Spatial localization of cathepsins: Implications in immune activation and resolution during infections

Elsa Anes*, David Pires, Manoj Mandal and José Miguel Azevedo-Pereira

Host-Pathogen Interactions Unit, Research Institute for Medicines, iMed-ULisboa, Faculty of Pharmacy, Universidade de Lisboa, Lisboa, Portugal

Cathepsins were first described, as endolysosomal proteolytic enzymes in reference to the organelles where they degrade the bulk of endogenous and exogenous substrates in a slightly acidic environment. These substrates include pathogens internalized via endocytosis and/or marked for destruction by autophagy. However, the role of cathepsins during infection far exceeds that of direct digestion of the pathogen. Cathepsins have been extensively investigated in the context of tumour associated immune cells and chronic inflammation. Several cathepsin-dependent immune responses develop in the endocytic pathway while others take place in the cytosol, the nucleus, or in the extracellular space. In this review we highlight the spatial localization of cathepsins and their implications in immune activation and resolution pathways during infection.

KEYWORDS
cathepsins, infection, inflammation, innate immunity, adaptive immunity, immune resolution

Introduction

The term cathepsin (CTS) was initially used to refer to eleven human lysosomal proteases namely CTSs B, C (J), F, H, K, L, O, S, V (L2), X (P,Y,Z), and W (lymphopain) [reviewed in (1–3)]. They all belong to the group of cysteine cathepsins named after the presence of a cysteine amino acid residue on their catalytic site responsible for hydrolysis of peptide bonds (3). In addition to cysteine cathepsins, aspartic cathepsins D and E and serine cathepsins A and G, were also introduced into the lysosomal CTS family (4, 5).

CTS are synthesized as procathepsins and are targeted to the lumen of the endoplasmic reticulum (ER) via a signal peptide. They are later modified in the Golgi, being tagged for lysosome sorting, usually via mannose-6-phosphate receptors (MPR)
(6–8). The tagged procathepsins are either directly or indirectly sorted to endosomes/lysosomes after escaping MPR and being secreted out of the cell (9–11). Around 5% of all CTSs are secreted out of the cell by the regular biosynthetic/secretory pathway (12).

Innate immune cells, such as macrophages, are able to rescue some of these extracellular CTSs to the lysosomes by expressing the cation-independent mannose 6-phosphate scavenger receptor (CI-MPR) (7, 8). There, in the low pH of the late endocytic vesicles they are processed and activated to the mature form (13).

Indeed, immune cells such as macrophages, neutrophils, natural killer cells or cytotoxic CD8+ T-lymphocytes, can store CTSs either in endocytic lytic granules or in secretory lysosomes, where exocytosis leads to delivery of CTS or their processed products to the extracellular environment (14, 15).

Lysosomal enzymes were also found in less common locations, such as the cytosol and the nucleus (16–20). The cytosolic release of mature CTS is observed as a consequence of controlled lysosomal membrane permeabilization (LMP) or as a result of a more drastic damage (15, 21). Regarding the trafficking of CTS to the nucleus, this is mostly a diversion from the biosynthetic pathway, through mechanisms involving alternative translation initiation of the nascent protein lacking a signal peptide targeting the ER (22). Another described mechanism is exon skipping that generates truncated CTS with modified signal sequences, enabling the retention in the cytosol (23) or their nuclear targeting (24).

In this mini review, we will present recent advances in the understanding of the spatial localization of CTS and their implications during immune responses to infections. A general schematic representation is depicted in Figure 1.

**Cathepsins in the endocytic pathway**

**Phagocytosis and autophagy**

CTS perform major roles in phagocytosis/endocytosis and autophagy which are important cell autonomous immune mechanisms common to all cells (25). These innate mechanisms are prominent in professional phagocytes such as macrophages, and neutrophils, which constitute the first line of defense against pathogens. CTS mediate the destruction of these pathogens due to their proteolytic activity at low pH, within the reducing environment of endolysosomes (26). It is not surprising that intracellular pathogens evolved virulence determinants to subvert the microbicidal mechanisms mediated by endolysosomal CTS as is the case for *Mycobacterium tuberculosis* (27–29), as well as for *Salmonella*, *Brucella*, Legionella or Chlamydia (30–33) or *Francisella novicida* (34). Autophagy intercepts the endolysosomal pathway (34–36) and may drive free cytosolic pathogens for destruction in lysosomes (37) or pathogens contained in vesicles (25, 38); both processes involving their entrapment in septin cages (39).

