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INTRODUCTION

Introduction to the Special Issue on Proteases and Proteolysis in Health and Disease

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Proteases are involved in fundamental processes such as cell death and survival. It is, therefore, not surprising that the human genome encodes 561 protease or protease-related genes and more than 150 protease inhibitors [1]. The importance of proteases is also underscored by their overlapping and redundant activities and their functional conservation throughout the eukaryotic lineage. The deregulation of protease function can affect multiple cellular pathways at once and have severe consequences on human health. Indeed, protease-targeting therapies have been the subject of intense research for decades and several protease inhibitors have already been successfully used to treat diseases. In this Special Issue on Proteases, experts in this diverse field review important and emerging topics, including caspases and cell death substrates [2], protease deregulation in human disorders [3–5], proteases as drug targets [6–8], the development of artificial substrates and detection methods to monitor protease activity *in vivo* [9–11] and the role of proteases in plant development [12]. We hope that these reviews are important and enlightening for both experts and newcomers to the field, and thank the authors and referees for their contributions.

Denault *et al.* set the stage for this special issue with their review on caspases [2]. Their contribution focuses on the role of caspases in the turnover of proteins involved in cellular trafficking. The review notably begins by laying out the rules for 'a good caspase substrate' and guidelines on the essential structural features of selective artificial substrates and inhibitors. The review then discusses the breadth of involvement of caspases in regulating intracellular trafficking, providing in-depth information on substrates, their subcellular localisation and associated human disorders.

Three reviews in this special issue cover the role of proteases in human disorders. Tanabe and List discuss type II transmembrane serine proteases (TTSPs) and their roles in cancer signalling [3]. The review highlights known TTSP substrates and signalling cascades, and inhibitors of TTSP-mediated signalling as candidates for anticancer therapies. Reinheckel *et al.* focus on the genetic disorders caused by mutations in cathepsin-encoding genes, while highlighting the clinical symptoms and the downstream effects of the mutant protease [4]. Blum *et al.* discuss the role of cysteine cathepsin proteases in the development and progression of atherosclerosis [5]. Specifically, the authors highlight the roles of cysteine cathepsins in inflammation, lipid metabolism and apoptosis – processes known to be deregulated in atherosclerosis – as well as the potential use of cysteine cathepsins as biomarkers of vascular pathologies and in the development of targeted therapies.

Many soluble proteases have also successfully been targeted for treating various disorders such as diabetes, hypertension, myeloma and human immunodeficiency virus infections. The success of these therapies and the involvement of proteases in numerous signalling pathways make them particularly attractive targets for continued drug discovery. McGowan *et al.* analyse the current knowledge of the family of M1 aminopeptidases – their structure, physiological roles and their potential as drug targets [6]. Importantly, this review highlights the necessity of accurate biochemical characterisation of M1 aminopeptidases, through the use of selective artificial substrates, if these proteases are to be considered as drug targets for a range of human diseases. Similarly, Steven Verhelst discusses the potential of intramembrane protease inhibitors as viable therapies and the challenges that remain before these can enter clinical trials [7]. O'Donoghue *et al.* discuss how approved drugs, such as proteasome inhibitors, can be used to target the proteasome of pathogenic organisms such as *Plasmodium falciparum* as well strategies to develop more potent and selective proteasome inhibitors to treat infectious diseases [8].

Although immense progress has been made in determining the structures and biochemical characteristics of individual proteases, accurately measuring or selectively inhibiting the activity of specific proteases *in vivo* remains challenging. Numerous proteases have

Abbreviations

ABPs, activity-based probes; PCD, programmed cell death; TTSPs, transmembrane serine proteases.

overlapping substrate specificities and similar catalytic mechanisms. The review by Drag *et al*., focuses on the experimental techniques and the best substrates and inhibitors needed to distinguish individual proteases with overlapping substrate specificity [9]. Activity-based probes (ABPs) can circumvent the limitations of fluorescence-based substrates by virtue of their modular design and capacity to form a covalent bond with the protease active-site residue. This is an area that our lab is actively pursuing, and two collaborative pieces between our group and the Flygare and Wertz groups at Genentech address this issue. We highlight broad-spectrum and subunit-specific ABPs that target the proteasome, with emphasis on the characteristics that confer selectivity and suitability for basic or clinical research [10]. A second review discusses the use of ABPs for studying deubiquitinases and ubiquitin-conjugating enzymes [11]. Here, we also discuss the key structural features that underlie selectivity for target enzymes and the suitability of ABPs in various experimental applications. In both reviews, key information such as chemical structures, common names and targets are provided to make these reviews a valuable resource for anyone using ABPs to study the ubiquitin-proteasome system.

We end our special issue with a look across the plant kingdom. While the role of caspases in apoptosis has been firmly established in animals, it is still unclear whether the same is true for plants. Studies have shown that programmed cell death (PCD) exists in plants and identified caspase-like activities and cysteine proteases in plant tissues, but no conserved, apoptosis-like, pathway was identified. Sueldo and van der Hoorn review the evidence implicating cysteine proteases in PCD during plant tissue differentiation and development [12]. In particular, the authors point out differences in the roles of proteases in PCD in various plant species and caution against extrapolating findings from one species to another. Regardless, the significant published work in this area suggests that proteases play important roles in PCD in plants.

We hope you find these pieces as engaging and informative as we have, and again thank our authors, referees and editorial board members for their key contributions to this issue.

References

1 Puente XS, Sánchez LM, Overall CM and López-Otín C (2003) Human and mouse proteases: a comparative genomic approach. *Nat Rev Genet* **4**, 544–558.
2 Duclos C, Lavoie C and Denault J-B (2017) Caspases rule the intracellular trafficking cartel. *FEBS J* **284**, 1394–1420.
3 Tanabe LM and List K (2016) The role of type II transmembrane serine protease-mediated signaling in cancer. *FEBS J* **284**, 1421–1436.
4 Ketterer S, Gomez-Auli A, Hillebrand LE, Petrera A, Ketscher A and Reinheckel T (2017) Inherited diseases caused by mutations in cathepsin protease genes. *FEBS J* **284**, 1437–1454.
5 Weiss-Sadan T, Gotsman I and Blum G (2017) Cysteine proteases in atherosclerosis. *FEBS J* **284**, 1455–1472.
6 Drinkwater N, Lee J, Yang W, Malcolm TR and McGowan S (2017) M1 aminopeptidases as drug targets: broad applications or therapeutic niche? *FEBS J* **284**, 1473–1488.
7 Verhelst SHL (2017) Intramembrane proteases as drug targets. *FEBS J* **284**, 1489–1502.
8 Bibo-Verdugo B, Jiang Z, Caffrey CR and O'Donoghue AJ (2017) Targeting proteasomes in infectious organisms to combat disease. *FEBS J* **284**, 1503–1517.
9 Kasperkiewicz P, Poreba M, Groborz K and Drag M (2017) Emerging challenges in the design of selective substrates, inhibitors and activity-based probes for indistinguishable proteases. *FEBS J* **284**, 1518–1539.
10 Hewings DS, Flygare JA, Wertz IE and Bogyo M (2017) Activity-based probes for the multicatalytic proteasome. *FEBS J* **284**, 1540–1554.
11 Hewings DS, Flygare JA, Bogyo M and Wertz IE (2017) Activity-based probes for the ubiquitin conjugation–deconjugation machinery: new chemistries, new tools, and new insights. *FEBS J* **284**, 1555–1576.
12 Sueldo DJ and van der Hoorn RAL (2017) Plant life needs cell death, but does plant cell death need Cys proteases? *FEBS J* **284**, 1577–1585.