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Elena A. Minina[1,2,*], **Jens Staal**[3], **Vanina E. Alvarez**[4], **John A. Berges**[5], **Ilana Berman-Frank**[6], **Rudi Beyaert**[3], **Kay D. Bidle**[7], **Frédéric Bornancin**[8], **Magali Casanova**[9], **Juan J. Cazzulo**[4], **Chang Jae Choi**[10], **Nuria S. Coll**[11], **Vishva M. Dixit**[12], **Marko Dolinar**[13], **Nicolas Fasel**[14], **Christiane Funk**[15], **Patrick Gallois**[16], **Kris Gevaert**[17], **Emilio Gutierrez-Beltran**[18], **Stephan Hailfinger**[19], **Marina Klemenčič**[13], **Eugene V. Koonin**[20], **Daniel Krappmann**[21], **Anna Linusson**[15], **Maurício F. M. Machado**[22], **Frank Madeo**[23], **Lynn A. Megeney**[24], **Panagiotis N. Moschou**[25,26,27], **Jeremy C. Mottram**[28], **Thomas Nyström**[29], **Heinz D. Osiewacz**[30], **Christopher M. Overall**[31], **Kailash C. Pandey**[32], **Jürgen Ruland**[33,34,35], **Guy S. Salvesen**[36], **Yigong Shi**[37], **Andrei Smertenko**[38], **Simon Stael**[17,39], **Jerry Ståhlberg**[1], **María Fernanda Suárez**[40], **Margot Thome**[14], **Hannele Tuominen**[41], **Frank Van Breusegem**[39], **Renier A. L. van der Hoorn**[42], **Assaf Vardi**[43], **Boris Zhivotovsky**[44,45], **Eric Lam**[46], **Peter V. Bozhkov**[1,*]

[1]Department of Molecular Sciences, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center for Plant Biology, Uppsala, Sweden [2]COS, Heidelberg University, Heidelberg, Germany [3]VIB Center for Inflammation Research; Department of Biomedical Molecular Biology, Ghent University; Ghent, Belgium [4]Instituto de Investigaciones Biotecnológicas, Universidad Nacional de San Martin, San Martin, Buenos Aires, Argentina [5]Department of Biological Sciences and School of Freshwater Sciences, University of Wisconsin-Milwaukee, Milwaukee, WI, USA [6]Department of Marine Biology, Leon H. Charney School of Marine Sciences, University of Haifa, Israel [7]Department of Marine and Coastal Sciences, Rutgers University, New Brunswick, NJ, USA [8]Novartis Institutes for BioMedical Research, Basel, Switzerland [9]Aix-Marseille Univ, CNRS, LISM, Institut de Microbiologie de la Méditerranée, Marseille, France [10]The University of Texas at Austin, Marine Science Institute, Port Aransas, TX, USA [11]Centre for Research in Agricultural Genomics (CRAG), CSIC-IRTA-UAB-UB, Campus UAB, Bellaterra, Barcelona, Spain [12]Department of Physiological Chemistry, Genentech, South San Francisco, CA, USA [13]University of Ljubljana, Faculty of Chemistry and Chemical Technology, Ljubljana, Slovenia [14]Department of Biochemistry, University of Lausanne, Epalinges, Switzerland [15]Department of Chemistry, Umeå University, Umeå, Sweden [16]Faculty of Biology, Medicine and Health, University of Manchester, Manchester, UK [17]VIB Center for Medical Biotechnology; Department of Biomolecular Medicine, Ghent University; Ghent, Belgium [18]Instituto de Bioquímica Vegetal y Fotosíntesis, Universidad de Sevilla and Consejo Superior de Investigaciones Científicas, Sevilla, Spain [19]Interfaculty Institute for Biochemistry, Eberhard Karls University, Tübingen, Germany [20]National Center for Biotechnology Information, National Library of Medicine, Bethesda, MD, USA [21]Research Unit Cellular Signal Integration, Helmholtz Zentrum München - German Research Center for Environmental Health, Neuherberg, Germany [22]Interdisciplinary 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 [23]Institute of Molecular Biosciences, NAWI Graz, University of Graz; BioTechMed Graz, Graz, Austria [24]Sprott Centre for Stem Cell Research, Ottawa Hospital Research Institute and Departments of Medicine and Cellular and Molecular Medicine, University of Ottawa, Ottawa, ON, Canada [25]Institute of Molecular Biology and Biotechnology, Foundation for Research and Technology - Hellas, Heraklion, Greece [26]Department of Biology, University of Crete, Greece [27]Department of Plant Biology, Uppsala BioCenter, Swedish University of Agricultural Sciences and Linnean Center for Plant Biology, Uppsala, Sweden [28]York Biomedical Research Institute, Department of Biology, University of York, York, UK [29]Institute for Biomedicine, Sahlgrenska Academy, Centre for Ageing and Health – AgeCap, University of Gothenburg, Gothenburg, Sweden [30]Institute for Molecular Biosciences, Faculty of Biosciences, Goethe University, Frankfurt/Main, Germany [31]Departments of Oral Biological and Medical Sciences / and Biochemistry and Molecular Biology, Life Sciences Institute, University of British Columbia, Vancouver, BC, Canada [32]Protein Biochemistry and Engineering Laboratory, ICMR-National Institute of Malaria Research, New Delhi, India [33]Institute of Clinical Chemistry and Pathobiochemistry, School of Medicine, Technical University of Munich, Munich, Germany [34]German Cancer Consortium (DKTK), partner site Munich, Germany [35]German Center for Infection Research (DZIF), partner site Munich, Germany [36]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA [37]School of Life Sciences, Westlake University, Xihu District, Hangzhou Zhejiang Province, China [38]Institute of Biological Chemistry, Washington State University, Pullman, WA, USA [39]Department of Plant Biotechnology and Bioinformatics, Ghent University; VIB-UGent Center for Plant Systems Biology; Ghent, Belgium [40]Departamento de Biologia Molecular y Bioquimica, Facultad de Ciencias, Universidad de Malaga, Campus de Teatinos, Malaga, Spain [41]Umeå Plant Science Centre, Department of Plant Physiology, Umeå University, Umeå, Sweden [42]Department of Plant Sciences, University of Oxford, Oxford, UK [43]Department of Plant and Environmental Sciences, Weizmann Institute of Science, Rehovot, Israel [44]Division of Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden [45]Faculty of Fundamental Medicine, MV Lomonosov Moscow State University, Moscow, Russia [46]Department 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 sub-divided 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*. Spliceoforms 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.

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