



HAL
open science

Classification and Nomenclature of Metacaspases and Paracaspases: No More Confusion with Caspases

Elena A Minina, Jens Staal, Vanina E Alvarez, John A Berges, Ilana Berman-Frank, Rudi Beyaert, Kay D Bidle, Frédéric Bornancin, Magali Casanova, Juan J Cazzulo, et al.

► To cite this version:

Elena A Minina, Jens Staal, Vanina E Alvarez, John A Berges, Ilana Berman-Frank, et al.. Classification and Nomenclature of Metacaspases and Paracaspases: No More Confusion with Caspases. *Molecular Cell*, 2020, 77 (5), pp.927-929. 10.1016/j.molcel.2019.12.020 . hal-03174581

HAL Id: hal-03174581

<https://amu.hal.science/hal-03174581>

Submitted on 19 Mar 2021

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Published in final edited form as:

Mol Cell. 2020 March 05; 77(5): 927–929. doi:10.1016/j.molcel.2019.12.020.

Classification and nomenclature of metacaspases and paracaspases: no more confusion with caspases

Elena A. Minina^{1,2,*}, Jens Staal³, Vanina E. Alvarez⁴, John A. Berges⁵, Ilana Berman-Frank⁶, Rudi Beyaert³, Kay D. Bidle⁷, Frédéric Bornancin⁸, Magali Casanova⁹, Juan J. Cazzulo⁴, Chang Jae Choi¹⁰, Nuria S. Coll¹¹, Vishva M. Dixit¹², Marko Dolinar¹³, Nicolas Fasel¹⁴, Christiane Funk¹⁵, Patrick Gallois¹⁶, Kris Gevaert¹⁷, Emilio Gutierrez-Beltran¹⁸, Stephan Hailfinger¹⁹, Marina Klemen i¹³, Eugene V. Koonin²⁰, Daniel Krappmann²¹, Anna Linusson¹⁵, Maurício F. M. Machado²², Frank Madeo²³, Lynn A. Megeney²⁴, Panagiotis N. Moschou^{25,26,27}, Jeremy C. Mottram²⁸, Thomas Nyström²⁹, Heinz D. Osiewacz³⁰, Christopher M. Overall³¹, Kailash C. Pandey³², Jürgen Ruland^{33,34,35}, Guy S. Salvesen³⁶, Yigong Shi³⁷, Andrei Smertenko³⁸, Simon Stael^{17,39}, Jerry Ståhlberg¹, María Fernanda Suárez⁴⁰, Margot Thome¹⁴, Hannele Tuominen⁴¹, Frank Van Breusegem³⁹, Renier A. L. van der Hoorn⁴², Assaf Vardi⁴³, Boris Zhivotovsky^{44,45}, Eric Lam⁴⁶, Peter V. Bozhkov^{1,*}

¹Department of Molecular Sciences, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center for Plant Biology, Uppsala, Sweden ²COS, Heidelberg University, Heidelberg, Germany ³VIB Center for Inflammation Research; Department of Biomedical Molecular Biology, Ghent University; Ghent, Belgium ⁴Instituto de Investigaciones Biotecnológicas, Universidad Nacional de San Martín, San Martín, Buenos Aires, Argentina ⁵Department of Biological Sciences and School of Freshwater Sciences, University of Wisconsin-Milwaukee, Milwaukee, WI, USA ⁶Department of Marine Biology, Leon H. Charney School of Marine Sciences, University of Haifa, Israel ⁷Department of Marine and Coastal Sciences, Rutgers University, New Brunswick, NJ, USA ⁸Novartis Institutes for BioMedical Research, Basel, Switzerland ⁹Aix-Marseille Univ, CNRS, LISM, Institut de Microbiologie de la Méditerranée, Marseille, France ¹⁰The University of Texas at Austin, Marine Science Institute, Port Aransas, TX, USA ¹¹Centre for Research in Agricultural Genomics (CRAG), CSIC-IRTA-UAB-UB, Campus UAB, Bellaterra, Barcelona, Spain ¹²Department of Physiological Chemistry, Genentech, South San Francisco, CA, USA ¹³University of Ljubljana, Faculty of Chemistry and Chemical Technology, Ljubljana, Slovenia ¹⁴Department of Biochemistry, University of Lausanne, Epalinges, Switzerland ¹⁵Department of Chemistry, Umeå University, Umeå, Sweden ¹⁶Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK ¹⁷VIB Center for Medical Biotechnology; Department of Biomolecular Medicine, Ghent University; Ghent, Belgium ¹⁸Instituto de Bioquímica Vegetal y Fotosíntesis, Universidad de Sevilla and Consejo Superior de Investigaciones Científicas, Sevilla, Spain ¹⁹Interfaculty Institute for Biochemistry, Eberhard Karls University, Tübingen, Germany ²⁰National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, USA ²¹Research Unit Cellular Signal Integration, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany ²²Interdisciplinary Center for Biochemical Research, University of Mogi das Cruzes, Mogi das

