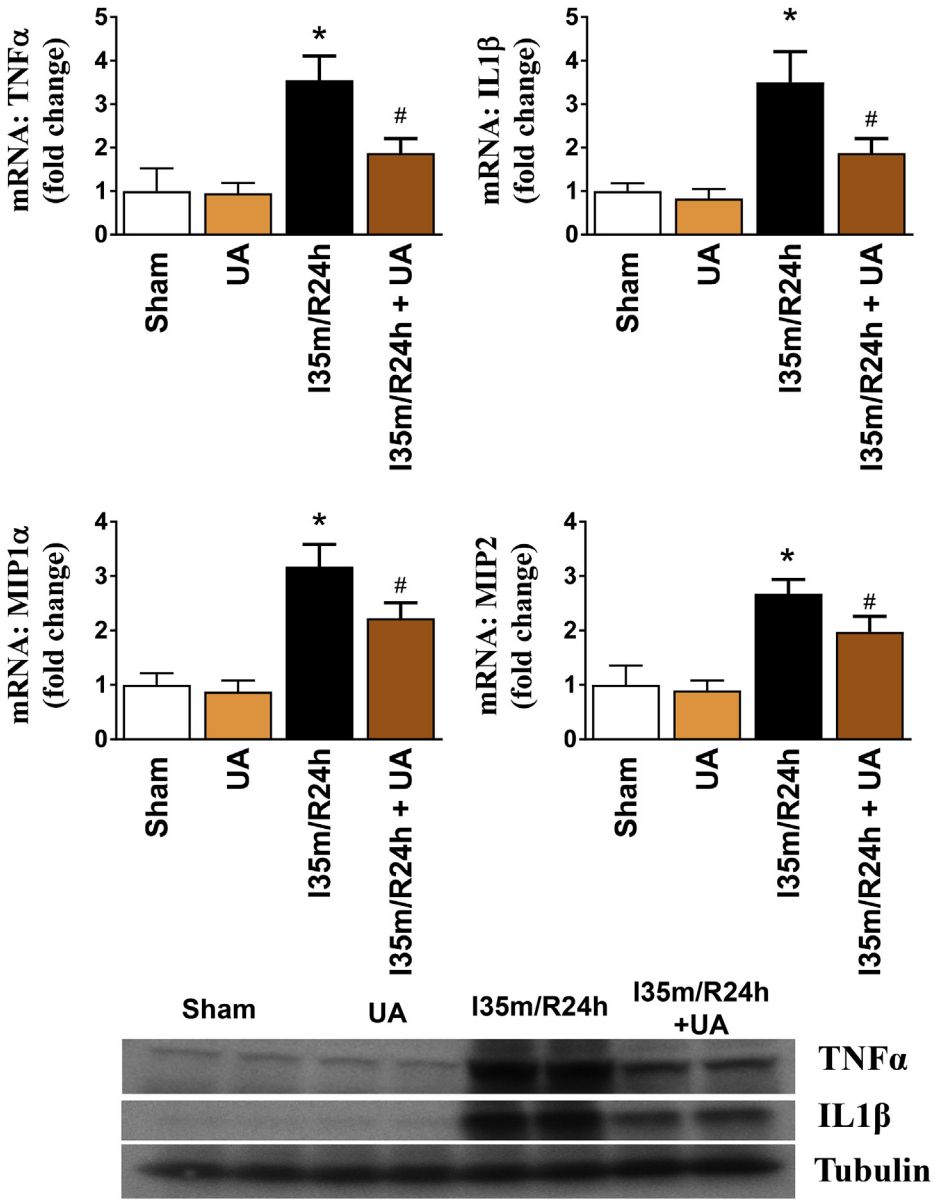

Fig. 7. Urolithin A protects against IRI induced inflammation in mice kidney. Real-time PCR analyses demonstrated an increase of inflammatory cytokines TNFα (a), IL1β (b), MIP1α (c), and MIP2 (d) were induced by IRI and reduced significantly by urolithin pretreatment. *p < 0.05 versus sham-operated mice, n = 6/group.

