Medical & Surgical Urology
ISSN: 2168-9857

Guan et al., Med Surg Urol 2014, 3:2
DOI: 10.4172/2168-9857.1000134

Review Article Open Access

From Humans to Experimental Models: The Cytoprotective Role of Clusterin the Kidney

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Abstract

Clusterin (CLU) is a chaperone-like protein and has been discovered more than thirty years ago; however, its biological significance is still not fully understood. This review aims to summarize the principal observations of CLU roles related to the kidney. In humans, three or more mRNA isoforms of CLU could be expressed due to different translation start sites, but only two forms of CLU protein, secreted (sCLU, isoform 2) and nuclear (nCLU, isoform 1), have been well characterized, whereas there is only sCLU form in mice. In the biopsies of renal tissue from patients, up regulated CLU expression has been found in rejecting kidney transplants or diseased kidneys, and a lower level of serum CLU is correlated with many types of kidney disease in patients. In mice, a deficiency in CLU expression specifically leads to the phenotype of age-dependent chronic glomerular injury - moderate to severe accumulation of the mesangial matrix, becomes more susceptible to ischemia-reperfusion injury (IRI), negatively impacts renal repair after IRI and worsens renal fibrosis after ureteral obstruction. All these observations may imply the biological significance of CLU for the maintenance of the tissue homeostasis in adult kidneys. However, how CLU protects the kidney from injury or by which extracellular and intracellular pathways mediate the cyto-protection of CLU in the kidney has not been well investigated. Understanding of the cyto-protective activities of CLU in the kidney could lead to the development of novel therapeutic strategies for the prevention and/or treatment of kidney injury or diseases.

Keywords: Clusterin; Extracellular chaperone; Kidney disease; Tissue homeostasis

CLU Gene, Isoforms and Cellular Localization

Clusterin (CLU) protein was first discovered more than thirty years ago [1], and a large volume of research has been dedicated to it since – there are more than two thousand publications in Pubmed/NCBI databases when using 'clusterin' as a keyword search criteria today. Human CLU gene (NCBI Gene ID: 1191) is located at chromosome 8p21-p12, and consists of 10 exons, in which the first two exons are alternative (designated 1 and 1') [2]. Thus, CLU gene can be transcribed into at least three mRNA variants (NCBI Reference No.: NM_001831.3; NR_038335.1; NR_045494.1) or perhaps even more [3]. The mRNA isoform 1 is a major form of CLU mRNA, whereas other forms including mRNA isoform 2 collectively count for less than 1% of total CLU mRNA [3]. Two isoforms of CLU proteins have been well characterized; nuclear isoform of CLU (nCLU, isoform 1) containing the nuclear localization signal that is translated due to the splicing at exon 1 and 3 together placing a downstream AUG at exon 3 as the first available translation and lacking of exon 2 [3,4], while pre-secreted isoform of CLU (sCLU) containing the endoplasmic reticulum (ER)-targeting signalencoding in exon 2 [3]. The nCLU is translocated into the nucleus after translation andprobably without glycosylation [3], whereas the pre-secreted sCLU is targeted to ER and Golgi bodies glycosylation and cleavage between Arg-205 and Ser-206 to produce mature sCLU, a secreted disulfide-linked heterodimer of α- and β-chains [5-7]. Under certain stress conditions, sCLU however can be retrotranslocalized into the cytosol instead of secretion [8]. However, the cellular localization of all these isoforms and their expression are largely unknown. Murine CLU gene (NCBI Gene ID: 12759; MGI ID: 88423) is found at chromosome 14, and contains nine exons that are only transcribed to a single mRNA (NCBI Reference No.: NM_013492.2, 1808 bp) [9]. nCLU isoform has not been found in mice as of yet. The homolog of mouse CLU to human sCLU is 75% at the amino acid level, and both have the same ER-targeting signal peptide and the cleavage site [9] (Figure 1). By immunohistological staining using the same anti-CLU α-chain antibody, CLU protein was localized inhuman kidney sections in the same pattern as that of mice (Figure 2). Thus, CLU in mice can serve as a counterpart for sCLU (both extracellular and intracellular) in humans, particularly in the study of the kidney disorders.

