

# Involvement of Microglial Cathepsin B in Pro-Interleukin-1 $\beta$ Processing and Persistent Pain

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## 1. Introduction

A group of proteases in the endosomal/lysosomal proteolytic system have been designated as cathepsins, which is derived from the Greek term meaning “to digest”. Considering that cathepsins can irreversibly cleave peptide bonds, the primary function of cathepsins has been believed to be their “disintegration action”. However, there is increasing evidence that cathepsins can also exert “modulator actions” by which substrates are activated after limited cleavage. There is substantial evidence that cathepsin B (EC 3.4.22.1), a typical cysteine lysosomal protease, is markedly upregulated in activated microglia that accumulate in pathological sites of the brain. Beyond its bulk proteolysis in the endosomal/lysosomal system, cathepsin B can be secreted from activated microglia in its mature form to induce neuronal apoptosis and degrade A $\beta$  peptides that accumulate in the brain. Furthermore, cathepsin B is also leaked into the cytosol, where it plays an essential role in the inflammatory response initiated by activated microglia in the brain.

Recently, the leakage of cathepsin B from the lysosomes has been suggested to trigger the activation of the NOD-like receptor (NLR) family, pyrin domain-containing 3 (NLRP3) inflammasome in microglia/macrophages after phagocytosis of various molecules including fibrillar A $\beta$ 42 and silica crystals. After activation, the NLRP3 inflammasome can mediate pro-caspase-1 activation to promote the processing and secretion of proinflammatory cytokines, such as interleukin-1  $\beta$  (IL-1  $\beta$ ) and IL-18. However, the precise role of leaked cathepsin B in the activation of the NLRP3 inflammasome remains to be determined. Furthermore, there is still evidence suggesting that cathepsin B is associated with the maturation of pro-IL-1 $\beta$  in the endosomal/lysosomal system, because cathepsin B can effectively cleave pro-caspase-1 in a cell-free system only at an acidic pH. I herein review our current understanding of the mechanism and roles of cathepsin B in the processing and secretion of IL-1 $\beta$  and IL-18. Further, I also discuss a possible involvement of cathepsin B in the induction of persistent pain.

## 2. Cathepsin B and neuronal death

### 2.1 Neuronal death induced by cathepsin B-secreted from microglia

Microglia are known to release a number of soluble molecules that can influence neuronal signaling and survival. Kingham and Pocock (2001) focused on cathepsin B, which increased in the culture medium of microglia following stimulation with chromogranin A (CGA), a glycoprophosphoprotein secreted by degenerating neurons. They demonstrated that cathepsin B is a major causative factor for CGA-activated microglia-induced neuronal apoptosis using neutralizing anti-cathepsin B antibodies. Gan et al. (2004) found that freshly sonicated A $\beta$ 42 did not cause neuronal death when added directly to neuron, but activated BV2 microglial cells to release toxic factors that caused significant neuronal death. To determine the toxic molecules secreted from A $\beta$ 42-stimulated microglia, they conducted a large scale expression profiling analyses using filter-based cDNA arrays made from BV2 cDNA libraries enriched for A $\beta$ 42-activated microglial genes. Cathepsin B was identified to be one of the 554 genes transcriptionally induced by freshly sonicated A $\beta$ 42. Furthermore, specific inhibition of cathepsin B using either siRNA-mediated gene silencing or a specific cathepsin B inhibitor completely abolished the neurotoxicity mediated by A $\beta$ 42-activated BV2 microglial cells, suggesting that cathepsin B plays a crucial role in neuronal death mediated by A $\beta$ -activated inflammatory responses. However, further studies will be needed to identify the mechanism of secretion of cathepsin B and its extracellular substrates.

### 2.2 Involvement of intracellular cathepsin B in microglia-induced neuronal death

Wendt et al. (2009) analyzed the neurotoxicity of conditioned medium from lipopolysaccharide (LPS)-activated microglia. Experiments with membrane-permeable and membrane-impermeable cathepsin B inhibitors suggested that blocking extracellular cathepsin B had no effect on LPS-stimulated microglia-mediated neuronal death. In contrast, intracellular cathepsin B may trigger the release of neurotoxic factors from activated microglia. In fact, it has been reported that cathepsin B is involved in the trafficking of tumor necrosis factor- $\alpha$ -containing vesicles to the plasma membrane of macrophages (Ha et al., 2008).

