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Editorial Letter: Carmela Giglione, Chahrazade El Amri and Gilles Lalmanach

Suggested title: "A yummy blend of homeostasis and proteolytic mechanisms".

1. Summary

In recent years, the field of proteolysis has experienced a surge in interest and notable achievements, which has led to a growing number of conferences, reviews, and publications centered around this topic. *Biochimie* has been a pioneer in promoting this progress. Since 2008, the journal has published four thematic issues devoted to the ever-evolving field of proteolytic enzymes: “Cellular proteolysis” (Vol. 90(2), February 2008), “Protease inhibitors and biological control” (Vol. 92(11), November 2010), “A potpourri of proteases and inhibitors: from molecular toolboxes to signaling scissors” (Vol. 122(C), March 2016) and "Proteases: goldies enzymes always on the agenda" (Vol. 166, November 2019). All issues received an extremely positive welcome, which materialized by both number of readings and rate of citations and quotations. Given these previous positive achievements, we are pleased to have accepted the role of Guest Editors for a fifth thematic issue of *Biochimie* entitled “At the crossroads of proteostasis and proteolysis”. In this special issue, we have curated a collection of articles that we hope will be both insightful and engaging. We extend our sincere thanks to Prof. Bertrand Friguet, Editor-in-Chief of *Biochimie*, for his invaluable role as the handling editor in managing the manuscripts for this issue.

But why this title "At the crossroads of proteostasis and proteolysis»? The adventure was inspired by the successful organization of a recent scientific joint conference between the "cellular proteolysis" thematic group of the French Society of Biochemistry and Molecular Biology (SFBBM) and one of the four working groups of the COST European network "ProteoCure" (so called "a sound proteome for a sound body: targeting proteolysis for proteome remodeling"). This conference (<https://proteolysis2023.sciencesconf.org/>), held in the beautiful and historical Campus Les Cordeliers-Sorbonne Université (May 22-24th, 2023, Paris, France), was co-organized by Chahrazade El Amri and Bertrand Friguet (Sorbonne Université, CNRS, INSERM, Paris, France), Carmela Giglione (Université Paris-Saclay, CEA, CNRS, Gif-sur-Yvette, France), and Gilles Lalmanach (Université de Tours, INSERM, Tours, France). It brought together more than a hundred people from 15 countries (mainly European as well as a large delegation from South Korea). Organized into six main sessions (Inflammation, Cancer, Autophagy, Omics and Drug Design, Host-Pathogens Interactions, Aging and Neurodegenerative Diseases), the conference was a tremendous success. It fostered rich scientific discussions among attendees, complemented by friendly social interactions, particularly during the enjoyable wine and cheese gatherings that further enhanced the collaborative atmosphere.

2. Original Contributions

Proteins are essential molecular actors in every cellular process. From their synthesis to their degradation, they are subject to constant and strict quality control mechanisms to ensure

that they properly and timely take on their functions to fulfil cellular needs. Proteolysis is a chief biological process that straightforwardly controls individual protein levels and ensures the degradation of abnormal proteins. Failures of this precise molecular machinery leading to accumulation of deleterious proteins or in the opposite to excessive hydrolysis of beneficial ones are implicated in multiple human diseases (e.g., cancers, obesity, neurodegeneration, infectious diseases).

In this issue, it was not feasible to cover all aspects of the proteostasis, including proteolysis, due to vast complexity of this landscape. Instead, our goal was to provide an outline of some foremost players and recent and awesome progress in the field. We believe that the objective has been satisfactorily reached, with a fair combination of sixteen articles authored by distinguished colleagues. These articles are assembled in five chapters blending bibliographic reviews and original research contributions.

2.1. To achieve a well-balanced cocktail

The introductory article (ProteoCure: an European network to fine-tune the proteome), an *ad hoc* contribution for this special issue, was proposed by Olivier Coux (Montpellier, France), Rosa Farràs (Valencia, Spain), the chair and the vice-chair of the ProteoCure COST Action, respectively, and the ProteoCure Core Group (*i.e.*, in alphabetical order: Mohamad Abbas, Rosa Barrio, Christine Blattner, Klaudia Brix, Georgia Chachami, Eric Chevet, Michael Clague, Nico Dantuma, Aleksandra Divac Rankov, Carles Galdeano, Carmela Giglione, Michael Glickman, Gilles Lalmanach, Catherine Lindon, Rune Matthiesen, Germana Meroni, Elah Pick, Carmen Rivas, Manuel Rodriguez, Esther Sammler, Ayala Shiber, Efthimios Skoulakis, Matthias Stein and Alfred Vertegaal).