In the human body, sCLU is a major glycoprotein in all the physiological fluids such as plasma, milk, urine, cerebrospinal fluid, and semen [6]. It is constitutively produced and secreted by almost all cell types that form the cellular interfaces of fluid compartments [6], and similarly by the liver [10]. The serum levels of sCLU in humans are present in a range of 35-353 μg/mL [11-14]. In tissue, upregulation of CLU expression (probably including nCLU) is associated with many pathophysiological processes, such as neuropathologies [15,16], heart disease [17], cancer [18-20], kidney transplant rejection, and kidney disease including glomerulonephritis [21,22]. In rodents, renal CLU is upregulated following a variety of insults, such as unilateral ureteral obstruction (UUO) and ischemia-reperfusion injury (IRI) [23,24], acute glycerol-induced renal failure, chronic vitamin E and selenium deficiency [25], lupus-like nephritis [26], and in resident glomerular cells exposed to complement-mediated injury [27]. The CLU expression in glomerular mesangial and epithelial cells, as well as renal proximal tubular epithelial cell (TEC) is increased in response to the stimulation of thrombin [28] and hypoxia in our unpublished observations. Further studies indicate that CLU is an apically secreted glycoprotein in renal TECs [29], and is detected in both viable and apoptotic cells following renal injury [23,30]. The molecular mechanism(s) for either constitutive or inducible expression of CLU have not been well investigated. It has been reported that CLU gene proximal promoter contains a 'clusterin element' (CLE) that is specifically bound by heat-shock factor (HSF)

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Received April 21, 2014; **Accepted** May 24, 2014; **Published** May 29, 2014

Citation: Guan Q, Alnasser HA, Nguan CYC, Du C (2014) From Humans to Experimental Models: The Cytoprotective Role of Clusterin the Kidney. Med Surg Urol 3: 134. doi:10.4172/2168-9857.1000134

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1    -MKILLLCVALLLIWDNGMVLGEQEVSDNELQELSTQGSRYINKEIQNAVQGVKHIKTLI   59
1    MMKTLLLFVGLLLTWESGQVLGDQTVSDNELQEMSNQGSKYVNKEIQNAVNGVKQIKTLI   60
      ** *** *.*** *:.* ***:* *********:*.***:*:*********:***:*****

60   EKTNAERKSLLNSLEEAKKKKEDALEDTRDSEMKLKAFPEVCNETMMALWEECKPCLKHT   119
61   EKTNEERKTLLSNLEEAKKKKEDALNETRESETKLKELPGVCNETMMALWEECKPCLKQT   120
     **** ***:**..*************::**:** *** :* ******************:*

120  CMKFYARVCRSGSGLVGQQLEEFLNQSSPFYFWMNGDRIDSLLESDRQQSQVLDAMQDSF   179
121  CMKFYARVCRSGSGLVGRQLEEFLNQSSPFYFWMNGDRIDSLLENDRQQTHMLDVMQDHF   180
     ******************:*************************.****:::**.*** *

180  ARASGIIDTLFQDRFFARELHDPHYFSPIGFPHKRPHFLYPKSRLVRSLMSPSHYGPPSF   239
181  SRASSIIDELFQDRFFTREPQDTYHYLPFSLPHRRPHFFFPKSRIVRSLMPFSPYEPLNF   240
     :***.*** ********:** :* ::: *:.:**:*****::****:*****  * * * .*

240  HNMFQPFFEMIHQAQQAMDVQLHSPAFQFPDVDFLREGEDDRTVCKEIRRNSTGCLKMKG   299
241  HAMFQPFLEMIHEAQQAMDIHFHSPAFQHPPTEFIREGDDDRTVCREIRHNSTGCLRMKD   300
     * *****:****:******:::******.* .:*:***:******:***:******:**

300  QCEKCQEILSVDCSTNNPAQANLRQELNDSLQVAERLTEQYKELLQSFQSKMLNTSSLLE   359
301  QCDKCREILSVDCSTNNPSQAKLRRELDESLQVAERLTRKYNELLKSYQWKMLNTSSLLE   360
     **:**:*************:**:**:**::*********.:*:***:*:* **********

360  QLNDQFNWVSQLANLTQGEDKYYLRVSTVTTHSSDSEVPSRVTEVVVKLFDSDPITVVLP   419
361  QLNEQFNWVSRLANLTQGEDQYYLRVTTVASHTSDSDVPSGVTEVVVKLFDSDPITVTVP   420
     ***:******:*********:*****:**::*:***:*** ***************.:*

420  EEVSKDNPKFMDTVAEKALQEYRRKSRAE   448   Q06890   CLUS_MOUSE
421  VEVSRKNPKFMETVAEKALQEYRKKHREE   449   P10909   CLUS_HUMAN
      ***:.*****:************:* * *
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Figure 1: Sequence alignment between mouse CLU (top sequence) and human sCLU (bottom sequence). The same amino acid residues were underlined with "★". ER-targeting signal peptide (mouse: 1-21; human: 1-22), and the cleavage site (Mouse: R^{226} – S^{227}; human: R^{227}-S^{228}).

