



**HAL**  
open science

## AJP-Cell physiology begins a theme series on the control of the proteostasis network in health and diseases

Eric Chevet, Remy Pedoux, Sophie Lotersztajn

### ► To cite this version:

Eric Chevet, Remy Pedoux, Sophie Lotersztajn. AJP-Cell physiology begins a theme series on the control of the proteostasis network in health and diseases. *American Journal of Physiology - Cell Physiology*, 2016, 311 (2), pp.C163-C165. 10.1152/ajpcell.00130.2016 . hal-01372754

**HAL Id: hal-01372754**

**<https://univ-rennes.hal.science/hal-01372754v1>**

Submitted on 18 Oct 2016

**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.

1 **AJP-Cell Physiology begins a theme series on the control of the proteostasis**  
2 **network in health and diseases**

3

4 Eric Chevet<sup>1,2</sup>, Remy Pedeux<sup>1,2</sup> and Sophie Lotersztajn<sup>3</sup>

5

6 <sup>1</sup>Inserm ERL440, « Oncogenesis, Stress, Signaling », Université Rennes 1, Rennes,  
7 France. <sup>2</sup>Centre de Lutte Contre le Cancer Eugène Marquis, Rennes, France. <sup>3</sup>Inserm  
8 U1149, Center for Research on Inflammation, 75018 Paris, France; Université Paris  
9 Diderot, Sorbonne Paris Cité, Faculté de Médecine Xavier Bichat, 75018 Paris, France

10

11 Correspondence to EC, Inserm ERL440, “Oncogenesis, Stress, Signaling” Centre de Lutte  
12 Contre le Cancer Eugène Marquis, Avenue de la bataille Flandres Dunkerque, 35042  
Rennes, France. Email: [eric.chevet@inserm.fr](mailto:eric.chevet@inserm.fr)

16 The maintenance of protein homeostasis (proteostasis) is essential for all functions of cells  
17 and the organism and results from a tightly controlled balance between synthesis, folding  
18 and selective degradation of damaged and aggregated proteins. Multiple physiological  
19 situations challenge the proteome, including developmental changes or adaptation to  
20 environmental stress conditions, as well as the accumulation of misfolded or damaged  
21 proteins. In the past years, characterization of the molecular machinery involved in the  
22 maintenance of cellular proteostasis has led to a better understanding of how this process  
23 controls physiological and pathological situations, hence allowing the design of novel  
24 therapeutic tools.

25 Protein homeostasis relies on a specific network that integrates numerous molecular  
26 partners and that is referred to as the proteostasis network (PN) (1). The PN is a  
27 multicompartamental system that coordinates the conserved molecular machines to ensure  
28 protein synthesis, folding, quality control, localization, modification, assembly, and turnover  
29 ((8); **Figure 1**).

30

31 Although the synthesis and degradation machineries are well characterized  
32 individually, the understanding of proteostasis control as a whole still needs to be further  
33 documented. Quality control mechanisms ensure the detection and degradation of  
34 misfolded proteins to prevent aggregation and deleterious effects of dysfunctional proteins  
35 (proteotoxicity). These events are often specific to a particular subcellular compartment (by  
36 variation of the composition of PN's molecular composition) and also depend on a finely  
37 tuned coordination of the two major proteolytic pathways, the ubiquitin-proteasome system  
38 (UPS) and autophagy (6), and on protein modifications by ubiquitination or sumoylation  
39 (**Figure 2**; (4, 6)). The adjustments of the PN in response to variation in protein  
40 synthesis/folding demand are ensured by coordination of stress signaling pathways that can  
41 also be compartment specific (e.g. Unfolded Protein Response(UPR)<sup>ER</sup> (5), Unfolded  
42 Protein Response (UPR)<sup>mito</sup> (7), or heat shock response (3)).

43

44 In addition to the common factors required for protein synthesis, maintenance and turnover,  
45 the expression of many PN components is adjusted to the specific protein demands  
46 exhibited by different cells and tissues (1). Furthermore, proteostasis control plays  
47 instrumental roles throughout development or when organisms/cells are exposed to  
48 challenging/disease conditions. As such, the activity of the PN can be altered permanently  
49 or transiently by developmental processes (e.g aging) (8), physiological alterations (e.g.  
50 oncogene expression, protein variants), or exposure to environmental stress (e.g. nutrient  
51 deprivation, hypoxia, heat) (2). Consequently, protein homeostasis adjustments through  
52 PN-mediated control can be viewed as a global adaptive mechanism to cope with the

53 accumulation of misfolded and/or damaged proteins, In addition to this homeostatic  
54 function, stress response pathways that are part of the PN can also trigger apoptosis in  
55 response to terminal stress. This is well illustrated in the context of the Unfolded Protein  
56 Response (5). Thus, PN temporal and spatial fluctuations in the PN could have profound  
57 consequences for disease occurrence and progression.

