Biochimie xxx (2015) 1–25

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.

Contents

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

http://dx.doi.org/10.1016/j.biochi.2015.09.022

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

Please cite this article in press as: E. Dall, H. Brandstetter, Structure and function of legumain in health and disease, Biochimie (2015), http://dx.doi.org/10.1016/j.biochi.2015.09.022