Indirectly, CTS regulate autophagy and may compromise intracellular pathogen clearance with direct implications on inflammation resolution and cell homeostasis (40–42). CTS S is required for autophagolysosome fusion events and its depletion results in accumulation of defective autophagosomes (43). CTS B suppresses the activity of a transcription factor required for expression of autophagy-related proteins (Atgs) by digestion of a calcium channel in the lysosomes (34). Also, the stimulation of the autophagy protein microtubule associated protein 1A/1B light chain 3...
(LC3) is compromised by CTS K downregulation of endosomal TLR9 (44).

Pattern recognition receptors and cytokine activation

Innate immune receptors, such as Toll-like receptors (TLRs), detect pathogen-associated or cell damage associated signatures (PAMPs or DAMPs) leading to secretion of inflammatory cytokines such as IL-1β and TNFα. CTS interfere with both mechanisms. CTSs B, L, F or S, by cleaving and processing the ectodomains of endosomal TLRs such as 3 and 9, allow recognition of nucleic acids from endocytosed pathogens (44–48). The ectodomain cleavage represents a strategy to restrict receptor activation to endolysosomal compartments and prevent TLRs from responding to self nucleic acids (48).

CTS activity was demonstrated to either directly activate or inhibit inflammatory cytokines. While spatial localization in endosomes was not clarified, CTS B has been shown to be required for posttranslational processing and trafficking of TNFα (49) containing vesicles, and their secretion in response to TLRs 2, 4 and 9 stimulation (50). IL-1β is a potent inflammatory cytokine that needs to be tightly controlled (51, 52). Several CTS are involved in IL-1β processing in the cytosol. However, in monocytes, which are professional IL-1β producers, caspase-1 and pro-IL-1β coexist with CTS within special secretory endolysosomes (53, 54). This colocalization in vesicles located in the periphery of the cell suggests a less acidic and degradative environment (55) and seems to provide a regulatory mechanism of CTS over the amount of caspase-1 and IL-1β that are secreted by monocytes. In conventional endolysosomes, IL-1β and their precursors are normally degraded. Thus, the lysosomal pathway mediates IL-1β secretion but also provides a shutdown mechanism when IL-1β secretion is no longer needed (53, 54). Moreover, the autophagic removal of IL-1β cell activators, such as intracellular DAMPs, NLRP3 inflammasome components, and cytokines, in lysosomes contributes for deactivating the inflammatory responses (56). Cathepsins as degrading proteases in lysosomes are major players in this inflammation resolution.

Activation of other proteases

During innate immune responses, neutrophils are cells involved in extracellular and intracellular pathogen clearance. Their effector functions depend on the activation of azurophil granules, serine proteases such as CTS G, granzymes, and elastase, all synthesised as inactive zymogens and activated by CTS C (57). Regulation of these neutrophil serine proteases activation is tightly controlled by sustained inhibition of CTS C through its natural inhibitor, cystatins (57).

In natural killer cells (NK cells) or in cytotoxic T lymphocytes (CTL), CTS C is responsible for the activation of progranzymes, generating granzymes A and B in secretory lysosomes (58). After immune activation they are processed and delivered out of the cell, where they induce apoptotic death of infected cells (58). CTS B is particularly relevant for protecting CTLs from their cytotoxic cargo (59). In addition, granzyme B is involved in regulating the function and maintenance of helper T cell populations (60). In regulatory T lymphocytes, activated granzymes can eliminate autologous effector cells by apoptosis, indicating an important role accomplished by Treg cells in exerting their anti-proliferative effects leading to immune resolution (61).