*Correspondence: Peter.Bozhkov@slu.se (P.V.B), Alena.Minina@slu.se (E.A.M.).

Cruzes, Brazil ²³Institute of Molecular Biosciences, NAWI Graz, University of Graz; BioTechMed Graz, Graz, Austria ²⁴Sprott Centre for Stem Cell Research, Ottawa Hospital Research Institute and Departments of Medicine and Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada ²⁵Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology - Hellas, Heraklion, Greece ²⁶Department of Biology, University of Crete, Greece ²⁷Department of Plant Biology, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center for Plant Biology, Uppsala, Sweden ²⁸York Biomedical Research Institute, Department of Biology, University of York, York, UK ²⁹Institute for Biomedicine, Sahlgrenska Academy, Centre for Ageing and Health – AgeCap, University of Gothenburg, Gothenburg, Sweden ³⁰Institute for Molecular Biosciences, Faculty of Biosciences, Goethe University, Frankfurt/Main, Germany ³¹Departments of Oral Biological and Medical Sciences / and Biochemistry and Molecular Biology, Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada ³²Protein Biochemistry and Engineering Laboratory, ICMR-National Institute of Malaria Research, New Delhi, India ³³Institute of Clinical Chemistry and Pathobiochemistry, School of Medicine, Technical University of Munich, Munich, Germany ³⁴German Cancer Consortium (DKTK), partner site Munich, Germany ³⁵German Center for Infection Research (DZIF), partner site Munich, Germany ³⁶Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA ³⁷School of Life Sciences, Westlake University, Xihu District, Hangzhou Zhejiang Province, China ³⁸Institute of Biological Chemistry, Washington State University, Pullman, WA, USA ³⁹Department of Plant Biotechnology and Bioinformatics, Ghent University; VIB-UGent Center for Plant Systems Biology; Ghent, Belgium ⁴⁰Departamento de Biología Molecular y Bioquímica, Facultad de Ciencias, Universidad de Málaga, Campus de Teatinos, Málaga, Spain ⁴¹Umeå Plant Science Centre, Department of Plant Physiology, Umeå University, Umeå, Sweden ⁴²Department of Plant Sciences, University of Oxford, Oxford, UK ⁴³Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot, Israel ⁴⁴Division of Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden ⁴⁵Faculty of Fundamental Medicine, MV Lomonosov Moscow State University, Moscow, Russia ⁴⁶Department of Plant Biology, Rutgers the State University of New Jersey, New Brunswick, NJ USA

Abstract

Metacaspases and paracaspases are proteases that were first identified as containing a caspase-like structural fold (Uren et al., 2000). Like caspases, meta- and paracaspases are multifunctional proteins regulating diverse biological phenomena, such as aging, immunity, proteostasis and programmed cell death. The broad phylogenetic distribution of meta- and paracaspases across all kingdoms of life and large variation of their biochemical and structural features complicate classification and annotation of the rapidly growing number of identified homologs. Establishment of an adequate classification and unified nomenclature of meta- and paracaspases is especially important to avoid frequent confusion of these proteases with caspases - a tenacious misnomer that unfortunately does not appear to decline with time. This letter represents a consensus opinion of researchers studying different aspects of caspases, meta- and paracaspases in various organisms, ranging from microbes to plants and animals.

Keywords

Caspases; Metacaspases; Paracaspases; Proteases; Classification; Nomenclature

Classification of meta- and paracaspases

The current classification of proteases provided by the MEROPS database clusters caspases, meta- and paracaspases to the same family, C14, within the CD clan (<https://www.ebi.ac.uk/merops/>). All members of C14 family are annotated to possess aspartate P1 cleavage specificity, and the family is further split into two subfamilies: C14A (caspases) and C14B (meta- and paracaspases).