## 3. Cathepsin B and A $\beta$

To determine the role of cathepsin B in the processing of amyloid precursor protein and A $\beta$  metabolism *in vivo*, Mueller-Steiner et al. (2006) crossed cathepsin B-deficient mice with transgenic mice that overexpressed human amyloid precursor protein (hAPP mice). Cathepsin B ablation in hAPP mice did not affect the levels of the C-terminal fragments of hAPP, suggesting that cathepsin B does not significantly affect the processing of hAPP. In contrast, cathepsin B ablation significantly increased the plaque deposition and A $\beta$ 42 levels in the hippocampus. On the other hand, the injection of Lenti-cathepsin B into the hippocampus significantly reduced A $\beta$  deposition in aged hAPP mice. These observations strongly suggest that cathepsin B is secreted from microglia accumulated around the senile plaques, and is involved in the degradation of A $\beta$ 42 and reduction of established plaques.

## 4. Cathepsin B and inflammation

### 4.1 The “lysosomal rupture model” and “reactive oxygen species (ROS) model” of activation of the NLRP3 inflammasome

Two different models, the “lysosomal rupture model” proposed by Latz’s group (University of Bonn) and the “ROS model” proposed by Tschopp’s group (University of Lausanne),

have recently been proposed to account for perturbations in phagocytic processes that activate the NLRP3 inflammasome. According to the lysosomal rupture model, phagocytosis of fibrillar A $\beta$ 42 or silica crystals by LPS-primed microglia/macrophages causes phagosomal destabilization and lysosomal rupture. The subsequent secretion of cathepsin B into the cytoplasm triggers the activation of the NLRP3 inflammasome directly or indirectly, leading to the production and secretion of mature IL-1 $\beta$  (Hornung et al., 2008; Halle et al., 2008).

Activator	Phagocyte	Cathepsin B-dependency	NLRP3-dependency	Disease	Reference
Fibrillar A $\beta$	Microglia	+ (cytosol)	+	Alzheimer's disease	Halle et al.
CGA	Microglia	+ (phagolysosome)	?	Inflammatory pain	Terada et al.
Silica crystal	Macrophage	+ (cytosol)	+	Silicosis	Hornung et al.
Cholesterol crystal	Macrophage	+ (cytosol)	+	Atherosclerosis	Duewell et al.
IAPP	Dendritic cell	+ (?)	+	Type 2 Diabetes	Masters et al.
MSU	Macrophage	?	+	Gout	Dostert et al.
Asbestos fiber	Macrophage	?	+	Asbestosis	Dostert et al.

CGA: chromogranin A; IAPP: islet amyloid peptide; MSU: monosodium urate crystal

Table 1. IL-1 $\beta$  production pathways and diseases

This model is supported by observations that a specific inhibitor of cathepsin B, CA074Me, significantly inhibited the IL-1 $\beta$  secretion from LPS-primed microglia and macrophages after phagocytosis of fibrillar A $\beta$  and silica crystal, respectively (Hornung et al., 2008; Halle et al., 2008). Furthermore, the mean level of IL-1 $\beta$  secreted from cathepsin B-deficient macrophages following the phagocytosis of fibrillar A $\beta$  was significantly lower than that from wild-type macrophages (Halle et al., 2008). Interestingly, CA074Me had no effect on the amount of IL-1 $\beta$  secreted from LPS-primed microglia following treatment with ATP (Table 1). Furthermore, a direct disruption of lysosomes by treatment with hypotonic media or L-leucyl-L-leucyl methyl ester was shown to be sufficient for the activation of NLRP3 (Hornung et al., 2008). On the other hand, according to the ROS model, particulate activators of the NLRP3 inflammasome including asbestos fibers and silica crystals trigger the generation of short-lived ROS, and treatment with various ROS scavengers blocks the activation of the NLRP3 inflammasome in response to these particulate activators (Dostert et al., 2008). Various danger signals stimulate phagocytes to induce various IL-1 $\beta$  production pathways, which are associated with various diseases (Table 1).

