Multi-faceted roles of cathepsins in ischemia reperfusion injury (Review)

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Abstract. Cathepsins are one of the most abundant proteases within the lysosomes with diverse physiological effects ranging from immune responses, cell death and intracellular protein degradation. Cathepsins are involved in extracellular and systemic functions such as systemic inflammation and extracellular matrix degradation. Ischemia reperfusion (IR) injury is responsible for numerous diseases including myocardial infarction, acute kidney injury, stroke and acute graft failure after transplant surgery. Inflammation plays a major role in the reperfusion phase of IR injury and previous research has shown that cathepsins are key mediators of the inflammation cascade as well as apoptosis. Taken together, cathepsins modulation could provide potential therapeutic approaches to attenuate IR injury. The present review summarized the current understanding of various cathepsin subtypes, their major physiologic functions, their roles in multi-organ IR injury and detailed selective cathepsin inhibitors with therapeutic potential.

Contents

1. Introduction

Cathepsins are proteases involved in multiple physiological roles ranging from ion channel activity, apoptosis, autophagy, immune regulation and complement system activation. They are divided into several subtypes-serine cathepsins, cysteine cathepsins and aspartic cathepsins (1). Various pathologies that can be attributed to dysregulation of cathepsins include pancreatitis, acute and chronic kidney disease, arthritis, auto-inflammatory diseases, stroke and IR injury.

Lysosomes are responsible for catabolism and recycling of multiple macromolecules and are key degradative compartments in the cell. There are two major proteins that mediate lysosomal activity; lysosomal membrane proteins and lysosomal hydrolases including the cathepsins (2). Their activity is facilitated by the acidic lysosomal environment. In addition to intracellular functions, cathepsins exert extracellular roles in proteolysis, antigen activation, extracellular matrix remodeling and tumor invasion (3,4).

Lysosomal membranes are vulnerable to IR injury and oxidative stress (5). The damage to these structures results in the release of cathepsins into the intracellular space and this can occur through two distinct pathways-lysosomal membrane permeabilization or lysosomal rupture. The release of these cathepsins have been described to play keys roles in both necrosis and apoptosis (6). IR injury is the mechanism by which multiple pathologies originate, such as: myocardial infarction, stroke, acute kidney injury and acute graft failure in transplant surgery. This review focuses on the roles of various cathepsin subtypes and IR injury across different organ systems.

In mammals, there are 3 classes of cathepsins based on the amino acid each specific cathepsin breaks down including serine cathepsins, cysteine cathepsins and aspartic cathepsins (1). Of these subtypes, serine and cysteine cathepsins are most abundant (7).

2. Cysteine cathepsins

There are at least 11 cysteine cathepsin subtypes in mouse and human cells (B, C, F, H, K, L, O, S, V, W and X)-all of which have specific roles, but some share similar functions creating a system with certain redundancy (3).

Cathepsin B is one of the most abundant cysteine cathepsins within the lysosome. It also is the most stable protease at physiological pH which translates to its excellent ability to function outside the lysosome in the cytoplasm and in the extracellular space (8). Cathepsin B also plays a major role in apoptosis (8). Cellular injury leads to lysosomal permeabilization or rupture leading to Cathepsin B release which in turn causes degradation

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of Bid (BH3-interacting domain death agonist, pro-apoptotic member of Bcl-2 protein family) resulting in its activation and translocation into the mitochondria with subsequent mitochondrial cytochrome c release and caspases 3 and 9 activation (9). Cathepsin B also regulates inflammation via NLRP3 (NOD-leucine rich repeat and pyrin containing protein 3) inflammasome activation (10). NLRP3 inflammasome is a critical component of the innate immune system, has multiple activators, such as, SiO_2, MonoSodium Urate (MSU), calcium pyrophosphate dehydrate crystals, nigerecin and ATP, upon stimulation of these activators, NLRP3 is able to form a transient complex with Cathepsin B which causes the inflammasome to recruit and activate pro-inflammatory caspase 1 and cytokines IL-1β and IL-18 (11). Moreover, the NLRP3 inflammasome complex modulates kidney inflammation due to renal IR injury (12).

