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Scientific Life

PROTEOSTASIS: A European network to break barriers and integrate science on protein homeostasis

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ABSTRACT

Protein homeostasis (proteostasis) is at the core of cellular functions. The European network PROTEOSTASIS was created to steer research and foster collaborations in the interconnected fields of posttranslational modifications by Ubiquitin-family members and protein turnover by proteasome, autophagy and lysosomal systems in health and diseases, across the kingdoms of life.

Proteostasis - The Topic

Proteostasis – the portmanteau of *protein* and *homeostasis* – is the term for the underlying molecular network balancing the entire proteome of a living organism. PROTEOSTASIS is also the running name of our recently terminated COST Action BM1307 “European network to integrate research on intracellular proteolysis pathways in health and disease” from the Biomedicine and Molecular Biosciences area of COST (European Cooperation in Science and Technology, see **Text Box**, funding period April 2014-April 2018; cost-proteostasis.eu).

The average number of proteins per individual cell is substantial and differs among species. In the single yeast cell, there are roughly 6,000 different proteins [1] summing up to 42 to 50 million protein molecules [1-3], while in human cells there are more than 10,000 different proteins per cell for a total of 2 to 3 billion protein molecules at any given time [4, 5]. Possible proteoforms occur on top of those numbers with variable concentrations and diverse distributions

throughout the cell types of multicellular organisms. This striking complexity requires tight regulation on multiple levels, which is achieved through robust and highly sophisticated mechanisms. Indeed, broadly more than 5% of all proteins throughout the kingdoms are involved in protein synthesis and turnover, highlighting the global importance of these processes [6-8]. Despite much progress over the past decades, understanding how these complex proteomes are constantly and dynamically monitored and remodeled remains an enormous challenge.

Proteostasis refers to the biological mechanisms controlling the biosynthesis, co- and posttranslational processing, folding, trafficking, neofunctionalization, i.e. changes in protein function, and degradation of proteins *in vivo*. Among these processes, intracellular proteolysis is not only critical for survival and cellular homeostasis of all living cells under unchallenged conditions, but also for rapid proteome remodeling in response to many environmental stresses. Furthermore, disturbed proteostasis may lead either to the accumulation of normally degraded proteins or to excessive protein degradation. Those can be associated with ageing and many pathologies, such as cancer, immune and neurological disorders in humans, as well as other diseases and responses to environmental stresses in plants and other organisms across the kingdoms of life.

Overall, since proteostasis plays pivotal roles in almost every biological process, including general growth and development in all organisms and mechanisms as diverse as heart development and plant tolerance to flooding, for example, its analysis has elevated the interest of scientists from diverse backgrounds and with different research foci. A wide variety of research approaches is used to identify the mechanisms that regulate proteostasis, typically involving a breadth of model organisms (fungi, invertebrates, vertebrates or plants) and different methodologies. This heterogeneity might restrain researchers into their own scientific niche, impairing knowledge exchange between fields that are in fact linked in real life. The PROTEOSTASIS network was built upon the conviction that connecting the different areas of research in this field would result in a boost of scientific exchange and sharing, and set the stage for an advance of our community knowledge through new possibilities of exchange and collaboration.

One central aspect of proteostasis is **protein degradation**. Often referred to as **proteolysis**, it has been studied for decades and publications on this topic are constantly increasing since the 1970s. Two major intracellular proteolysis pathways, namely the **Autophagy-Lysosomal Pathway (ALP)** and the **Ubiquitin-Proteasome System (UPS)**, synergistically play critical roles inside cells for the maintenance of cellular homeostasis and organism (patho)physiology. Thanks to the ever increasing understanding of these pathways, and also to recent technical developments in cell imaging, proteomics and more generally “-omics” studies, we now realize that these research fields are strongly entwined and coordinated.

[Figure 1 near here]

The small 8-kDa 'ubiquitous' protein **Ubiquitin** (Ub), is a common endogenous molecular tag working as posttranslational protein modification used by both UPS and ALP to control the stability of most if not all proteins in a highly specific and regulated manner. Due to its central role in cell metabolism, Ub is thus commonly accepted as a critical signature for the engagement of these sophisticated intracellular machineries. However, Ub also exerts proteolysis-independent functions, such as regulation of signaling pathways, transcription or protein trafficking. Also in the **ERAD (ER-associated protein degradation)** system, Ub plays an important role in cargo retrotranslocation that finally also concludes in proteolysis via the proteasome. The field expanded by understanding that Ub is just a member of a family of UbLs (Ub-Like proteins) that cooperate together to fine-tune the intracellular proteome. The most studied UbLs, such as SUMO (small Ub-like modifier) or NEDD8 (neural precursor cell expressed, developmentally down-regulated 8), are extremely versatile and crosstalk, i.e. functionally interact in a dynamic manner with various modes of posttranslational modifications of target proteins by Ub, modulating the fate of cellular proteins in response to external and intracellular stimuli.

PROTEOSTASIS - The Network

Even if we still do not clearly understand when, how and why many proteostatic systems function and collaborate within the cell, they enable alternative solutions to complicated problems, ranging from protein degradation to relocalization and neofunctionalization, and increase cellular plasticity for adaptation and survival in a continuously changing environment. Addressing all of these aspects of proteostasis was the ambition of the PROTEOSTASIS network.

To be able to dissect the molecular bases of complex proteostatic systems, in the health and disease of multiple species and with numerous approaches, we nurtured synergies between research groups to bridge the gap between parallel but closely related fields, bringing together researchers working on various processes in different organisms, using diverse but complementary approaches. By reaching hundreds of European scientists working on protein homeostasis, PROTEOSTASIS offered the possibility to develop a large exchange space that broke artificial but real barriers, thus unleashing connectivity and creativity in our field.