Importantly, the MEROPS approach of grouping proteases into families or subfamilies is based on statistically significant similarities of the amino acid sequence within the peptidase domain or part thereof, without considering their biochemical properties (Rawlings et al., 2018). Being valuable for high-throughput protease classification, this approach, however, has substantial drawbacks if implemented without further adjustment. Indeed, in contradiction with the MEROPS description, none of the meta- or paracaspases characterized so far cleave after an aspartate residue. Instead, paracaspases are arginine-specific (Coornaert et al., 2008; Hachmann et al., 2012; Rebeaud et al., 2008), whereas metacaspases can cleave after either arginine or lysine (Figure S1A; Sundström et al., 2009; Vercammen et al., 2004). Such fundamental differences in the proteolytic specificity between caspases, meta- and paracaspases imply distinct repertoires of new proteoforms that they generate and point to the complex diversification and coevolution of their substrates and downstream pathways. One unfortunate consequence of the current classification is the misuse of caspase-specific probes for studying meta- and paracaspases that is commonly found in the literature and leads to false conclusions.

Apart from substrate specificity, caspases, meta- and paracaspases feature other fundamental differences (Figure S1A). For example, active metacaspases are monomers and their activation usually requires millimolar concentrations of calcium (Hander et al., 2019; McLuskey et al., 2012; Wong et al., 2012). In contrast, active caspases and paracaspases are calcium-independent dimers (Hachmann et al., 2012; Weismann et al., 2012; Yu et al., 2011). This indicates that upstream pathways regulating activation of caspases, meta- and paracaspases are likewise different.

In the past two decades we have learned about important differences between caspases, meta- and paracaspases. Thus, simple extrapolation of features typical for caspases to all other members of the C14 family is not justified anymore. Instead caspases, meta- and paracaspases should be separated into three corresponding groups within the family and each group should be properly annotated by providing its key biochemical and structural characteristics. We kindly request curators of MEROPS database to make corresponding changes.

Since structure and substrate specificity of prokaryotic caspase-like proteases named “orthocaspases” remain largely unknown (Klemenčič et al., 2015) we leave their

classification and nomenclature open until their structural and biochemical properties have been clarified.

Nomenclature of meta- and paracaspases

The name “caspase” stands for “cysteine-dependent aspartate-specific protease”. Thus, the names “metacaspase” and “paracaspase” imply the wrong substrate specificity for these proteases. However, since these names have been used for two decades we propose to keep them, provided that caspases, meta- and paracaspases are recognized as three separate groups within the C14 family.

Based on domain composition and arrangement, meta- and paracaspases are further subdivided into three and two types, respectively (Figure S1A). For the sake of consistency, we propose to maintain a common nomenclature for the different types of meta- and paracaspases using Latin numerals (e.g. type I metacaspases). As for the conserved protein structures, they will be referred to as the p20-like region, the p10-like region, the linker region and the N-terminal pro-domain, matching the nomenclature of caspases (Figure S1A; Alnemri et al., 1996). The p20, p10 and linker regions have been previously defined for the caspase group of the C14 family (Fuentes-Prior and Salvesen, 2004) and can be easily identified in meta- and paracaspase homologs based on a hidden Markov model (HMM) alignment with the C14 peptidase domain (Figure S1B). Notably, although not always clearly stated in the literature, most known members of the C14 family contain the linker region. Furthermore, type II metacaspases are distinguished by a long linker between the p20 and p10 regions and an additional linker within the p10 region (Figure S1A), which are frequently referred to as a single linker.

We suggest to consider the active form of meta- or paracaspases being a monomer if it is a cleaved or intact polypeptide chain derived from a single translational event, and a dimer if it comprises uncut or processed products of two translational events.

We propose to establish a unified nomenclature of meta- and paracaspases in order (i) to facilitate comparison of orthologs from different organisms and (ii) to make it suitable for annotating homologs of species with partially sequenced genomes. Thus, we suggest using simple root symbols such as MCA for metacaspases and PCA for paracaspases. When naming individual family members, these root symbols will be preceded by the abbreviated Latin name of the species and followed by a hyphen, Latin number representing the type and then a small alpha character indicating in alphabetical order the number of the homolog of this type in a given genome (Figure S1C). Proenzymes that require proteolytic processing for activation could be annotated with a prefix “pro-“, e.g. pro-AtMCA-Ia for the metacaspase 1 of type I from *A. thaliana*. Spliceforms should be indicated by a decimal number (e.g. AtMCA-Ia.1). Please note that these conventions do not consider the letter case, which should conform to gene and protein nomenclature established for a given model organism or taxonomic group.