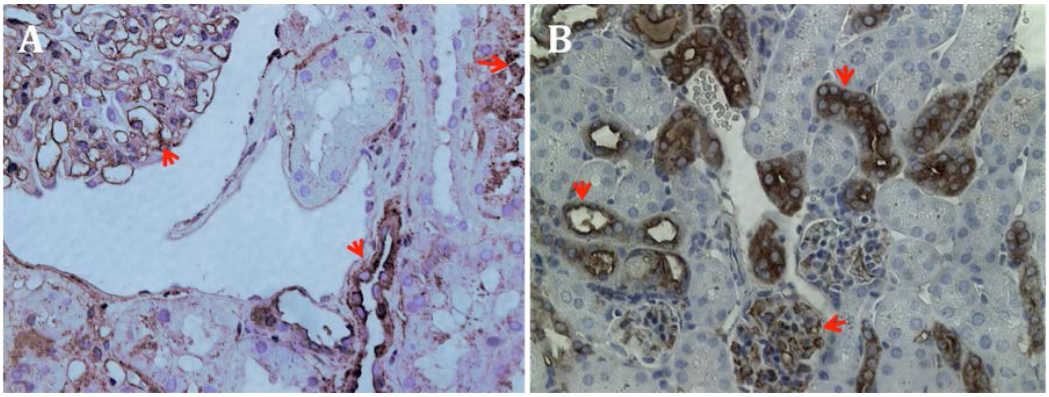

Figure 2: Induction of CLU protein in both tubules and glomeruli following transplant rejection or IRI. Kidney tissues were fixed in 10% buffered formaldehyde, embedded in paraffin, and then sectioned for immunohistochemical staining with goat polyclonal anti-CLU-α (C-18). (A) Biopsy sample of rejecting kidney transplant (Banff 97 grade 1 chronic rejection) from a 15-year old female patient (provided by Dr. Alex Magil, St. Paul's Hospital, Vancouver, BC, Canada). (B) Mouse kidneys with renal ischemia-reperfusion injury. Brown color (also pointed by red arrows): positively stained cells. The data are presented as a typical image from each examination.

1 after heat shock, or by HSF1-HSF2 up on proteasome inhibition [31,32], resulting in the induction of CLU gene transcription.

Biochemistry and Functions of sCLU

The primary structure of sCLU in both α- and β-chain subunits contains several large molten globule domains, amphipathic regions and coiled-coil α-helices [9,33-35], which are typical of molecular chaperone - conformational adaptability to allow CLU protein to bind its substrate proteins or lipids with high affinity and low specificity [35-37]. Furthermore, one study has revealed that the glycosylation of sCLU may not be required for its overall secondary structure content and binding activity to its substrate [38].

The biological activities of extracellular sCLU have been studied extensively; it was initially found to induce cell aggregation [39-41], and in the plasma it inhibited the cytolysis of complement membrane attack complex (MAC) by binding to the complement components [42-44], and was associated with both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) complexes [33,45,46]. These studies suggest that sCLU in the blood may serve not only as an inhibitor of the lytic terminal complement cascade, but also as a regulator of lipid transport and local lipid redistribution. Furthermore, addition of sCLU prevents cell apoptosis in cultured cells treated with TNF-α, H_2O_2 or gentamicin probably by activation of magalin-phosphatidylinositol 3-kinase/Akt pathway [47-49], and mediates clearance of cellular debris into non-professional phagocytes [50].

Based on all of these observations, it has been proposed that sCLU functions as an extracellular chaperone, a previously unknown quality-control system for protein folding that mediates the recognition and disposal of extracellular misfolded proteins via receptor (i.e. megalin)-mediated endocytosis and lysosomal degradation [51]. This hypothesis is supported by a recent study showing that sCLU in the blood binds to a panel of proteins, including ceruloplasmin, fibrinogen, and albumin, in response to physiologically relevant stress [52].