58

59 The proteostasis network is also challenged or rewired in a wide range of diseases,  
60 including degenerative, metabolic, inflammatory, immune diseases or cancer, and has  
61 consequently become an attractive therapeutic target (1). In keeping, pharmacological  
62 targeting of the PN has proven successful for the treatment of proteostasis diseases, for  
63 instance by the use of the chemical chaperone phenyl butyrate in patients with cystic  
64 fibrosis patients (10), or proteasome inhibitors in patients with multiple myeloma (9).  
65 However, the development of therapeutic strategies targeting the PN has been limited by  
66 the size, complexity, dynamics and partial redundancy of the PN (1). Therefore, the  
67 extensive characterization of disease-associated PN(s) may be essential to predict disease  
68 outcome as well as drug sensitivity/resistance parameters.

69

70 This Review series will cover different aspects of protein homeostasis control.  
71 Articles will discuss the involvement of Ubiquitin and SUMO proteins in the proteostasis  
72 network, as well as their cross-talk to yield proper biological outcomes. Protein degradation  
73 machineries will also be discussed including autophagy and coordinated degradation  
74 through the proteasome and the lysosome. Finally, deregulation of proteostasis pathways in  
75 pathophysiological situations will be illustrated in the context of muscle wasting and cancer.  
76 We believe that readers will find the Review articles in this Theme of interest. In addition,  
77 we hope that the ideas and results discussed in the articles will stimulate experiments that  
78 address unanswered, important questions regarding cellular mechanisms that contribute to  
79 the regulation of proteostasis. We look forward to receiving manuscripts that provide such  
80 results at *AJP-Cell Physiology*.

81

82 Eric Chevet, Guest Editor

83 Sophie Lotersztajn, Associate Editor

84

### 85 **Acknowledgements**

86 The authors would like to acknowledge networking support by the Proteostasis (BM1307)  
87 and Transautophagy (CA 15138) COST actions.

88

89

90 **References**

- 91 1. **Balch WE, Morimoto RI, Dillin A, and Kelly JW.** Adapting proteostasis for disease  
92 intervention. *Science* 319: 916-919, 2008.
- 93 2. **Chevet E, Hetz C, and Samali A.** Endoplasmic Reticulum Stress-Activated Cell  
94 Reprogramming in Oncogenesis. *Cancer Discov* 5: 586-597, 2015.
- 95 3. **Dai C, and Sampson SB.** HSF1: Guardian of Proteostasis in Cancer. *Trends Cell*  
96 *Biol* 26: 17-28, 2015.
- 97 4. **Franz A, Ackermann L, and Hoppe T.** Create and preserve: proteostasis in  
98 development and aging is governed by Cdc48/p97/VCP. *Biochim Biophys Acta* 1843: 205-  
99 215, 2013.
- 100 5. **Hetz C, Chevet E, and Oakes SA.** Proteostasis control by the unfolded protein  
101 response. *Nat Cell Biol* 17: 829-838, 2015.
- 102 6. **Hipp MS, Park SH, and Hartl FU.** Proteostasis impairment in protein-misfolding and  
103 -aggregation diseases. *Trends Cell Biol* 24: 506-514, 2014.
- 104 7. **Jensen MB, and Jasper H.** Mitochondrial proteostasis in the control of aging and  
105 longevity. *Cell Metab* 20: 214-225, 2014.
- 106 8. **Labbadia J, and Morimoto RI.** The biology of proteostasis in aging and disease.  
107 *Annu Rev Biochem* 84: 435-464, 2015.
- 108 9. **Nathwani N, Larsen JT, and Kapoor P.** Consolidation and Maintenance Therapies  
109 for Newly Diagnosed Multiple Myeloma in the Era of Novel Agents. *Curr Hematol Malig Rep*  
110 11: 127-136, 2016.
- 111 10. **Roomans GM.** Pharmacological approaches to correcting the ion transport defect in  
112 cystic fibrosis. *Am J Respir Med* 2: 413-431, 2003.

113

114

115

116 **Figure Legends**

117

118 **Figure 1:** Schematic representation of the different cellular modules that constitute the  
119 proteostasis network.

120

121 **Figure 2 :** Role of ubiquitin and ubiquitin-like proteins in the control of protein homeostasis.  
122 Proteins are synthesized in an unfolded state and can either fold to a folded conformation,  
123 or misfold if the latter cannot be completed. Misfolded proteins are directly triggered to  
124 proteasomal degradation through a mechanism dependent on polyubiquitination, and some  
125 proteins are also prone to aggregation. Aggregates can be removed mainly through  
126 autophagy-dependent mechanisms. Sumoylation (green) or monoubiquitination can impact  
127 on protein stability and on the folding state and these protein modifications can cooperate to  
128 impact on quality control issues.

129

130

131