Importantly, this nomenclature should be used synonymously for meta- and paracaspase homologs with well-established names, e.g. human MALT1/HsPCA-Ia and *A. thaliana*

AtMC1/AtMCA-Ia or AtMC4/AtMCA-IIa. We encourage all researchers to adopt these recommendations. The new classification and unified nomenclature of meta- and paracaspases will facilitate a more comprehensive exchange of relevant findings within the scientific community and help to bridge already existing knowledge with newly discovered homologs, thus promoting mechanistic understanding of these ancient, evolutionarily conserved proteases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by Knut and Alice Wallenberg Foundation. We apologize to colleagues whose work has not been cited due to space limitation.

References

- Alnemri E, Livingston D, Nicholson D, Salvesen G, Thornberry N, Wong W, and Yuan J (1996). *Cell* 87, 171. [PubMed: 8861900]
- Coornaert B, Baens M, Heyninck K, Bekaert T, Haegman M, Staal J, Sun L, Chen ZJ, Marynen P, and Beyaert R (2008). *Nat. Immunol* 9, 263–271. [PubMed: 18223652]
- Fuentes-Prior P, and Salvesen GS (2004). *Biochem. J* 384, 201–232. [PubMed: 15450003]
- Hachmann J, Snipas SJ, Van Raam BJ, Cancino EM, Houlihan EJ, Poreba M, Kasperkiewicz P, Drag M, and Salvesen GS (2012). *Biochem. J* 443, 287–295. [PubMed: 22309193]
- Hander T, Fernández-Fernández ÁD, Kumpf RP, Willems P, Schatowitz H, Rombaut D, Staes A, Nolf J, Pottier R, Yao P, et al. (2019). *Science* 363, 1–10.
- Klemenčič M, Novinec M, and Dolinar M (2015). *Mol. Microbiol* 98, 142–150. [PubMed: 26114948]
- McLuskey K, Rudolf J, Proto WR, Isaacs NW, Coombs GH, Moss CX, and Mottram JC (2012). *Proc. Natl. Acad. Sci. U. S. A* 109, 7469–7474. [PubMed: 22529389]
- Rawlings ND, Barrett AJ, Thomas PD, Huang X, Bateman A, and Finn RD (2018). *Nucleic Acids Res.* 46, D624–D632. [PubMed: 29145643]
- Rebeaud F, Hailfinger S, Posevitz-Fejfar A, Tapernoux M, Moser R, Rueda D, Gaide O, Guzzardi M, Iancu EM, Rufer N, et al. (2008). *Nat. Immunol* 9, 272–281. [PubMed: 18264101]
- Sundström JF, Vaculova A, Smertenko AP, Savenkov EI, Golovko A, Minina E, Tiwari BS, Rodriguez-Nieto S, Zamyatnin AA Jr., Välineva T, et al. (2009). *Nat. Cell Biol* 11, 1347–1354. [PubMed: 19820703]
- Uren A, O’Rourke K, Aravind L, Pisabarro MT, Seshagiri S, Koonin EV, and Dixit VM (2000). *Mol. Cell* 6, 961–967. [PubMed: 11090634]
- Vercammen D, De Cotte B Van, De Jaeger G, Eeckhout D, Casteels P, Vandepoele K, Vandenberghe I, Van Beeumen J, Inzé D, and Van Breusegem F (2004). *J. Biol. Chem* 279, 45329–45336. [PubMed: 15326173]
- Wiesmann C, Leder L, Blank J, Bernardi A, Melkko S, Decock A, D’Arcy A, Villard F, Erbel P, Hughes N, et al. (2012). *J. Mol. Biol* 419, 4–21. [PubMed: 22366302]
- Wong AHH, Yan C, and Shi Y (2012). *J. Biol. Chem* 287, 29251–29259. [PubMed: 22761449]
- Yu JW, Jeffrey PD, Ha JY, Yang X, and Shi Y (2011). *Proc. Natl. Acad. Sci. U. S. A* 108, 21004–21009. [PubMed: 22158899]