Inside human cells, in addition to nCLU isoform that is mainly localizing in the nucleus and triggers cell death [53], sCLU could redirect to the cytosol under cellular stress [8, 54]. In mice, CLU in normal tissues (heart and kidney) is present as a single protein band at approximately 40 kDa in Western blot analysis in our studies [24,55,56], while in cultured cells from these tissues two protein bands at approximately 60 kDa and 40 kDa are detected [24,55,56], suggesting that mouse CLU probably is also retrotranslocated to the cytosol following exposure to sub lethal stress in culture conditions. A variety of biological activities of intracellular sCLU or cytoplasmic CLU (cCLU) have been reported; it inhibits apoptosis by the interaction with BAX or GRP78 [54,57,58] or promotes cell survival by the activation of Akt and NF-κB pathway [48,59]. It is of much more interest to see that sCLU (~70 kDa) acts as an intracellular chaperone to interact with both ATP7A and ATP7B (Cu-ATPases) and facilitates degradation of misfolded/mislocalized mutant ATP7B [60]. Whether or not intracellular sCLU plays a role in ER quality control machinery that facilitates the degradation of mis/un-folded proteins in ER remains further investigation.

Requirement of CLU for organogenesis

During rodent embryogenesis, CLU expression is detected in a variety of the tissues in many developing organs, such as the epithelial cells of comma and S-shaped bodies of the primordial kidney [61], developing islet of Langerhans of the primordial pancreas [62], myocardial cells adjacent to developing endocardial cushions of both atrioventricular canal and truncusarteriosus, stromal connective tissue throughout leaflet formation of the developing hearts [63], hypothalamic region, neocortex and hippocampus of the developing brain [64,65]. Interestingly however, complete knockout (KO) of CLU expression in CLU KO mice has not been found to cause any phenotypic change in postnatal development as compared to WT mice [66], suggesting that CLU may not be absolutely required for the differentiation and morphogenesis of an organ (i.e. kidney). Although brain weight, neurons, astrocytes and oligodendrocytes are not significantly different between WT and CLU KO mice during postnatal development, it is noted that there is a significant deficit in motor cells (~16%) in the facial nucleus in CLU KO compared with WT mice [64], suggesting that CLU may have a negative impact on neuronal development in certain motor nuclei. Indeed, in cultured progenitor or undifferentiated cells, CLU enhances neuronal differentiation from neural precursor cells [67], and ectopic over expression of CLU significantly up-regulates the expression of morphogenic factor Pdx-1 and Ngn-3 that is correlated with an increase in β-cell transformation from neogenic ductal cells [68], and increases CXCR4 expression and migration of cardiac progenitor cells by [69]. We have recently demonstrated that kidney repair or tissue regeneration is impaired after IRI in CLU KO mice [55], suggesting that CLU may play a key role in the differentiation and migration of renal stem/progenitor cells that have been found to contribute to renal repair after injury [70-72] which however remain elusive.

CLU as a Kidney 'Bodyguard'

The cytoprotection of sCLU in human kidney disease

sCLU in the body fluids has been reported to bind to MAC component(s) [42-44], all types of immunoglubins, particularly aggregated IgG [73], and lipoprotein particles [33,45,46]. In renal biopsies from all forms of kidney disease, the terminal complement complex is identified, at least partly, in sCLU-SC5b-9 complex both in the specific immune glomerular deposition and in the "non-specific" deposition in areas of renal injury [11,21,74,75], and glomerular CLU is co-localized with LDL receptor (LDR-R) in patients with membranous glomerulonephritis (MGN) and is associated with a reduction of proteinuria after a follow-up of 1.5 years [74]. In patients' sera, sCLU levels are markedly lower with active membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), and in children with steroid-responsive nephritic syndrome (NS) compared to controls [76]. So far, the role of sCLU in the pathogenesis of human kidney disease has not been well investigated. Saunders et al. [77] have reported that perfusion with sCLU-depleted plasma from patients with Heymann nephritis induces glomerular injury and significantly greater proteinuria in an isolated rat kidney model, and sCLU prevents MGN serum-activated cellular stress in cultured podocytes [74]. All these observations may uncover an important role for serum sCLU in the protection of the kidney fromplasma-induced injury, which however remains further investigation.