Cathepsin C cleaves protease zymogens to their active form. Among the proteases cleaved by Cathepsin C are elastase, proteinase 3, neutrophil serine protease 4, chymase, tryptase, granzymes A and B (13). These proteases have been linked to causing early primary lung graft dysfunction in transplant patients (14).

Cathepsin L like Cathepsin B is abundant in the lysosomes and can cleave Bid directly promoting cytochrome c release to initiate apoptosis. It also shares similar molecular structure to Cathepsin B, explaining redundancy in various physiological functions. One of the more prominent roles for Cathepsin L is its role in autophagy; specifically, degradation of the autophagosome as Cathepsin L knockout mice have pathological accumulation of autophagosomes (15).

Cathepsin S is expressed in antigen presenting cells (16). In addition, it is known to cleave receptor-interacting protein 1 kinase in macrophages; a crucial step in necroptosis (16). Moreover, Cathepsin S has similar ability as Cathepsin B to upregulate inflammasome activity and cleave IL-1β suggesting a redundant system of regulation (10). It also has a role cleaving extracellular matrix proteins; collagen, laminin, and elastin. These peptides and their fragments increase inflammation by macrophage chemotaxis (17).

Cathepsin X is highly expressed in monocytes and macrophages (18). It has a role in phagocytosis and immune regulation (19). It cleaves neuron specific enolase which shows evidence that can regulate neuronal cell survival and death after IR injury (20). Lastly, Cathepsin X plays a role in cell adhesion via integrin's which are cell adhesion molecules; specifically, β_2 integrin; which can play role in both phagocytosis and T-cell activation (21).

Cathepsin W is mainly expressed in cytotoxic T lymphocytes and Nature Killer (NK) cells and is upregulated via IL-2 (22). There is some debate as to whether Cathepsin W has an important functional role in cytotoxicity, given mixed reports on this subject; some stating that Cathepsin W is upregulated in Cytotoxic NK cells (23); whilst others report inhibition of Cathepsin W showed no changes in cytotoxicity (24).

3. Aspartic cathepsins

Cathepsin E is mainly found in dendritic cells, microglia and macrophages and has a role in regulating endosomal/lysosomal microenvironment and protein sorting in these compartments (25). Multiple studies also show that it can play a role in MHC-II mediated antigen processing, which enhances the inflammatory response in the reperfusion phase of IR by increased tumor necrosis factor α (26,27). Intracellular functions of some cathepsins are summarized in Fig. 1.

Cathepsin D plays a role in MHC-II (Major histocompatibility complex class II) mediated antigen presentation to $CD4^+$ cells responsible for initiating antigen-specific immune response, similar to Cathepsin E and B (28). In addition, Cathepsin D shares a redundant function alongside Cathepsin L in autophagy for its role for initiation, autophagosome formation and fusion with lysosomes this is evidenced due to Cathepsin D upregulation in Cathepsin L knock out mice (10). Similar to Cathepsin B; Cathepsin D has been implicated in degradation of Bid, thus initiating apoptosis (29). Furthermore, Cathepsin D has been implicated in initiating apoptosis via caspase-8 activation (30); specifically in T cells it activates Bax, releasing cytochrome c and apoptosis-inducing factor; this process initiates apoptosis independent of Bid (31).

4. Serine cathepsins

Cathepsin A (also known as Lysosomal Protective Protein) regulates blood pressure via regulation endothelin-1 (ET-1) a potent vasoconstrictor and forms part of the elastin-binding complex which is responsible of the biogenesis of elastin fibers (32). Furthermore, upregulation of Cathepsin A can degrade peptide hormones such as bradykinin and angiotensin II, both which promote release of norepinephrine and enhance arrhythmias in myocardial IR (33). Cathepsin A in cardiac tissue shows a potential role in IR injury associated pathologies.