T lymphocytes priming and polarization

During adaptive immune responses, T lymphocyte priming by antigen-presenting cells (APCs) requires the recognition of processed antigenic peptides bound to major histocompatibility complex (MHC). CTS are crucial for the generation of these antigenic peptides from exogenous antigens in the endocytic pathway, and thus for CD4+ T lymphocytes priming. Furthermore, MHC class II requires CTS mediated proteolysis for degradation of the invariant chain (II) that blocks MHC class II molecule peptide binding site (62, 63). CTSs S, F, and L are cysteine proteases particularly implicated in these processes, with Cts S and F major players in in APCs and the last in thymocytes (29, 42, 64–67). CTS have also been shown to generate antigenic peptide motifs that favor particular T lymphocyte polarization, such as Th2 to Th1, in a mouse model of leishmaniasis (68).

CTS also impact MHC class I-mediated antigen presentation. While MHC class I molecules usually present cytosolic peptide antigens, exogenous pathogen antigens can be presented by this complex via cross-presentation. Exogenous antigens captured by dendritic cells are initially processed in the endocytic pathway by CTS S followed by their final processing in the cytosol before being presented to CD8+ T lymphocytes (69).

In addition to T cell priming, CTS were found to regulate T lymphocyte polarization independent of APCs (70). The complement system integrates innate and adaptive responses and could influence the magnitude of T cell activation (70). Naïve CD4+ T lymphocytes store C3 in endosomes that can be cleaved by CTS L generating C3a and C3b. The C3aR-mediated intracellular signaling induces low levels of mechanistic target of rapamycin (mTOR) activation that regulate T cell survival (70). During infection, downstream
signaling pathways of mTOR facilitates Th1 cell polarization from naive T cells (70, 71).

**Cathepsins in the cytosol and in the nucleus**

**Programmed cell death**

CTS, as stated before, may be released into the cytosol by controlled or uncontrolled lysosomal membrane permeabilization (LMP), leading to lysosomal dependent cell death (reviewed in (16, 21)). Extensive permeabilization leads to necrosis (72) while a less drastic release induces apoptosis (16, 73–77). Stringent controlled release of CTS will allow the cells to survive and physiologic responses to CTS either in the cytosol or in the nucleus (16, 78–80). In the case of Salmonella infection a control of necrotic cell death was found associated with accumulation of active cathepsins in the nucleus (20). The additional control of cathepsin activity in these compartments depends on the balance and expression of natural inhibitors (78–80). For instance, it was demonstrated that the cysteolic inhibitor Spi2A protected memory CD8+ T lymphocytes from lysosomal breakdown and cell death by inhibiting CTS B activity (81). Spi2A is a serine protease inhibitor with an unusual role inhibiting cysteine cathepsins after lysosomal permeabilization (81). Consequently, this extends the lifespan of memory T cells.

The B-cell lymphoma-2 (Bcl-2) family proteins regulate the mitochondrial pathway of apoptosis. Interestingly, this family includes proteins with anti-apoptotic (e.g., Bcl-2 and Bcl-xl) and pro-apoptotic (e.g., Bax, Bak and Bid) activities and CTSs have direct roles in regulating several members of Bcl-2 proteins. For example, CTSs B, D, and L induce the activation of Bid, resulting in its translocation to mitochondria resulting in cytochrome C release and caspase activation. Moreover, CTSs degrade anti-apoptotic proteins Bcl-2, Bcl-xl, Mcl-1, and XIAP (X-linked inhibitor of apoptosis), promoting apoptosis (82, 83). In T lymphocytes, CTS D degrades Bax, triggering apoptosis via release of cystatin C and AIF (apoptosis-inducing factor) which directly activates caspase-8 (84–86). Finally, additional CTSs (e.g., C, F, H, K, L, O, S, V, W, and X) also function as mediators of lysosomal cell death either in immune and non-immune cells (10).

Other forms of programmed cell death lead to inflammation through cell lysis as is the case of necroptosis and pyroptosis. Necroptosis requires the kinase activity of receptor-interacting serine/threonine kinase 1 (Rip1), a protein that is cleaved by CTS B and S thus controlling inflammatory cell death (17). Pyroptosis is mediated by gasdermin, a pore forming protein dependent on inflammasome activation (87, 88). After LMP, CTS B and L are major inflammasome inducers that may lead to this form of cell death therefore enhancing the inflammatory responses (89).