This contribution highlights the vast potential of manipulating the proteolytic machinery to control protein abundance as a strategy for therapeutic intervention. ProteoCure (<https://proteocure.eu/>) gathers European researchers from the academic, clinical, and industry sectors, interested to develop a knowledge-based network fostering research on this issue. By organizing community-building activities, fostering synergies among European scientists and reinforcing the training of the next generation of European researchers, ProteoCure participates in a large and creative exchange hub focusing on normal and pathologic proteolysis, and on the development of innovative tools modulating the level of specific proteins. The final aim is to facilitate the translation of novel discoveries into products of clinical and/or economical value.

2.2 First, you need a generous portion of cysteine cathepsins with a peel of acid cathepsin

Boris Turk and his group (Ljubljana, Slovenia) offered an outstanding review (Ercegovič Rot et al) on the roles of cysteine cathepsins as diagnostic markers and therapeutic targets in cancer. The review aims to provide worthy insights into the clinical relevance of cathepsins in personalized and targeted medical interventions in oncology.

Fabien Lecaille and colleagues (Tours, France) present original findings on how short-term exposure of mice to cigarette smoke increased the expression and activity of cysteine cathepsin S, which could contribute to the defect of zonula occludens 1 (ZO-1), an epithelial tight junction protein that stabilizes barrier assembly (Estur et al).

Inherited deficiency of cathepsin D (CSTD), a lysosomal aspartic protease, causes a severe pediatric neurodegenerative disease called neuronal ceroid lipofuscinosis (NCL) type

10. By using an innovative mass-spectrometry based proteome analysis, Thomas Reinheckel and Lisa Heß (Freiburg, Germany), in collaboration with Oliver Schilling group (Freiburg, Germany) demonstrated that prominent change was observed for mitochondrial proteins indicating a failure of energy production in CTSD-inhibited Lund human mesencephalic (LUHMES) cells, and hypothesized that mitochondrial dysfunction upon CTSD inhibition is a driving force for the successive loss of neurons in patients with NCL type 10 (Schneider et al).

Klaudia Brix and her group (Bremen, Germany) together with Stefan Pöhlmann and Markus Hoffmann groups (Göttingen, Germany) nicely demonstrated that the mere interaction of the SARS-CoV-2 with neuronal cells (SH-SY5Y cell line) can affect cellular architecture and proteolytic capacities. Indeed SARS-CoV-2 mainly infects the respiratory tract but can also target central nervous system. The expression of the spike protein-processing cathepsin L was up-regulated by wild type, Alpha and Delta spike protein pseudo types, while SARS-CoV-2 spike protein mediates the entry of pseudo typed particles into SH-SY5Y cells and affect the spike variants to rearrange the cytoskeleton of these cells (Oliveira et al).

Alterations in the expression of cathepsins have been observed in many diseases. These changes are not exclusively harmful but may have also a compensatory role on the lack of one cathepsin to maintain tissue integrity. The upregulation of specific cathepsins in response to the inhibition or dysfunction of other cathepsins suggests a fine-tuned system of proteolytic balance. Ana Mitrović and Janko Kos (Ljubljana, Slovenia) proposed a salient review to better understand the compensatory role of these enzymes (Pečar Fonović et al).

2.3 Then, add generous serving sizes of serine proteases balanced with metalloproteinases

Alzheimer's diseases (AD) and related dementias constitute a major global health challenge. Kallikrein-related peptidases (KLKs) have been implicated in key processes such as neurodegeneration, neuroinflammation and synaptic dysfunction. Chahrazade El Amri and her colleagues (Paris, France) conducted a comprehensive survey that explores the intricate interplay between KLKs and key AD molecular pathways. Their work highlights the potential of KLKs not only as valuable biomarkers but also as promising therapeutic targets for addressing these complex neurodegenerative diseases (Boumali et al).

The fungal serine protease (NHSSP) from *Onygena corvina* displays remarkable biochemical properties (broad temperature and pH activity ranging) and may represent an alternative to proteinase K for an industrial use. Marcin Drag, Paulina Kasperkiewicz and their collaborators (Wroclaw, Poland) offered an original article of primary interest. They have completed the in-depth characterization of NHSSP substrate specificity by using a positional scanning substrate combinatorial library (PS-SCL), before tailoring the first covalent (diphenylphosphonate as a warhead) NHSP inhibitor (Kasperkiewicz et al).

Targeted proteomics allows a greatly sensitive and specific investigation of complex tissue samples compared to conventional techniques. For the first time here, Andrea Heinz (Copenhagen, Denmark) and collaborators depicted the MMP (matrix metalloproteinase) landscape in imiquimod (IMQ)-induced skin inflammation mouse model analyzed and showed that MMP profiles in inflamed mouse skin resemble those in skin of psoriasis patients, supporting that IMQ-induced inflammation as compared to non-inflamed control skin can be exploited as a model to investigate drug efficacy (Kyung Noddeland, Canbay et al). This work is dedicated to Prof. Ulrich auf dem Keller (Technical University of Denmark, Kongens Lyngby,

Denmark) who sadly passed away shortly before the submission of this article.

