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

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

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

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

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

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

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

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

Eric Chevet, Guest Editor
Sophie Lotersztajn, Associate Editor

Acknowledgements

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

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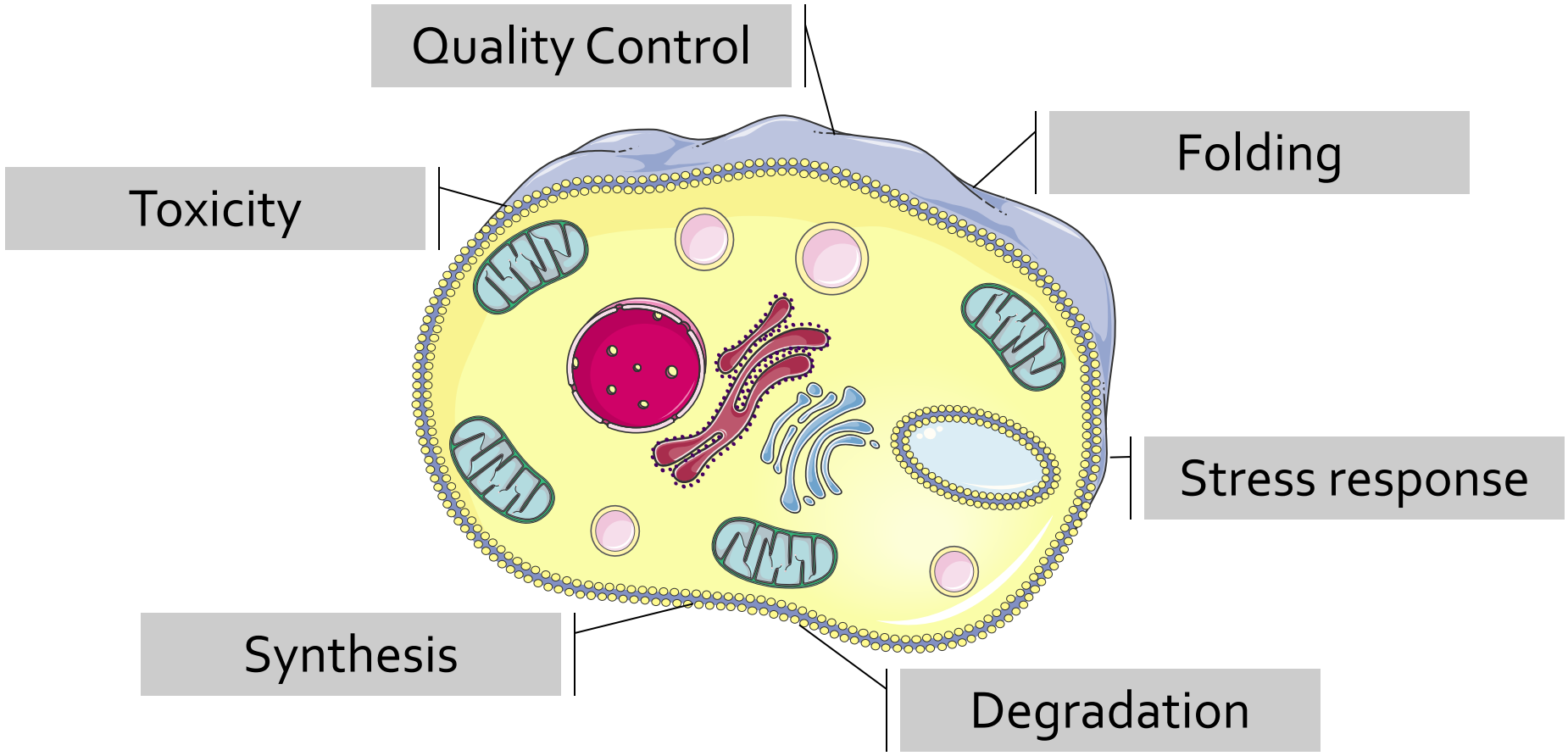
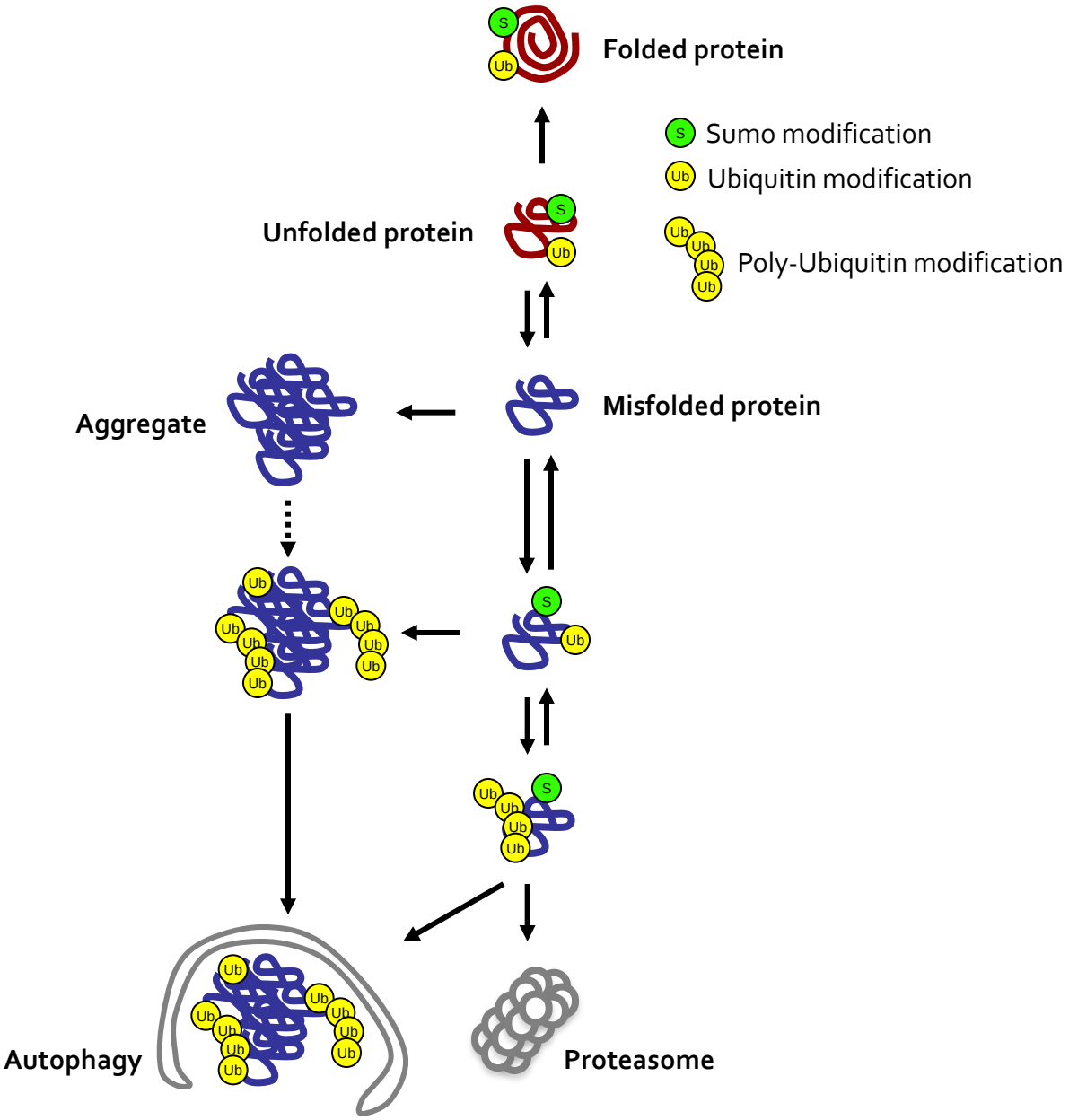
116 **Figure Legends**
117
118 **Figure 1:** Schematic representation of the different cellular modules that constitute the
119 proteostasis network.
120
121 **Figure 2** : Role of ubiquitin and ubiquitin-like proteins in the control of protein homeostasis.
122 Proteins are synthesized in an unfolded 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


Folded protein
Sumo modification
Ubiquitin modification
Poly-Ubiquitin modification
Unfolded protein
Misfolded protein
Aggregate
Autophagy
Proteasome