**Cytosolic driven inflammation**

As stated, CTS released to the cytosol following LMP are relevant activators of inflammasomes, structures involved in innate immune responses (18, 90). Among inflammasomes the NLRP3 inflammasome is a major complex of assembled proteins in response to LMP, DAMPS or PAMPS (91–94). It is required for caspase-1 activation in the cytosol that in turn cleaves pro-IL-1β to their inflammatory mature form (90). Although CTS B and L have been associated with NLRP3 inflammasome activation, several siRNA experiments implicated CTS S and X (Z), particularly in contexts were they may compensate the lack of activity of CTS B and L (18, 95).

Inflammation is concomitant with migration of immune cells into tissues, such as lymphocytes and macrophages. CTS X is highly expressed in immune cells namely macrophages, dendritic cells and T lymphocytes (79). Its function has been associated to inflammatory responses such as cell adhesion, cell migration and phagocytosis. Some of these processes are the result of CTS X activation of transmembrane surface proteins, β2 integrins (96–98). To do so CTS X cleaves the last four amino-acids contained in the cytosolic part of C-terminal region of β2 integrins, either Mac-1 receptor in macrophages and dendritic cells, or LFA-1 in T lymphocytes. Activation of Mac-1 enhances adhesion of macrophages and dendritic cells to extracellular matrix (ECM), improving phagocytosis and subsequent maturation of dendritic cells, a process essential for antigen processing and presentation (96). Activation of LFA-1 causes proliferation and tissue homing of T lymphocytes characteristic of acute and chronic inflammations (98).

**Regulation of transcription**

CTS traffic to the nucleus has been associated to activation of transcription factors that control cell proliferation and differentiation (19, 22). Among transcription factors, CDP/Cux/Cut is activated by CTS L enabling accelerated cell cycle progression and carcinogenesis (19). Nuclear activity of CTS L was associated to an abnormal nuclear trafficking of the full length protein when stefinB, a CTS L inhibitor, is absent (19).

CTSs K and S were shown to interfere with nuclear membrane transport and control TGF-β signaling, leading to ECM synthesis required for cell growth and tissue fibrosis that often occurs during infections (99). They modulate the nuclear import of Smad proteins transcription factors that in turn regulate the expression of profibrotic genes such as collagen and fibronecin. In opposition, CTS B and L in nuclear membrane inhibit the effects of CTS K and S leading to decreased TGF-β signaling (99). This fibrotic pathological response may indeed be mitigated by extracellular CTS while promoting ECM degradation and helping tissue repair (100).
Cathepsins in the extracellular space

Cathepsins emerge therefore as relevant players in the extracellular space as full degrading enzymes of ECM components, but the paradigm is now changing to enzymes that can specifically modify other extracellular proteins. Their secretion and activity are often dysregulated during inflammatory responses including infection [recently reviewed in (28)].

ECM remodeling

The structure of the ECM is dynamic and depends on the equilibrium between synthesis and degradation of a multitude of proteins (collagens, fibronectin, elastins), growth factors, proteoglycans, among others (11). ECM is vital to cell support and tissue integrity and has a series of regulatory functions. CTs K, S, and V possess strong collagenolytic and elastolytic activities suggesting their involvement in ECM remodeling (2, 11). The best studied is CT K that degrades type I collagens being essential for normal bone resorption (101). Other targets of CTs are cell adhesion contacts, influencing epithelial barriers, and cell adhesion to ECM, leading to changes in cell growth, cell migration, angiogenesis (102) and tissue repair (11, 103, 104). CTs B and L have been shown to be released by lysosomal exocytosis playing a role in repair of the plasma membrane (105). CT B, released from keratinocytes, attaches to cell surface where it is known to be involved in keratinocyte migration by degrading components of ECM during wound healing (106).

Extracellular driven inflammation during infection

CTs secretion to ECM is usually high during infection. Microorganisms are sensed by innate immune receptors in mucosal cells that respond with an increased secretion of a myriad of proteases including antimicrobial peptides and CTs all having antimicrobial effects (28, 104, 107). This is the case of CT K, highly expressed in intestinal Goblet cells, or CT G, secreted from Paneth cells, that contributes to pathogen and microbiota control, and epithelial barrier repair (104, 107). In bronchial mucosa a protective effect was attributed to CTs B and L (28) while CT S, expressed mainly in macrophages, may favor the motility of cilia by preventing unspecific binding with airway circulating proteins (6).