Besides the archetypal role of thrombin in blood clotting, recent work has unraveled its constitutive release by intestinal epithelial cells, opening new research avenues on the role of thrombin in the gut. In a stylish review, Nathalie Vergnolle (Toulouse, France) examined the putative role of thrombin in the gut and its regulation and discussed the potential interest of targeting thrombin for treatments of intestinal pathologies.

2.4 Don't forget: the recipe's secret depends on post-translational flavoring and proteostatic spices

N-terminal (Nt) acetylation is a key regulatory event of protein lifetime and proteostasis, which is catalyzed by N-terminal acetyltransferases (NATs). Thomas Arnesen and his team (Bergen, Norway) have very convincingly characterized a specific antibody that recognizes Nt-acetylated Met-starting proteins, displaying selectivity for some subtypes of Met-starting N-termini. Appropriately, they proposed that this antibody could be a useful device for studies and identification of NatC, NatE and NatF substrates (Larsen et al).

Caroline Cieniewski-Bernard (Lille, France) and her collaborators offered an original and stimulating work, aiming to identify whether phosphorylation and/or O-GlcNAcylation are involved in α B-crystallin targeting towards cytoskeleton in proteotoxic stress induced by proteasome inhibition in myotubes. They demonstrated that proteotoxicity led to phosphorylation and O-GlcNAcylation patterns changes of α B-crystallin, but not of desmin. These post-translational modifications correlated with α B-crystallin translocation towards cytoskeleton (Bulangalire et al).

PA28 γ is a proteasomal interactor whose main and most known function is to stimulate the 20S proteasome independently of ubiquitin and ATP. PA28 γ plays numerous pivotal functions such as cellular division, neoplastic transformation, chromatin organization or DNA repair mechanisms. In this noteworthy update, Paolo Cascio (Turin, Italy) focused on contemporary evidence showing that PA28 γ participates in cell-mediated acquired immunity with a particular role in attenuating MHC class I antigen presentation, especially in relation to neoplastic transformation and autoimmune diseases.

The proteostasis network and associated protein quality control (PQC) mechanisms ensure proteome functionality and are essential for cell survival. While PQC mechanisms have been investigated for decades in the cytoplasm and the endoplasmic reticulum, our knowledge of nuclear PQC pathways is only emerging. Frédéric Frottin (Gif-sur-Yvette, France), along with Julia Buggiani, Thierry Meinnel and Carmela Giglione, reviewed and explored the specificity of the nuclear compartment, the effectors of the nuclear proteostasis network, and the PQC roles of nuclear membrane-less organelles in metazoans (Buggiani et al).

2.5 After a final *ad hoc* quality control, quickly serve the "ProteoCuracao" cocktail

Maintenance of mitochondrial homeostasis requires a plethora of coordinated quality control, in which mitochondrial proteases play a key role (e.g., molecular and organellar quality control, metabolic adaptations, lipid homeostasis or transcriptional stress responses). Defective mitochondrial proteolysis results in mitochondrial diseases as well neurodegeneration and cancer. In a comprehensive review article, Nicoleta Moiso (Leicester, UK) discussed how mitochondrial proteases and mitochondria stress signalling impact cellular homeostasis and

determine the decision to survive or die, as well how modulation of mitochondrial proteolysis may offer novel therapeutic strategies.

Dipeptidyl peptidase (DPP9) is an intracellular amino-dipeptidase playing crucial biological roles in the immune system, DNA repair and mitochondria homeostasis while its deregulation is linked to cancer progression and immune-associated defects. Also, DPP9 acts as a molecular switch that regulates key proteins, such as the tumor-suppressor BRCA2. Ruth Geiss-Friedlander and her group (Freiburg, Germany) offered us an outstanding discussion on key concepts underlying the outcomes of protein processing by DPP9, including substrate turnover by the N-degron pathway. Moreover, they examined regulatory mechanisms and non-enzymatic roles of DPP9, with an emphasis on its interactome (Samuel Zolg et al).

3. Concluding statements

We extend our heartfelt thanks to all friends and colleagues who have contributed to this thematic issue of *Biochimie*, titled “At the crossroads of proteostasis and proteolysis”. We acknowledge the reviewers for their fruitful and relevant comments. We are very grateful to Prof. Bertrand Friguet, the Editor-in-Chief of *Biochimie*, for his impressive efficiency and dedication as the Handling Editor. Finally, we warmly acknowledge Malika Hassini, the Editorial Office Manager of *Biochimie*, for her invaluable, proficient and friendly assistance.

Prof. Chahrazade El Amri ¹, Dr. Carmela Giglione ² and Prof. Gilles Lalmanach ³

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