An emerging hypothesis suggests that extracellular chaperones (ECs) including sCLU likely patrol biological fluids for misfolded proteins and facilitate their clearance via endocytic receptors to maintain protein proteostasis in fluids such as plasma [51,78,79]. If this hypothesis is correct, sCLU may protect the kidney from injury by at least two mechanisms: First, extracellular sCLU may facilitate the clearance of mutant, misfolded or unfolded proteins that are the result of immune activation and/or direct nephrotoxicity. Hence, a lack of sCLU or the imbalance of sCLU to "nephrotoxic" proteins will result in the aggregation/deposition of these proteins in the kidney and cause kidney damage. Indeed, a high level of aberrantly glycosylated IgA1 and its associated immunocomplexes induce glomerular injury, and are a pathogenic factor for the development of IgA nephropathy [80-83], and extracellular mis-/unfolded amyloidogenic "precursor proteins", such as serum amyloid A, apolipo protein AII, and Ig light/heavy, form amyloid fibril deposition in the kidney, causing kidney injury and failure (amyloidosis-associated kidney disease) [84]. Second, extracellular sCLU may be required for the efficiency of the kidney in metabolic clearance of proteins. It has been recognized previously that the kidney is responsible for 30% to 80% of the metabolic clearance of protein/peptide 'waste' in the plasma [85,86], and recently, Wilson et al. has demonstrated that proteins injected into rats are cleared more rapidly from circulation when complexed with sCLU [79], suggesting that in low sCLU states, the inefficiency of the metabolic clearance of protein waste will induce cellular stress in the kidney, resulting in the disturbance of tissue homeostasis. Further experimental studies are needed to confirm this novel observation.

CLU and kidney injury in animal models

The effort to understand the role of sCLU in the pathogenesis of kidney disease using CLU KO mice has been carried out by our lab and others. Total knockout CLU expression in mice does not change their phenotype [66]; organ development and reproduction in young CLU KO mice are not different from wild type (WT) mice. However, by 21 months of age, up to 75% of glomeruli in CLU KO mice exhibit moderate to severe mesangial lesions - the accumulation of the