However, the proteolytic activity of CTs may also aid infections by cleaving viral envelope proteins activating their receptor-binding or fusogenic activities, thus favoring viral infection (108–111). In chronic inflammatory conditions high concentrations of CTs B, L, and S have been shown to cleave and inactivate several proteases, impairing their antimicrobial properties (2, 112, 113). The extensive destruction of lung parenchyma in tuberculosis is related with high levels of CTs K, S, and V (114). CTs G and D favor autolysis inside tuberculosis granulomas contributing to their liquefaction and disruption thus facilitating pathogen dissemination (28, 115).

The ECM breakdown products produced by extracellular proteases, including cathepsins, may act themselves as DAMPs, leading to the activation of NLRP3 inflammasomes exacerbating tissue inflammatory responses (116).

Extracellular CTs are also able to process cytokines and chemokines. CTs L, S, and K, were shown to activate the glutamate-leucin-arginine motif (ELR) CXC ELR and inactivate non-ELR (CXCL9–12) chemokines thereby contributing to leukocyte recruitment during protective or pathological inflammation (117). CT S secreted from fibroblasts and CT G secreted from macrophages, neutrophils, and epithelial cells are activators of IL-8 (CXCL8). IL-8 acts both as a strong neutrophil chemoattractant, and as a proinflammatory cytokine (118, 119). In addition, CT G activates IL-1β and TNFα as well as various signaling receptors (120). In contrast, CT G can reduce dramatically the activity of IL-6 in fluids from inflammatory sites (121).

In the extracellular space CTs are able to cleave ectodomains of receptors and cell adhesion molecules at the cell surface, influencing by this mechanism several signaling pathways (122, 123). CTs L and S secreted from macrophages were shown to shed CAM adhesion proteins and receptor tyrosine kinases (123). Dysbiosis-induced disruption of the epithelial barrier was found to be related with ectodomain activation of protease-activated receptor 4 (PAR 4) by neutrophil CT G (124).

Discussion

Cathepsins spatial localization is associated with distinct key roles of immune responses, with strong implications for infection control and inflammation resolution. Thus, CT manipulations within these spatial contexts constitute potential targets for the development of new therapeutic strategies to fight infections, particular for those pathogens that developed drug resistance mechanisms to conventional treatments. The enhancement of their activity in situations where pathogen survival relies on their inhibition (e.g., drugs targeting autophagy) may help pathogen eradication from infected cells. Conversely, when infection results in poor antigen presentation, manipulation of CT activity may improve the adaptive response and vaccine efficacy. Pathological inflammation is
often a consequence of an infection. Targeting the control of inflammatory pathways may help to prevent or resolve tissue destruction and fibrotic events. There is still plenty to be investigated in this very promising area of research to fight the increasing threat of infections.

Author contributions

Conceptualization and writing: EA. Review and editing: DP, JA-P, and MM. Image: EA. Supervision and funding acquisition: EA. All authors contributed to the article and approved the submitted version.

Funding

This study was supported by grants from the National Foundation for Science, FCT Fundação para a Ciência e Tecnologia – Portugal, PTDC/SAU-INF/28182/2017 to EA, UIDB/04138/2020 (to IMed-ULisboa).