More recently, however, reports opposing both of these models have appeared. Dostert et al. (2009) demonstrate that cathepsin B-deficient macrophages exhibited a normal NLRP3 inflammasome-dependent IL-1 $\beta$  production in response to silica crystals, urea crystals or aluminum salts, which raises questions about the specificity of CA074Me. Lysosomal rupture is associated with the release of numerous other enzymes, therefore CA074Me might inhibit other released proteases that acts as the essential signal to activate the NLRP3 inflammasome (Montaser et al., 2002). In fact, cathepsin L-deficient macrophages were also used to show that cholesterol crystals led to a diminished release of IL-1 $\beta$  in comparison with wild-type cells (Duewell et al., 2010). However, the dependence of cholesterol crystal-

induced IL-1 $\beta$  release on cathepsin B or L was less pronounced at higher concentrations, thus suggesting the functional redundancy of cathepsin B/L, or the potential presence of additional proteases. Furthermore, Masters et al. (2010) showed that the secretion of IL-1 $\beta$  from bone marrow-derived dendritic cells after phagocytosis of islet amyloid polypeptide, a unique polypeptide constituent of amyloid found in pancreatic islet, was significantly inhibited by a specific inhibitor of either cathepsin B or ROS. Proving the importance of the lysosomal rupture model will require identification of the putative cathepsin B substrate(s) that activate the NLRP3 inflammasome. Detailed analyses are also needed to clarify the involvement of cathepsins other than cathepsin B for activation of the NLRP3 inflammasome. On the other hand, proving the importance of the ROS model will require that the source of the ROS that activate the NLRP3 inflammasome be clarified. Phagocytosed particulates that are too large to be efficiently cleared are likely to induce the production of ROS on their way to lysosomes. Therefore, the lysosomal rupture model could be viewed as forming part of a more general ROS pathway. It is likely that the activation of the NLRP3 is more complex and may require a combination of factors, including both enzymatic activities of cathepsins and ROS activity.

#### **4.2 Alternative mechanisms underlying the cathepsin B-dependent activation of pro-caspase-1**

There is still evidence suggesting that cathepsin B is directly associated with the proteolytic cleavage of pro-IL-1 $\beta$  in the endosomal/lysosomal system. Cathepsin B can efficiently cleave pro-caspase-11 in a cell-free system even at a neutral pH, but it cleaves pro-caspase-1 only at an acidic pH (Vancompernelle et al., 1998). Furthermore, Hentze et al. (2003) found that cathepsin B is directly involved in the proteolytic cleavage of pro-caspase-1 in THP-1 monocytic cells after stimulation with the microbial toxin nigericin. However, the size of the cleaved fragments of pro-caspase-1 generated by cathepsin B (37 and 40 kDa) is different from the active fragments that are produced by caspase-1 self-processing (10 and 20 kDa). It is possible that the fragments of pro-caspase-1 resulting from the cleavage by cathepsin B may be further cleaved to the active fragments by self-processing. It should also be considered whether cathepsin B is indirectly involved in the activation of pro-caspase-1 though its direct activation of pro-caspase-11, because caspase-11 is known to be play a crucial role in the activation of pro-caspase-1 (Kang et al., 2000).

During the course of experiments to examine the role of cathepsin B in microglial apoptosis, we found that cathepsin B-deficiency abrogated the secretion of IL-1 $\beta$  from microglia following treatment with CGA (Terada et al., 2010). Detailed analyses revealed that cathepsin B-deficiency and CA074Me significantly inhibited the proteolytic processing of pro-IL-1 $\beta$  and secretion of mature IL-1 $\beta$  from microglia following treatment with CGA without affecting the increased production of pro-IL-1 $\beta$ . Furthermore, there was no sign of any leakage of cathepsin B in microglia following treatment with CGA. The typical size of the primary lysosomes is below 1  $\mu$ m in diameter, whereas the mean diameter of cathepsin B-containing enlarged lysosomes in CGA-stimulated microglia was 4.2  $\mu$ m. Furthermore, cathepsin B-positive enlarged lysosomes were found to be acidic compartments. These findings are consistent with previous observations that IL-1 $\beta$  and cathepsin D are colocalized within endolysosome-related vesicles, and that the secretion of IL-1 $\beta$  involves the exocytosis of these vesicles in LPS-activated human monocytes (Andrei et al., 1999). Interestingly, CGA is known to activate microglia through scavenger receptor class-A (SR-A; Hooper et al., 2009). Cathepsin B-containing enlarged lysosomes are considered to be