stimulate pro-inflammatory response (Thurman, 2007). In accordance with earlier reports, we observed an increase in TNFα, IL1β, MIP1α and MIP2 mRNA levels to 3.6 ± 0.6, 3.7 ± 0.7, 3.4 ± 0.4 and 2.4 ± 0.4 fold change respectively (Fig. 7). Urolithin A pretreatment reduced all four cytokine levels significantly. Both TNFα and IL1β cytokines were examined at the protein level by Western blot (Fig. 7). These pro-inflammatory chemokines and cytokines productions affect neutrophil and other immune cell influx, which in turn generates more oxidative damage.

4. Discussion

Kidney ischemia leads to critical insight on the endogenous mechanism of protection of organ by itself. Thus IRI is a powerful method to understand the changes at the molecular level and to develop necessary intervention therapeutics. In response to IRI, significant damages to kidney tubular cell led to increases in BUN, Creatinine, NGAL, and KIM-1. IRI induced HIF-1 due to hypoxia and reperfusion led to massive oxidative damages. Oxidative damage causes cell death and inflammatory response (Aragno et al., 2003). Cells adapt to this stress by autophagy (Kaushal and Shah, 2016). The balancing act of cell death and recycling is a crucial step in the recovery process. In this study, we explored the details of autophagy regulation and the protective role of urolithin A in kidney IRI.

Both apoptosis and autophagy in kidney IRI involving tubular cells have been reported a decade ago (Chien et al., 2007). BCL-2 and HIF dependent HSP60 plays a crucial role in autophagy (Yeh et al., 2010). Jiang et al. demonstrated that autophagy protects against IRI injury (Jiang et al., 2012). Reno-protective effect of autophagy also depends on the extent of damage by IRI (Huber et al., 2012; Jiang et al., 2010). Our data suggested that autophagy activation occurred at 24 h reperfusion and decreased at 72 h time points. Earlier studies also demonstrated a similar time frame and the time frame coincides with kidney injury (Bylander et al., 2008; Chandrika et al., 2015; Reeves et al., 2008).

In our study, TFEB was accumulated in a nuclear fraction in

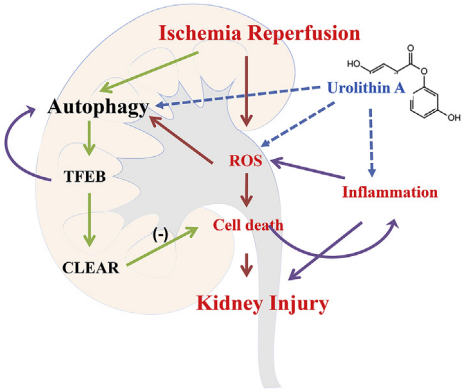

Fig. 8. Schematic diagram of IRI induced events that lead to tissue injury. Ischemia-reperfusion generates ROS and oxidative stress. Oxidative stress leads to cell death followed by inflammation. Inflammation leads to tissue injury and more ROS and amplifies tissue injury. Depending on the extent of damage both hypoxia and oxidative stress send signals to autophagy. These signals mediate to survival signal. During this process, TFEB is translocated to the nucleus and induced a series of genes that regulate lysosomal biogenesis as well as autophagy itself, known as CLEAR network. CLEAR network negatively regulate cell death by recycling oxidative stress induced damaged cells and preventing inflammation. Urolithin A reduced IRI induced kidney injury by modulating autophagy and inflammation.