References

1. Patel S, Homai A, El-Seedi HR, Akhtar N. Cathepsins: Proteases that are vital for survival but can also be fatal. BioMed Pharmacother (2018) 105:526–32. doi: 10.1016/j.biopha.2018.05.148
2. Lecaille F, Lalmanach G, Andraut P-M. Antimicrobial proteins and peptides in human lung diseases: A friend and foe partnership with host proteases. Biochimie (2016) 122:151–68. doi: 10.1016/j.biochi.2015.08.014
3. Turk V, Stoka V, Vasileva O, Renko M, Sun T, Turk B, et al. Cysteine cathepsins: from structure, function and regulation to new frontiers. Biochim Biophys Acta (2012) 1824:68–88. doi: 10.1016/j.bjba.2011.10.002
4. Rawlings ND, Barrett AJ, Thomas PD, Huang X, Bateman A, Finn RD. The MEROPS database of proteolytic enzymes, their substrates and inhibitors in 2017 and a comparison with peptidases in the PANTHER database. Nucleic Acids Res (2018) 46:D624–32. doi: 10.1093/nar/gks1134
5. Rawlings ND, Waller M, Barrett AJ, Bateman A. MEROPS: the database of proteolytic enzymes, their substrates and inhibitors. Nucleic Acids Res (2014) 42:D503–9. doi: 10.1093/nar/gkt953
6. Chapman HA, Riese RJ, Shi GP. Emerging roles for cysteine proteases in human biology. Annu Rev Physiol (1997) 59:63–88. doi: 10.1146/annurev.physiol.59.1.63
7. Pohlmann R, Boeker MW, Figura von K. The two manganese 6-phosphate receptors transport distinct complements of lysosomal proteins. J Biol Chem (1995) 270:27311–8. doi: 10.1074/jbc.270.45.27311
8. Colletje J, Bocock IP, Ahn K, Chapman RL, Godbold G, Yeyeodu S, et al. Biosynthesis and alternate targeting of the lysosomal cysteine protease cathepsin L. Int Rev Cytol (2004) 241:1–51. doi: 10.1016/S0074-7696(04)41001-8
9. Brasulke T, Bonifacino JS. Sorting of lysosomal proteins. Biochim Biophys Acta (2009) 1793:605–14. doi: 10.1016/j.bbamcr.2008.10.016
10. Yadati T, Houben T, Bistora A, Shiri-Sverdlov R. The ins and outs of cathepsins: Physiological function and role in disease management. Cells (2020) 9:1679. doi: 10.3390/cells90301679
11. Vidak E, Javorski O, Viziovek M, Turk B. Cysteine cathepsins and their extracellular roles: Shaping the microenvironment. Cells (2019) 8:264:1–24. doi: 10.3390/cells8030264
12. Reizer J, Adair B, Reinheckel T. Specialized roles for cysteine cathepsins in health and disease. J Clin Invest (2010) 120:3421–31. doi: 10.1172/JCI42918
13. Savina A, Amigorena S. Phagocytosis and antigen presentation in dendritic cells. Immunol Rev (2007) 219:143–56. doi: 10.1111/j.1600-065X.2007.00552.x
14. Eder C. Mechanisms of interleukin-1beta release. Immunobiology (2009) 214:543–53. doi: 10.1016/j.imbio.2008.11.007
15. Konjar S, Sutton VR, Hoves S, Repnik U, Yagiha H, Reinheckel T, et al. Human and mouse perforin are processed in part through cleavage by the lysosomal cysteine protease cathepsin L. Immunology (2010) 131:257–67. doi: 10.1111/j.1365-2567.2010.03299.x
16. Reinheckel T, Tholen M. Low-level lysosomal membrane permeabilization for limited release and sublethal functions of cathepsin proteases in the cytosol and nucleus. FEBS Open Bio (2022) 12:694–707. doi: 10.1002/2211-5463.13385
17. McComb S, Shatinovski B, Thurston S, Cessford E, Kumar K, Sad S. Cathepsins limit macrophage necroptosis through cleavage of BIP1 kinase. J Immunol (2014) 192:5671–8. doi: 10.4049/jimmunol.1303880
18. Campden RJ, Zhang Y. The role of lysosomal cysteine cathepsins in NLRP3 inflammasome activation. Arch Biochem Biophys (2019) 670:32–42. doi: 10.1016/j.bioc.2019.02.015
19. Tambone T, Illikumbrana R, Lu S, Muelaesmo GM, Haugen MH, Brix K. Nuclear cathepsin L activity is required for cell cycle progression of colorectal carcinoma cells. Biochimie (2016) 122:208–18. doi: 10.1016/j.bioc.2015.09.003
20. Selkirk J, Li N, Hausmann A, Mangan MSJ, Zietek M, Mateus A, et al. Spatiotemporal proteomics uncovers cathepsin-dependent macrophage cell death during salmonellosis infection. Nat Microbiol (2020) 5:1119–33. doi: 10.1038/s41564-020-0736-7
21. Repnik U, Stoka V, Turk V, Turk B. Lysosomes and lysosomal cathepsins in cell death. Biochim Biophys Acta (2012) 1824:22–33. doi: 10.1016/j.bjba.2011.08.016
22. Goulet B, Baruch A, Moon N-S, Poirier M, Sansregret LL, Erickson A, et al. A cathepsin L isoform that is devoid of a signal peptide localizes to the nucleus in sarkosomcs and processes the CDP/Cux transcription factor. Mol Biol Cell (2019) 30:1119–33. doi: 10.1091/mbc.E18-12-0736
23. Müntener K, Zwicky R, Csucs G, Rohrer J, Baici A. Exon skipping of cathepsin L is required for its heterogeneity. J Biol Chem (2004) 279:41012–20. doi: 10.1074/jbc.M405333200
24. Bestvater F, Dallner C, Spiess E. The terminal subunit of artificially truncated human cathepsin b mediates its nuclear targeting and contributes to cell viability. BMC Cell Biol (2005) 6:16–9. doi: 10.1186/1471-2121-6-16
25. Randow F, MacMicking JD, James LC. Cellular self-defense: how cell-autonomous immunity protects against pathogens. Science (2013) 340:701–9. doi: 10.1126/science.1235028