Cathepsin G is expressed primarily in myeloid cells including neutrophils (34). It regulates inflammation via modification of chemokine, cytokines and cell surface receptors by proteolytic modification (35). In addition, it's able to alter the permeability of both epithelial and endothelial cells (36). Cathepsin G is able to promote migration of antigen presenting cells, neutrophils and monocytes via changing both chemokine ligand 5 and 15 into their more potent chemotactic forms (37); furthermore it cleaves chemokine ligand 23, resulting in a more potent form able to attract both monocytes and neutrophils *in vitro* and able to attract leukocytes *in vivo* (38). Moreover, it stimulates monocytes to release soluble CD23 (low-affinity receptor for IgE) fragments from $CD23^+$ B cells, which produce oxidative burst and pro-inflammatory cytokines (39). These immune functions make Cathepsin G a good target for therapy against IR injury. Summarized functions of cathepsins are listed in Table I.

5. Roles for cathepsins in ischemia reperfusion (IR) injury

Cerebral ischemia reperfusion injury. The ischemic phase of a stroke not only can cause irreversible damage, but after treatment the reperfusion phase is capable of further enhancing neuronal cell death, brain edema even hemorrhage (40). Multiple studies have shown the role of cathepsins in brain IR, specifically their function in inducing neuronal cell death. Cathepsins B, L and D have been the major proteases studied after seeing major increases in their levels in the hippocampus after induction of experimental cerebral IR (41). Cathepsin

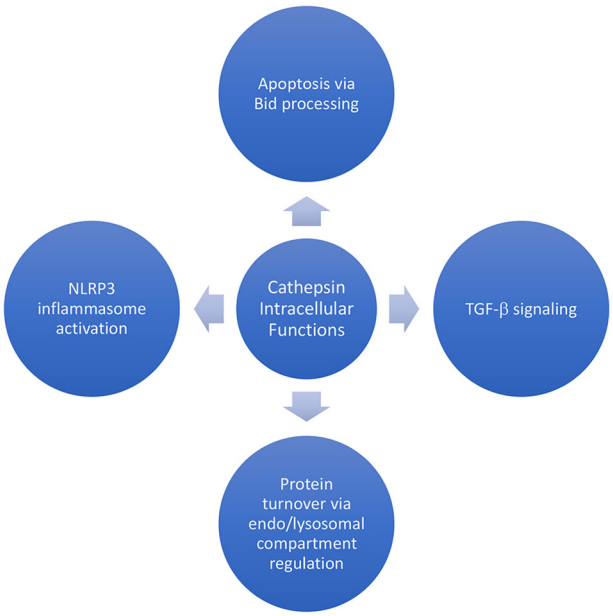

Figure 1. Cathepsin intracellular functions. Cathepsin B has been extensively linked to NLRP inflammasome activation (10-12) and degradation Bid which activates mitochondrial cytochrome c release and caspase 3 and 9 activation to induce apoptosis (8,9). Cathepsin E has been described to play a role in protein turnover in the endo/lysosomal compartment which in turn plays a role in antigen presenting cells (25). Cathepsin S is described to potentially regulate TGF-β signaling in post-myocardial infarcted tissue in regulating post-infarction left ventricular remodeling (63). NLRP3, NOD-leucine rich repeat and pyrin containing protein 3.

Table I. Cathepsin function summary.