phagolysosomes formed by a fusion of SR-A-mediated phagosomes and primary lysosomes. Therefore, pro-caspase-1 and pro-IL-1 $\beta$  in the cytoplasm may be trapped in these cathepsin B-containing phagolysosomes during their formation triggered by a binding of CGA to SR-A. Furthermore, cathepsin B activates pro-caspase-1 and caspase-1 subsequently proteolytically cleaves pro-IL-1 $\beta$  and pro-IL-18 to their mature forms. Finally, mature IL-1 $\beta$  and IL-18 are secreted extracellularly by exocytosis (Figure 1).

## 5. Cathepsin B and Inflammatory pain

Cathepsin B deficiency or treatment with a specific inhibitor of cathepsin B, CA074Me, was found to abrogate CGA-induced activation of pro-caspase-1 and subsequent processing of the inactive forms of IL-1 $\beta$  and IL-18 to their mature forms in microglia. Furthermore, the existence of multiple pathways that can induce the proteolytic cleavage of pro-IL-1 $\beta$  and pro-IL-18 in microglia was further demonstrated, probably indicating that there is a backup system for generating these cytokines. CGA activates cathepsin B-dependent but NLRP3-independent pathways for the processing of both IL-1 $\beta$  and IL-18, whereas ATP activates NLRP3-dependent but cathepsin B-independent pathways for their processing. These *in vitro* observations using cultured microglia prompted us to further investigate the role of cathepsin B in chronic pain generation, because both IL-1 $\beta$  and IL-18 are involved in the initiation of inflammatory and pain hypersensitivity (Samad et al., 2001; Sweitzer et al., 2001; Kawasaki et al., 2008; Miyoshi et al., 2008). Furthermore, Inoue's group (Kyushu University) introduced the concept that signals derived from spinal microglia after spinal nerve injury are the core mechanisms underlying neuropathic pain (Tsuda et al., 2003; Coull et al., 2005; Scholz & Woolf, 2007). Following intra-plantar injection of complete Freund's adjuvant (CFA), both hyperalgesia (an augmented pain response to noxious stimulation) and allodynia (a pain produced by normally non-painful stimulation) develop in the injected paw. As expected, cathepsin B deficiency or the intrathecal administration of a specific cathepsin B inhibitor significantly inhibited both CFA-induced mechanical allodynia and thermal hyperalgesia without affecting peripheral inflammation. In contrast, cathepsin B-deficiency had no significant effect on spinal nerve injury-induced mechanical allodynia. At the same time, mature IL-1 $\beta$  and IL-18 were expressed in the spinal microglia of cathepsin B-deficient mice following spinal nerve-transection, but not after CFA treatment. Treatment with minocycline, a microglial activation inhibitor, completely prevented the development of CFA-induced mechanical allodynia and thermal hyperalgesia, thus suggesting that microglial activation and inflammatory immune responses in the spinal cord are involved in CFA-induced mechanical allodynia and thermal hyperalgesia (Shan et al., 2007). Therefore, it is considered that peripheral CFA-treatment triggers cathepsin B-dependent caspase-1 activation pathways for the processing of both IL-1 $\beta$  and IL-18 in spinal microglia, leading to pain hypersensitivity (Figure 1). On the other hand, spinal nerve-injury activates cathepsin B-independent pathways for the processing of both IL-1 $\beta$  and IL-18 in spinal microglia. A MMP-9-dependent mechanism has been proposed as an alternative pathway for the proteolytic cleavage of pro-IL-1 $\beta$  in the spinal cord following nerve injury (Kawasaki et al., 2008).

Following the peripheral inflammation, IL-1 $\beta$  and IL-18 are secreted from activated spinal microglia in a cathepsin B-dependent manner. IL-1 $\beta$  and IL-18 subsequently induce COX-2 in spinal neurons, leading to the production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>). PGE<sub>2</sub> activates protein kinase A (PKA) through increase in cAMP levels by binding to PGE<sub>2</sub> receptors of the

EP2 subtype. PKA then causes phosphorylation and inhibition of glycine receptors containing the  $\alpha 3$  subunits (GlyR $\alpha 3$ ). This disinhibition induces hypersensitivity of pain. IL-1 $\beta$  and IL-18 are also known to directly enhance responses mediated by NMDA receptors.