Acknowledgments

ADEIM-FFUL (Associação para o Desenvolvimento do Ensino e Investigação em Microbiologia).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.
structural determinants of host defence.

tuberculosis survival in infected macrophages.

Front Cell Infect Microbiol

doi: 10.1016/j.cell.2004.11.038

processes.

J Cell Sci

autophagy by CTSB/cathepsin b.

et al. Cathepsins are required for toll-like receptor 9 responses.

ectodomain of toll-like receptor 9 is cleaved to generate a functional receptor.

Traf

Anes et al. 10.3389/

Proc Natl Acad Sci USA

et al. Cleavage of toll-like receptor 3 by cathepsins b and h is essential for signaling.

Protein Sci

expression resulting in higher pathogen survival and poor T-cell activation.

interferes with miR-3619-5p control of cathepsin s in the process of autophagy.

4598-13-43

by promoting M2 polarization.

4. Man SM, Kanneganti T-D. Regulation of lysosomal dynamics and endocytosis - interconnections between the two processes.

5. Birgisdottir ÅB, Johansen T. Autophagy and endocytosis - interconnections.

6. doi:10.1007/978-1-60761-421-0_25

7. Liszewski MK, Kolev M, Le Friec G, Leung M, Bertram PG, Fara AF, et al. Intracellular complement activation sustains T cell homeostasis and mediates effector differentiation.

8. doi: 10.1016/j.immuni.2004.09.002

9. Riese RJ, Champman RA, Villadangos JA, Shi GP, Palmer JT, Karp ER, et al. Cathepsin s activity regulates antigen presentation and immunity. J Clin Invest (2010) 121:2351–63. doi:10.1172/JCI11518

10. Liszewski MK, Kolev M, Le Friec G, Leung M, Bertram PG, Fara AF, et al. Intracellular complement activation sustains T cell homeostasis and mediates effector differentiation.