Cathepsin	Cathepsin type	Function
Cathepsin B	Cysteine	• Apoptosis via Bid cleaving (9) • NLRP3 inflammasome activation (10)
Cathepsin C	Cysteine	• Zymogen cleaving (elastase, proteinase 3, neutrophil serineprotease 4, chymase, tryptae) (13)
Cathepsin L	Cysteine	• Apoptosis via Bid cleaving (15) • Autophagy (15)
Cathepsin S	Cysteine	• Necroptosis (16) • Upregulate inflammasome activation via cleaving IL-1β (10)
Cathepsin X	Cysteine	• Phagocytosis (19) • Cleaves neuron specific enolase (20) • Cell adhesion via β_2-integrin regulation (21)
Cathepsin W	Cysteine	• Upregulates IL-2 (22)
Cathepsin E	Aspartic	• Regulates endosomal/lysosomal microenvironment (25) • MHC-II mediated antigen processing (26)
Cathepsin D	Aspartic	• MHC-II mediated antigen processing (28) • Autophagy (10) • Apoptosis via Bid cleaving (29) • Caspase-8 and Bax activation (30,31)
Cathepsin A	Serine	• Blood pressure regulation via endothelin-1 regulation (32) • Norepinephrine release via degrading bradykinin and angiotensin II (33)
Cathepsin G	Serine	• Regulates inflammation (35) • Regulates chemokine ligand 5, 15, and 23 (37,38) • Modulates CD 23 fragment release (39)

NLRP3, NOD-leucine rich repeat and pyrin containing protein 3; MHC-II, major histocompatibility complex class II.

B has been heavily implicated in a potential role to induce apoptosis via TNF-α and cytochrome c release (42,43). Several cathepsin inhibitors attenuate cerebral IR injury including E64d (aloxistatin, cathepsin B/L inhibitor), CA-074me (membrane permeable cathepsin B inhibitor), Ginkgolide-B (Ginkgo biloba derivative, showed reduced Cathepsin B/L activity), Cysteine Protease Inhibitor 1 (CP-1, cathepsin B and L inhibitor), Probenecid (gout medication, showed reduced cathepsin B activity), Sevoflurane (volatile anesthetic, showed reduced cathepsin B activity), Propofol (intravenous anesthetic, showed reduced cathepsin B/D activity) and Tomatidine (green tomato extract, enhanced cathepsin B/D activity) (5,41,44-49). Furthermore; the specific mechanism responsible for the release of cathepsins in the brain come from lysosomal membrane permeabilization or lysosomal membrane rupture (50). In terms of mechanisms of cathepsins in cerebral IR injury, there is evidence that Heat shock protein 70 (Hsp70) and Lysosome Associated Membrane Protein 1 and 2 (LAMP-1/2) are major players in maintaining lysosomal membrane stability; therefore, preventing major cathepsin leakage which can have the potential to attenuate cerebral IR injury in addition to other organ systems IR injuries (51-53).

Cardiac ischemia reperfusion injury. Myocardial ischemia is one of the leading causes of death in the world, the earlier the ischemic period is treated results in better prognosis; yet the reperfusion phase is responsible for another sequela of stressors such as myocardial stunning, inflammation, apoptosis, necrosis and microvascular obstruction (54,55). The inflammatory damage that occurs in the early reperfusion period is mediated by early activation of neutrophils and mast cells, which their products serve as major chemoattractant for other leukocytes (56,57). Cathepsin G has been