response to kidney injury and autophagy. TFEB is a master regulator and is implicated in cardiac IRI (Godar et al., 2015; Settembre et al., 2013). After translocation of TFEB to the nucleus, it modulated lysosomal and autophagic markers. These findings suggest that TFEB is mobilized to activate CLEAR network and to neutralize various cellular stress due to hypoxia followed by oxidative injury (Fig. 8). TFEB regulated CLEAR network gene by one or more copies of GTCACGTGAC regulatory motif (Sardiello and Ballabio, 2009). Interestingly, we observed that those genes were not only involved in lysosomal complement/biogenesis but also played in autophagic machinery. We observed induction of lysosomal hydrolases Ctsa and Psap, which are regulated by TFEB as shown earlier (Palmieri et al., 2011). These lysosomal hydrolases are required for cellular degradation process in addition to acidification (Klionsky and Emr, 2000). Proton pump accessory gene Atp6ap1 was also induced in response to IRI injury. The lysosomal membrane proteins LAMP1 and LAMP2 consist of 50% of all lysosome proteins and plays roles in the accumulation of autophagic vacuoles, lysosomal appearance, and cholesterol metabolism (Eskelinen, 2006). LAMP1 is also a target of TFEB (Spampanato et al., 2013) and it was induced in kidney IRI. The most interesting aspect of TFEB target genes that those can influence lipid metabolism (glycosaminoglycan degradation, hemoglobin degradation, chitin degradation, and sphingolipid degradation), energy metabolism (glycolysis, TCA cycle), steroid biosynthesis, antigen processing and presentation, signaling pathways (Chemokine,p53, JAK-STAT, insulin *etc.*) and DNA metabolism (Palmieri et al., 2011). Future studies to understand each pathway modulated by TFEB will open new avenues in kidney IRI pathophysiology and therapeutic potential.

It is important to note that TFEB regulates numerous genes that also modulate non-lysosomal proteins involved in lysosomal biogenesis in addition to autophagy. M6pr and Nagpa are members in this category and also part of the CLEAR network. In our study, both of them were induced by IRI and thus demonstrates how IRI involved in restructuring the cells during damage. Our findings of the involvement of TFEB mediated CLEAR network are an important step to an understanding of degradation mechanism and is the first such report demonstrating the exact role of lysosomes during this process.

We also observed two TFEB upregulated genes in response to kidney IRI (Palmieri et al., 2011), which are crucial to autophagy: Beclin1 and vacuolar protein sorting-associated protein 11. Beclin regulates not only autophagy but also apoptosis (Kang et al., 2011). Beclin1 is also modulated by the NF-κB pathway, which is well known for inflammatory modulation (Copetti et al., 2009). The study to understand the link between cell death, autophagy, and inflammation involving NF-κB is beyond the scope of our study.

Autophagy, also known as macroautophagy, is a complex process involving multiple steps (Feng et al., 2014). It starts from phagophore to autophagosome and then to autophagolysosome (Wong et al., 2011). Our data in kidney IRI demonstrated that autophagy including autophagosome and autophagolysosome were involved in the process and one was not excluded from others. Due to complexity by itself and its complex interactions with protein degradation pathway, cell death, autophagy is considered as a double-edged sword (Shintani and Klionsky, 2004). It is important to note that TFEB positively regulates lysosomal biogenesis through the CLEAR network (Settembre et al., 2011). An earlier report that curcumin activates TFEB, which also lead to lysosomal biogenesis (Zhang et al., 2016). Based on our findings, a similar role of urolithin A is a possibility. Our autophagy induced TFEB CLEAR by IRI added a new dimension to that complex process. The interplay of oxidative stress, autophagy and inflammation are also important in kidney IRI like other disease models (Mukhopadhyay et al., 2018).

In this study, we have described the specific alteration in the autophagy pathway occurring in kidney IRI and cause as well as effectors associated with these changes. It is likely that these changes are a compensatory mechanism in response to hypoxia and an oxidative/inflammatory insult to cells. Urolithin A attenuates IRI by modulating these pathways and reduced inflammation and kidney injury. However, the direct role urolithin A as anti-oxidant and anti-inflammatory cannot be excluded. Overall, our results broaden the understanding of autophagy to kidney IRI and those insights may help to develop new therapeutic strategies to protect against IRI.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.110591.

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