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

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2 **network in health and diseases**
3
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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 homoestasis 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   multicompartmental 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)[ER] (5), Unfolded
42   Protein Response (UPR)[mito] (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*.

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82   Eric Chevet, Guest Editor

83   Sophie Lotersztajn, Associate Editor

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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

Quality Control

Folding

Toxicity

Stress response

Synthesis

Degradation