11. Science (2005) 310:1492–7. doi:10.1126/science.1120225

12. Hentze H, Lin X,Y, Choi MSK, Porter AG. Critical role for cathepsin b in mediating caspase-1-dependent interleukin-18 maturation and caspase-1-
independent necrosis triggered by the microbial nuclease. Cell Death Differ (2003) 10:385–90. doi:10.1038/sj.cdd.4401309
73. Laforge M, Petit F, Estaquier J, Senik A. Commitment to apoptosis in CD4 (+) T lymphocytes productively infected with human immunodeficiency virus type 1 is initiated by lysosomal membrane permeabilization, itself induced by the isolated expression of the viral protein nef. J Virol (2007) 81:11426–40. doi:10.1128/JVI.00597-07
74. Guicciardi ME, Leist M, Gores GJ. Lysosomes in cell death. Oncogene (2004) 23:2881–90. doi:10.1038/sj.onc.1207512
75. Robeg K, Ollinger K. Oxidative stress causes relocation of the lysosomal enzyme cathepsin D with ensuing apoptosis in neonatal rat cardiomyocytes. Am J Pathol (1998) 152:1151–6.
76. Kægeld K, Zhao M, Svensson I, Bunkt U. Sphingosine-induced apoptosis is dependent on lysosomal proteases. Biochem J (2011) 359:335–43. doi:10.1042/20160264-6021159335
77. Boley MA, Marriot HM, Tulone C, Francis SE, Mitchell TJ, Read RC, et al. A cardinal role for cathepsin D in Co-ordinating the host-mediated apoptosis of macrophages and killing of pneumococci. PLoS Pathog (2011) 7:e1001262. doi:10.1371/journal.ppat.1001262
78. Koptiar-Jerala N. The role of cystatins in cells of the immune system. FEBS Lett (2006) 580:6295–301. doi:10.1016/j.febslet.2006.10.055
79. Magister Ľ, Koz S. Cystatins in immune system. J Cancer (2013) 4:45–56. doi:10.7150/jca.5044
80. Shah A, Bano B. Cystatins in health and diseases. Int J Pept Res Ther (2008) 15:85–6. doi:10.1007/s10495-008-9160-1
81. Byrne SM, Aucber A, Alyahya S, Elder M, Olson ST, Davis DM, et al. Cathepsin b controls the persistence of memory CD8+ T cells: selective apoptosis-inducing factor (AIF) relocation in T lymphocytes entering the early commitment phase to apoptosis. J Immunol (2012) 189:1133–43. doi:10.4049/jimmunol.1200406
82. Chwieralski CE, Welte T, Bühling F. Cathepsin-regulated apoptosis. Apoptosis (2006) 11:143–9. doi:10.1007/s10495-006-3466-y
83. Droga-Mazovec G, Bojic L, Petelin A, Ivanova S, Romih R, Repnik U, et al. Distinct cathepsins control necrotic cell death mediated by pyroptosis. J Pathol (2018) 246:2881–90. doi:10.1002/path.5109
84. Feng S, Fox D, Man SM. Mechanisms of gasdermin family members in cell death. Mediators Inflamm (2012) 2012:139
85. Bidère N, Lorenzo HK, Carmona S, Laforge M, Dumont C, et al. Cystatins in health and disease. Int J Pept Res Ther (2008) 14:95–106. doi:10.1007/s10495-008-9160-1
119. Padrines M, Wolf M, Wahl A, Baggioini M. Interleukin-8 processing by neutrophil elastase, cathepsin G and proteinase-3. FEBS Lett (1994) 352:231–5. doi: 10.1016/0014-5793(94)00952-x

120. Meyer-Hoffert U. Neutrophil-derived serine proteases modulate innate immune responses. Front Biosci (Landmark Ed) (2009) 14:3409–18. doi: 10.2741/3462

121. Bank U, Küpper B, Reinhold D, Hoffmann T, Ansorge S. Evidence for a crucial role of neutrophil-derived serine proteases in the inactivation of interleukin-6 at sites of inflammation. FEBS Lett (1999) 461:235–40. doi: 10.1016/s0014-5793(99)01466-0

122. Sambrano GR, Huang W, Faruqi T, Mahrous S, Craik C, Coughlin SR. Cathepsin G activates protease-activated receptor-4 in human platelets. J Biol Chem (2000) 275:6819–23. doi: 10.1074/jbc.275.10.6819

123. Sobotic B, Vizovisek M, Vidmar R, Van Damme P, Gocheva V, Joyce JA, et al. Proteomic identifi cation of cysteine cathepsin substrates shed from the surface of cancer cells. Mol Cell Proteomics (2015) 14:2213–28. doi: 10.1074/mcp.M114.044628

124. Dubek M, Ferrier L, Roka R, Gecce K, Annahazi A, Moreau J, et al. Luminal cathepsin g and protease-activated receptor 4: a duet involved in alterations of the colonic epithelial barrier in ulcerative colitis. Am J Pathol (2009) 175:207–14. doi: 10.2353/ajpath.2009.080986