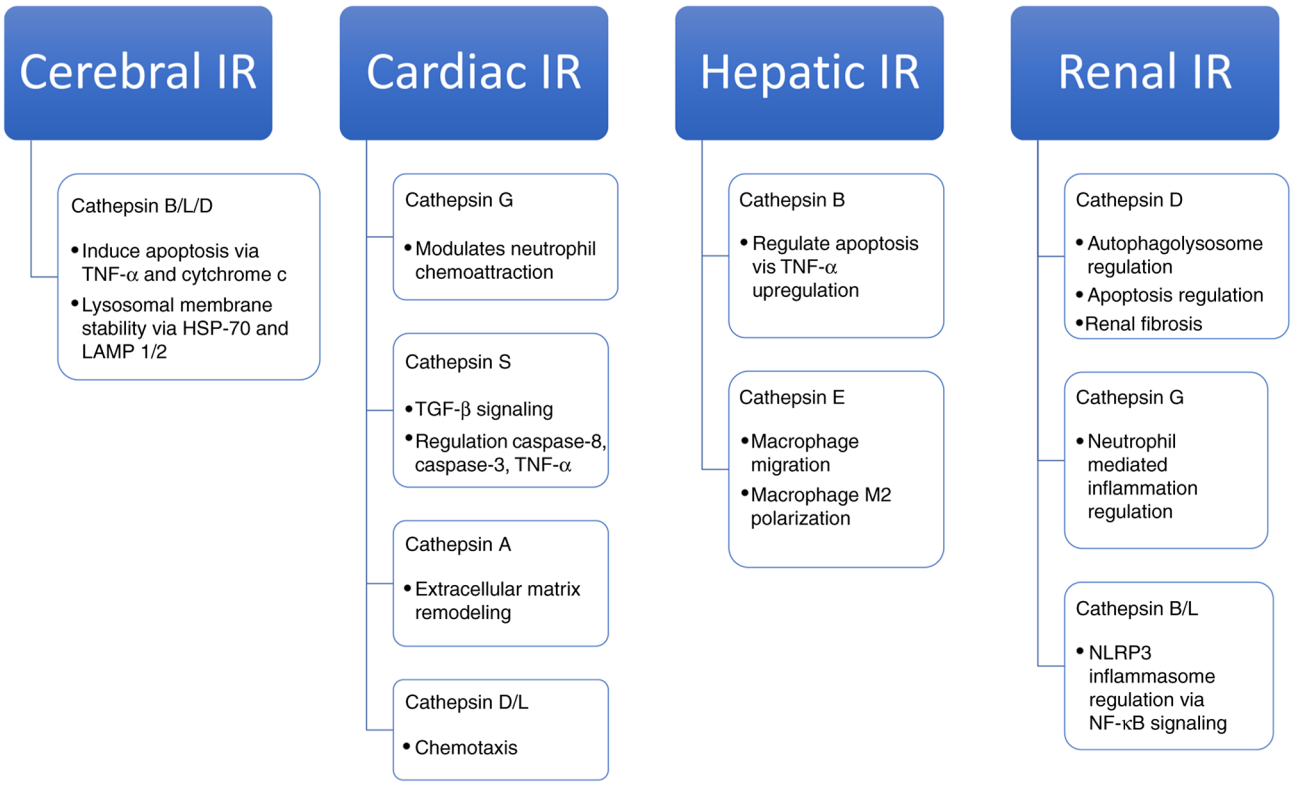

Figure 2. Roles of cathepsins in ischemia-reperfusion injury by organ system. IR, ischemia reperfusion. NLRP3, NOD-leucine rich repeat and pyrin containing protein 3; HSP70, heat shock protein 70; LAMP1/2, lysosome-associated membrane protein 1 and 2.

shown to be a modulator for neutrophil chemoattractant along with the ability to cause morphological changes that disrupt focal adhesion and intracellular contacts in cardiomyocytes (58-60). Inhibition of Cathepsin G with DCCI (dual cathepsin G and chymase inhibitor) attenuated collagen deposition within the myocardium, marked improvement in left ventricle (LV) function, implicating that these could decrease further progression of heart failure (61). Cathepsin S has also been linked with LV remodeling post ischemia specifically as a potent protease in degrading collagen and fibronectin (62,63). Furthermore, Cathepsin S inhibition preserves LV function via TGF-β1 signalling, myofibroblast trans-differentiation and extracellular matrix (ECM) synthesis (63) and possible role in apoptosis and inflammation via regulation of caspase 8, caspase-3 and TNF-α (64). Similarly, Cathepsin A has shown a role in atrial fibrosis via potential in ECM remodeling (65). In addition, Cathepsin A inhibition in cardiac IR preserved greater LV viable myocardium, along with reduced ECM remodeling which in turn decreased the risk of developing arrhythmias, specifically atrial arrhythmias (66). Moreover, both Cathepsins D and L have been studied in conjunction for their potential role in degradation of myofibrillar proteins, specifically in IR injury via coronary artery bypass graft (CABG); which demonstrated increased levels of both D and L occur in the intralysosomal compartment during the ischemic period vs. increased levels in the extralysosomal compartment during reperfusion phase; indicating their potential for being chemoattractant in the reperfusion period (67,68). Taken together, cathepsins seem to share a system of roles in ECM remodeling specifically for cardiac IR injury, furthermore linking all the cathepsins in a potential redundant role.