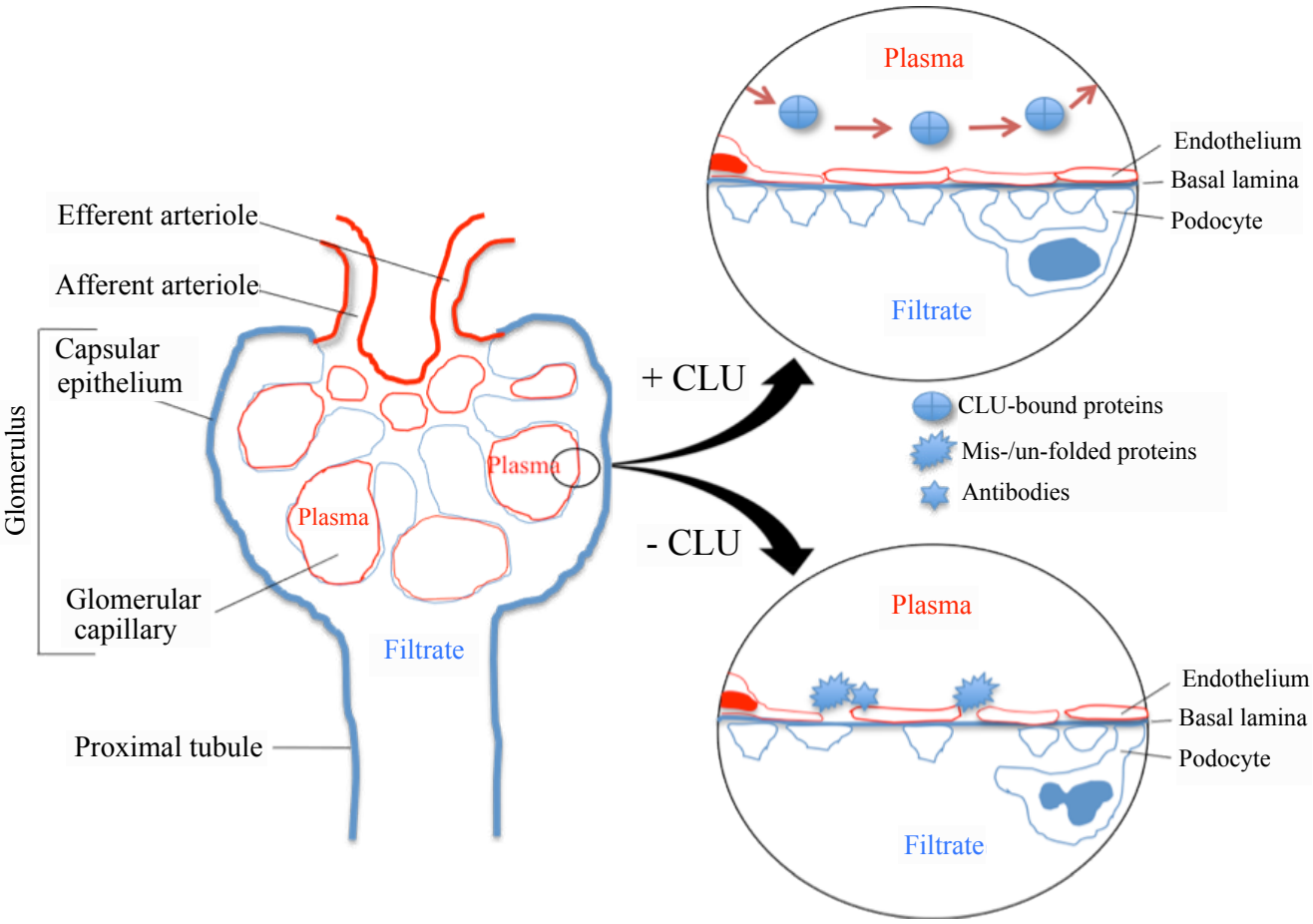

Figure 3: A simple scheme of hypothesis for the cytoprotection of sCLU in the kidney. Under normal condition or when physiological stress is minimal (+ CLU), sCLU in the plasma acts as a non-specific extracellular chaperone for all kind of mutant, misfolded and unfolded proteins, and prevents autoimmune response to and renal deposition of these 'nephrotoxic' proteins. Serum sCLU may also facilitate the protein clearance and intracellular sCLU maintains tissue homeostasis in the kidney. When the physiological stress is increased or under certain pathological condition (- CLU), misfolded and/or unfolded proteins are up-regulated both in the plasma and inside the cell. As a result, there is not enough sCLU to neutralize the accumulation of these proteins – leading to the immune activation and the deposition of these proteins in glomerular capillaries, and renal cell death via ER stress.

mesangial matrix and the presence of intra mesangialtubulo-fibrillary structures as compared to little or no glomerular injury in WT controls [87]. Furthermore, the immune complexes of IgG, IgM, IgA, and in some cases C1q, C3, and C9 in the glomeruli could be detectable as early as 4 weeks of age of CLU KO mice, and these immune complex lesions can be induced as early as 3 months of age by unilateral nephrectomy [87]. The phenotype of age-dependent glomerular injury in CLU KO mice clearly suggests the biological significance of CLU for tissue homeostasis of the kidney. Recently, we and others have demonstrated that following renal IRI or UUO, renal CLU expression is up-regulated [24,55,88], and the lack of CLU expression in the kidneys worsens IRI [24], impairs renal tissue repair after IRI [55] and accelerates renal fibrosis or increases the levels of plasminogen activator inhibitor (PAI)-1, type I collagen, and fibronectin in response to obstruction [88]. These results may suggest that upregulation of CLU during renal injury is a protective response that may prevent cell death during IRI, facilitate renal tubular cell proliferation for renal repair after IRI, and maintain renal tissue homeostasis against the development of renal fibrosis. These observations suggest there is still much to learn about the role of sCLU in development various kidney pathologies. Further studies by using CLU KO mice as a negative control to investigate the cytoprotection of CLU in the kidneys of WT mice are needed.

Conclusion

The study of CLU in acute kidney injury and chronic kidney disease is but one segment of a host of additional biomedical research fields such as cancer, cardiovascular disease and Alzheimer's disease, which are actively studying the role of CLU since it was discovered more than 30 years ago. Accumulating evidence in the literature reveals the chaperone activity of sCLU in both extracellular and intracellular fluids to maintain the protein proteostasis, by which sCLU could protect the kidney from injury (Figure 3). We believe that further understanding of the role of sCLU in the development of kidney disease is required and may help to develop therapeutic strategies specific for the prevention or treatment of a variety of renal pathological states.

Acknowledgements

This study was supported by a grant of the Kidney Foundation of Canada. HAA was a graduate student supported by the scholarship from King Saud University (Riyadh, Saudi Arabia).

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