



Contents lists available at ScienceDirect

Biochimie

journal homepage: www.elsevier.com/locate/biochi

Review

Structure and function of legumain in health and disease

Elfriede Dall, Hans Brandstetter*

Dept. of Molecular Biology, University of Salzburg, A-5020 Salzburg, Austria

ARTICLE INFO

Article history:

Received 14 August 2015

Accepted 18 September 2015

Available online xxx

Keywords:

Electrostatic stabilization

Cellular localization

Allostery

Caspase

Death domain

Context-dependent activities

ABSTRACT

The last years have seen a steady increase in our understanding of legumain biology that is driven from two largely uncoupled research arenas, the mammalian and the plant legumain field. Research on legumain, which is also referred to as asparaginyl endopeptidase (AEP) or vacuolar processing enzyme (VPE), is slivered, however. Here we summarise recent important findings and put them into a common perspective. Legumain is usually associated with its cysteine endopeptidase activity in lysosomes where it contributes to antigen processing for class II MHC presentation. However, newly recognized functions disperse previously assumed boundaries with respect to their cellular compartmentalisation and enzymatic activities. Legumain is also found extracellularly and even translocates to the cytosol and the nucleus, with seemingly incompatible pH and redox potential. These different milieus translate into changes of legumain's molecular properties, including its (auto-)activation, conformational stability and enzymatic functions. Contrasting its endopeptidase activity, legumain can develop a carboxypeptidase activity which remains stable at neutral pH. Moreover, legumain features a peptide ligase activity, with intriguing mechanistic peculiarities in plant and human isoforms. In pathological settings, such as cancer or Alzheimer's disease, the proper association of legumain activities with the corresponding cellular compartments is breached. Legumain's increasingly recognized physiological and pathological roles also indicate future research opportunities in this vibrant field.

© 2015 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

Contents

1. History & nomenclature	00
2. Classification within the protease world	00
3. Phylogenetic distribution – who has it?	00
4. Tissue distribution – where is it?	00
4.1. (extra-)Cellular localization	00
4.2. How do proteins get to the lysosomal/vesicular system?	00
4.3. (patho-)Physiologic localization of mammalian legumain outside the lysosome	00
4.4. How to exit the endo-lysosome?	00
4.5. How does legumain survive at near neutral pH in the cytosol, nucleus or at the cell surface?	00
5. Physiological functions	00
5.1. Digestion	00
5.2. Immunity	00
5.3. Antimicrobial activity	00
5.4. (Immune) signalling	00
5.5. Apoptosis	00
5.6. Transcription factor	00
5.7. Osteoclast remodelling	00
5.8. Legumain deficient mice	00
6. Domain architecture – how does legumain look like?	00

* Corresponding author.

E-mail address: hans.brandstetter@sbg.ac.at (H. Brandstetter).

6.1.	Recombinant access	00
6.2.	Crystal structures of legumain	00
6.3.	The catalytic-domain – legumain is protease and ligase	00
6.3.1.	Protease substrates	00
6.4.	The LSAM-domain – signalling	00
7.	Activation of legumain	00
7.1.	Activation to asparagine-specific endopeptidase (AEP)	00
7.2.	Activation to ACP	00
7.3.	Catalytic mechanism of legumain protease activities (AEP/ACP)	00
7.4.	Comparison of legumain with caspases and cathepsins	00
8.	Substrate specificity	00
8.1.	P1 Asn/Asp	00
8.2.	P3–P2 and P1'	00
8.3.	Tuning legumain protease activity: k_{cat} selection	00
8.4.	ACP substrate specificity	00
9.	Ligase activities	00
9.1.	ATP-dependent ligases	00
9.2.	ATP-independent transpeptidases	00
9.3.	Catalytic mechanism of legumain ligase activity	00
9.4.	Ligase substrates and specificity	00
9.4.1.	P1 Asn/Asp	00
9.4.2.	P1' and P2'	00
10.	Activity regulation	00
10.1.	Protein inhibitors	00
10.1.1.	Cystatins	00
10.1.2.	Clitocypin/macrocypin	00
10.1.3.	Prodomain – reversible activation and zymogenization	00
10.1.4.	How to prevent cleavage of protein substrates or canonical inhibitors	00
10.2.	The environment is regulating legumain activity	00
10.3.	Activators	00
10.3.1.	Direct conformational stabilization	00
10.3.2.	Allosteric stabilization by integrin binding	00
10.3.3.	Accelerators of activation	00
10.4.	Low molecular weight inhibitors	00
11.	Pathological functions	00
11.1.	Legumain in and around cancer	00
11.2.	Multiple sclerosis	00
11.3.	Legumain in Alzheimer's disease	00
11.4.	Therapeutic and diagnostic options	00
11.4.1.	Prodrugs and targeted drug delivery	00
11.4.2.	DNA vaccines	00
11.4.3.	Legumain imaging and its use as prognostic marker	00
11.4.4.	Inhibition/knock down of legumain to suppress tumour progression and Alzheimer's disease	00
12.	Future perspectives, outlook	00
12.1.	Smart Legumain Activity Modulation (SLAM)	00
12.2.	Legumain web	00
	Conflict of interest	00
	Acknowledgements	00
	References	00

1. History & nomenclature

Already in the early 1980s the cysteine protease legumain was identified in the vetch seedlings and the common bean *Phaseolus vulgaris*, however not classified yet [1,2]. Only three years later, a putative 32 kDa cysteine protease was found in the trematode *Schistosoma mansoni* [3]. Another two years later, in 1989, the 32 kDa protein Sm32 was confirmed to be a protease [4]. The sequence of plant legumains was then cross-confirmed by the sequence of the homologous *Schistosoma* enzyme [5]. In 1990 legumain was initially named as haemoglobinase in *S. mansoni* [6]. Later it was also referred to as endoprotease B in germinating barley seeds [7]. Given its localization and function in plant vacuoles [5,8], and its strict specificity for cleaving after asparagine residues [9] legumain was named vacuolar processing enzyme (VPE) or

asparaginyl endopeptidase (AEP), and these names are still used today. In 1993 the term 'legumain' was introduced by Kembhavi et al. [10], which is nowadays its most frequently used name. Already in 1993 it was shown that legumain very likely harbours a protease and a ligase activity [9]. Mammalian legumain was identified in 1996 as putative cysteine protease PRSC1 in humans [11] and confirmed as legumain only one year later in pig. In 2007 legumain activity was for the first time also found in arthropods [12]. Further names were used for legumain to emphasise specific functions, including ACP (asparaginyl carboxypeptidase) because of its activity as a mono-carboxy-peptidase [13], or nucellain, because of its localization to nucellar cell walls in barley [14]. Recently the name "butelase 1" was used for a legumain isoform from the seeds of *Clitoria ternatea* [15]. While the use of the term AEP seems justifiable for its brevity or if the endopeptidase activity should be

Download English Version:

<https://daneshyari.com/en/article/8304462>

Download Persian Version:

<https://daneshyari.com/article/8304462>

[Daneshyari.com](https://daneshyari.com)