Hepatic ischemia reperfusion injury. Hepatic IR is the major cause for primary non-function of liver grafts after liver transplantation, hemorrhagic shock and liver resections (69). Moreover, Cathepsin B and its link to the lysosomal pathway of apoptosis via TNF-α upregulation has been found to play a large role in hepatic IR, where studies of both pharmacological and gene knockout have shown to attenuate apoptosis (70,71). Similarly, Cathepsin E knockout mice in combination with TGR5 (G-protein coupled bile acid receptor) deficiency have attenuated hepatic IR injury by restraining macrophage migration and facilitating macrophage M2 polarization (72).

Renal ischemia reperfusion injury. Renal IR injury is a major cause of acute kidney injury (AKI) (73). Patients undergoing cardiac, vascular or transplant surgeries have significantly elevated risks of developing AKI via renal IR injury (74) this in turn can lead to extra-renal systemic complications resulting in other organ system dysfunctions which can increase mortality (75). Multiple studies on Cathepsin D and renal IR have produced various results in its role; using Cathepsin D deficient renal tubular epithelial knock out mice found increased sensitivity against renal IR with marked increase of multiple inflammation markers, it concluded that Cathepsin D role in autophagolysosome regulation contributed to tolerance against renal IR (76). In contrast, Cathepsin D inhibition with Pepstatin A attenuated multiple inflammatory markers, apoptosis and renal fibrosis (77,78).

Furthermore, renal transplant biopsies showing acute tubular necrosis had increased levels of Cathepsin D in damaged tubular cells (77). Moreover, Cathepsin D was not only implicated in its potential roles in apoptosis, but also in collagen turnover due to reduced renal fibrosis formation due to renal IR (77). Cathepsin G deficient mice subjected to renal IR had a precipitous reduction in inflammatory response after 24 h as well as decreased collagen deposition 30 days after renal IR, this study concluded that Cathepsin G plays a role in sustaining neutrophil-mediated inflammation for a longer time (79). Furthermore, Cathepsin B and Cathepsin L downregulate NF-κB signaling which resulted in reduced NLRP3 inflammasome activation and attenuation of renal IR injury (12). Taken together, Cathepsins have potential roles in not only acute phase of AKI, but also long term effects like renal fibrosis due to IR injury.

6. Summary

Taken together, cathepsins are proteases with various roles ranging from apoptosis, immunity and metastasis. Serine, cysteine and aspartic cathepsins share among them some similar structural and physiological roles, yet also have distinct differences. The role of cathepsins in IR injury has gained attention biomedical research, establishing them as potential pharmacological targets. In summary, cerebral IR injury the cathepsins most studied were B, L and D; for cardiac IR were cathepsins G, S, A, D and L; hepatic IR cathepsins B and E; and renal IR were cathepsins D, G, B and L. Summarized roles of cathepsins in different organ systems are mentioned in Fig. 2. However, multiple cathepsins are yet to be studied under different IR models, future research should focus to test other cathepsin targets and understanding the specific pathway involvement of cathepsins in IR injury across multiple organ systems. Specifically, test cathepsins C, X and W which have been associated with different mechanisms within the immune system and inflammation, both components of IR injury. Furthermore, there is a need to investigate cathepsins F, H, K, L, O and V in the setting of inflammation or other components of the immune system to see if there is potential to them being also researched in the setting of IR injury.

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Availability of data and materials

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Authors' contributions

JH acquired, analyzed and compiled all cathepsin articles pertaining to ischemia reperfusion injury and manuscript drafting. HTL contributed to manuscript drafting, critical revisions of intellectual content and approved final manuscript version to be published. Both authors have read and approved the final manuscript. Data sharing is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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