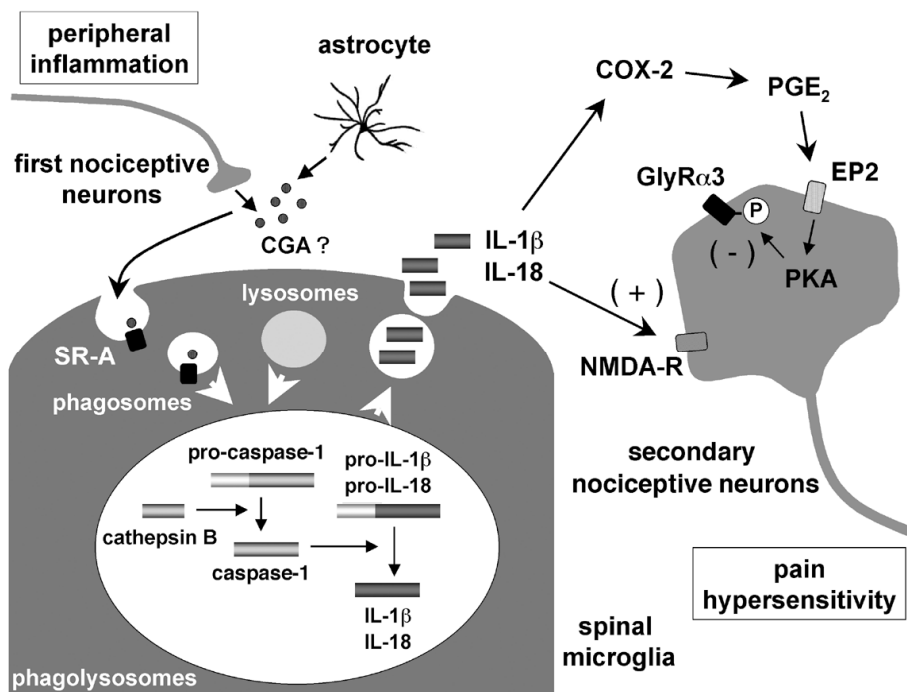


Fig. 1. Schematic representation of the role of cathepsin B in the initiation of inflammatory pain.

## 6. Conclusion

The lysosomal rupture and subsequent leakage of cathepsin B has been proposed as the common molecular basis underlying apoptosis and inflammation. Although a lysosomal rupture has pathological significance, we have demonstrated that cathepsin B is involved in the proteolytic processing of pro-caspase-1 to its active form in the phagolysosomes of microglia, even in the absence of leakage. Therefore, it is considered that cathepsin B-dependency and the mechanism of action depend on the activator or stimulus. The growing understanding of the proteolytic systems of cathepsins in the central nervous system could contribute to the development of protease inhibitors as therapeutic interventions against chronic inflammation-related diseases including chronic pain.

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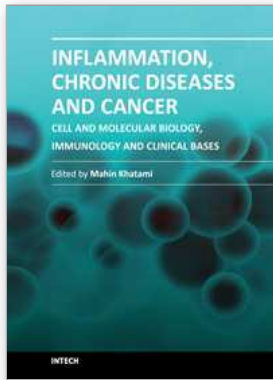
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This book is a collection of excellent reviews and perspectives contributed by experts in the multidisciplinary field of basic science, clinical studies and treatment options for a wide range of acute and chronic inflammatory diseases or cancer. The goal has been to demonstrate that persistent or chronic (unresolved or subclinical) inflammation is a common denominator in the genesis, progression and manifestation of many illnesses and/or cancers, particularly during the aging process. Understanding the fundamental basis of shared and interrelated immunological features of unresolved inflammation in initiation and progression of chronic diseases or cancer are expected to hold real promises when the designs of cost-effective strategies are considered for diagnosis, prevention or treatment of a number of age-associated illnesses such as autoimmune and neurodegenerative diseases as well as many cancers.

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