Supplemental Table 1: Summary of clan CD peptidases

Peptidases / Family*	**Found in**	**Cleave after**	**Physiological substrates / biological activity**	**Refs.**
Caspases/C14; EC 3.4.22.36	Metazoans	Asp	IL-1β and IL-18; multiple intracellular substrates/ Inflammatory responses; cell death initiation and execution.	[77, 88]
Metacaspases/ C14(?); not classified	Plants, fungi, protozoa and bacteria	Lys/Arg	Cell death and embryogenesis in plants. Apoptosis in yeast (?).	[44, 306-309, 325]
Paracaspases/ C14; not classified	Metazoans, *Dictyostelium* and bacteria	Un-charged residue†	Unknown‡/NF-κB activation, cytokine production and lymphocyte proliferation.	[44, 306, 310]
Separins (separases)/C50; EC 3.4.22.49	Eukaryotes	Arg	Phosphorylated Scc1/Rad21 subunit of the cohesin complex/ separation of sister chromatids at the metaphase to anaphase transition.	[311-314]
Eukaryotic haemoglobinases/ C13; EC 3.4.22.34	Eukaryotes	Asn§/ Asp	Bacterial antigens; haemoglobin; seed storage proteins/vacuolar protein degradation, antigen processing for MHC II presentation; assimilation of haemoglobin; maturation of seed storage proteins; virus-induced apoptosis in plants.	[315-319]
Bacterial haemoglobinase-like proteins/ C13(?); not classified	Bacteria	?	?/?	[44]
Gingipain K (R)/ C25; EC 3.4.22.37	Bacteria	Lys (Arg)	Host antibodies, components of the complement and coagulation systems/impair defence response and fibrin formation.	[45, 320]
Clostripains/C11; EC 3.4.22.8	*Clostridia*‖	Arg	Host structural proteins/ establishment of clostridial infections (?)	[57]
HetF family/ C50(?); not classified	Bacteria and archaea¶	?	?/Signal transduction (?); development of N_2-fixing heterocysts.	[44, 321, 322]
Generic PMC**-related proteins/ C14(?);	Bacteria	?	?/Signal transduction (?); assembly of fruiting bodies (*Myxococcus xanthus*).	[44, 321]

not classified				

*According to the MEROPS ([9], http://delphi.phys.univ-tours.fr/Prolysis/cysfam.htm) and IUBMB classifications respectively.

†Predicted from homology modelling of the catalytic domain [306]. Some authors link IETD-ase or VEID-ase activities in yeast [308] and in plants [309] to metacaspases. However, two residues responsible for Asp-ase activity of caspases are replaced either by a leucine (Arg-179) or by an aspartate (Gln-283) in all known metacaspases, and so it might be premature to directly associate plant or yeast Asp-ase activity with these caspase relatives. (Compare alignment of caspase-haemoglobinase family members in [44] and see main paper for a discussion of caspase-specificity determinants).

‡Recent results suggest that the caspase-like domain of human paracaspase MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) possesses ubiquitin ligase activity, at least *in vitro*. In mammals, IKKγ (IκB kinase γ)/NEMO appears to be the physiological target [323]. However, another study suggests that the catalytic domain of the paracaspase functions as an adaptor of the ligase TRAF6 (TNF receptor-associated factor 6) within a large multiprotein complex [324].

§No cleavage after glycosylated asparagine residues [317].

||Related proteins have been found in the archaeon *Methanosarcina acetivorans*, an acetate-utilizing methanogen, as well as in *Thermotoga maritima*.

¶Homologous pseudoenzymes are found in eukaryotes.

**PMC, paracaspase/metacaspase/caspase.

Supplemental References
(these are cited in Supplemental Table 1, but not in the main paper)

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