The COST Action PROTEOSTASIS coordinated and integrated efforts made by research teams in different areas to translate novel discoveries into products of clinical and/or economical value. In other words, PROTEOSTASIS grew a fertile ground to impulse a comprehensive and holistic approach to tackle scientific challenges, by capitalizing on our diversity and complementary expertise, potentiating the resources and competencies available in each group.

As a networking tool, PROTEOSTASIS was successful in engaging more than 270 research groups, including researchers from 30 different countries covering all scientific areas of proteostasis. The main goal of PROTEOSTASIS was to foster

exchanges between fields that tended to ignore each other for years by facilitating collaborative research and broad scientific exchange. To bring together expertise from different disciplines and to openly discuss recent scientific developments, researchers from diverse backgrounds were invited to actively participate and join the community. Special emphasis was placed on the transfer from basic to translational science, novel technologies, and training next-generation scientists. Sharing unpublished data was the rule during the meetings organized by PROTEOSTASIS in the last four years. This strongly promoted collaboration among experienced and early stage academic, clinical and industry-based researchers.

PROTEOSTASIS was structured around six wide thematic blocks, covering a broad and complementary scientific spectrum within protein homeostasis. **Protein Modification** dealt with molecular and structural properties of proteostatic components; **Proteolytic Systems** gathered scientists around mechanisms and structures of intracellular proteolytic systems like proteasomes, autophagy, lysosomes, and apoptosis; **Cell Signaling** focused on signaling cascades, protein trafficking, and transcriptional regulation; **Quality Control** covered folding and misfolding, chaperones, aggregation, and ERAD; **Cell Proliferation and Differentiation** touched many aspects of cell cycle, cell growth, and development; and **Diseases and Biotechnology** explored the molecular basis of diseases and biomarkers in cancer, inflammation and neurodegeneration, addressing drug targets and biotechnology.

Activities, Outcomes and Highlights

Whether from the academic or the private sector, the PROTEOSTASIS network helped scientists to develop fundamental or translational research thanks to the multiple instruments that it offered to the community, namely the organization or co-organization of 14 scientific meetings and workshops, eight training schools, and 47 scientific staff exchanges (STSMs). Additional dissemination instruments included the website (cost-proteostasis.eu), webinars, newsletters, and social media (**Figure 2**). The co-organization of workshops and other activities together with relevant European or national bodies in the life sciences such as EMBO, FEBS, and other scientific societies was instrumental. The meetings, workshops and conferences covered broadly the topics of the proteasome and signalosome complexes, autophagy, aging and neurodegeneration, apoptosis and cell death, cell polarity and movement, vesicular biology, system biology, Ub, SUMO and other UbLs, N-end rule pathway, protein degradation in plants, agronomy, biotechnology, and bioeconomy. Two examples of these meetings, ZOMES IX – “PCI complexes and ubiquitin defining a hub for protein homeostasis” and “N-term 2017 – Proteostasis via the N-terminus”, were described in meeting reports elsewhere [9, 10]. The eight training schools aimed to teach the analysis of *in vitro* and *in vivo* processes of ubiquitylation and SUMOylation, the proteostatic basis of ageing and redox regulation of metabolic processes and Ub-assisted autophagy.

Regarding networking, PROTEOSTASIS facilitated the consolidation or the

initiation of collaborations and the generation of novel international consortia dedicated to specific issues. Those resulted in more than 50 joint publications in peer-reviewed scientific journals plus three thematic books “Proteostasis”, “SUMO” and “Plant Proteostasis” with additional 74 contributions of network members [11-13]. Importantly, the international scientific exchanges enabled the mobility of researchers between laboratories and the development of joint research projects that were successfully funded. Examples of those are TrainERS (train-ers.eu) on endoplasmic reticulum stress; META-CAN (metacan.eu), combining cancer metabolism, cell death, cancer immunity, data analysis and immunometabolism; UbiCODE (ubicode.eu), deciphering the mechanistic of the Ub code; or TRIM-NET, exploring the functions of TRIM E3 ligases (**Figure 2**). Future joint applications are in the planning stages among members of the network.

[Figure 2 near here]

Conclusions

The goal of PROTEOSTASIS was to foster and concentrate interdisciplinary scientific exchange and development of novel research ideas. The network coordinated and integrated the efforts made by research teams to better understand protein homeostasis and facilitated the interchange with the private sector. The network has contributed significantly towards reversing the national and scientific fragmentation of research efforts within the European research area and beyond. After four exciting years of activities, we look back at a wonderful time of multifaceted exciting research, exchange of data and ideas, networking, training and numerous newly built interactions and joint collaborations. PROTEOSTASIS as a network, including its social media and website activities, is continued after the ending of the funding period. It will serve as a platform to communicate science, assist to organize meetings and conferences, and launch proposals in relevant funding calls. We aim to preserve those in the long term to facilitate and foster future interactions. We believe this type of network will be useful to other areas of research that might experience field fragmentation.

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RESOURCES

i cost-proteostasis.eu

ii www.cost.eu/actions/BM1307

iii twitter.com/Proteostasis

iv www.youtube.com/channel/UCmQZiJ9a4OfS97T6Q2-g_sA

v www.facebook.com/Proteostasis-839198092811311/

Supplemental Information

Supplemental Information associated with this article can be found in the online version.

Figure Captions

Figure 1. A scientific field in constant development: PROTEOSTASIS areas of study.

Figure 2. Achievements and milestones of the PROTEOSTASIS network – an overview of activities and new funded networks.

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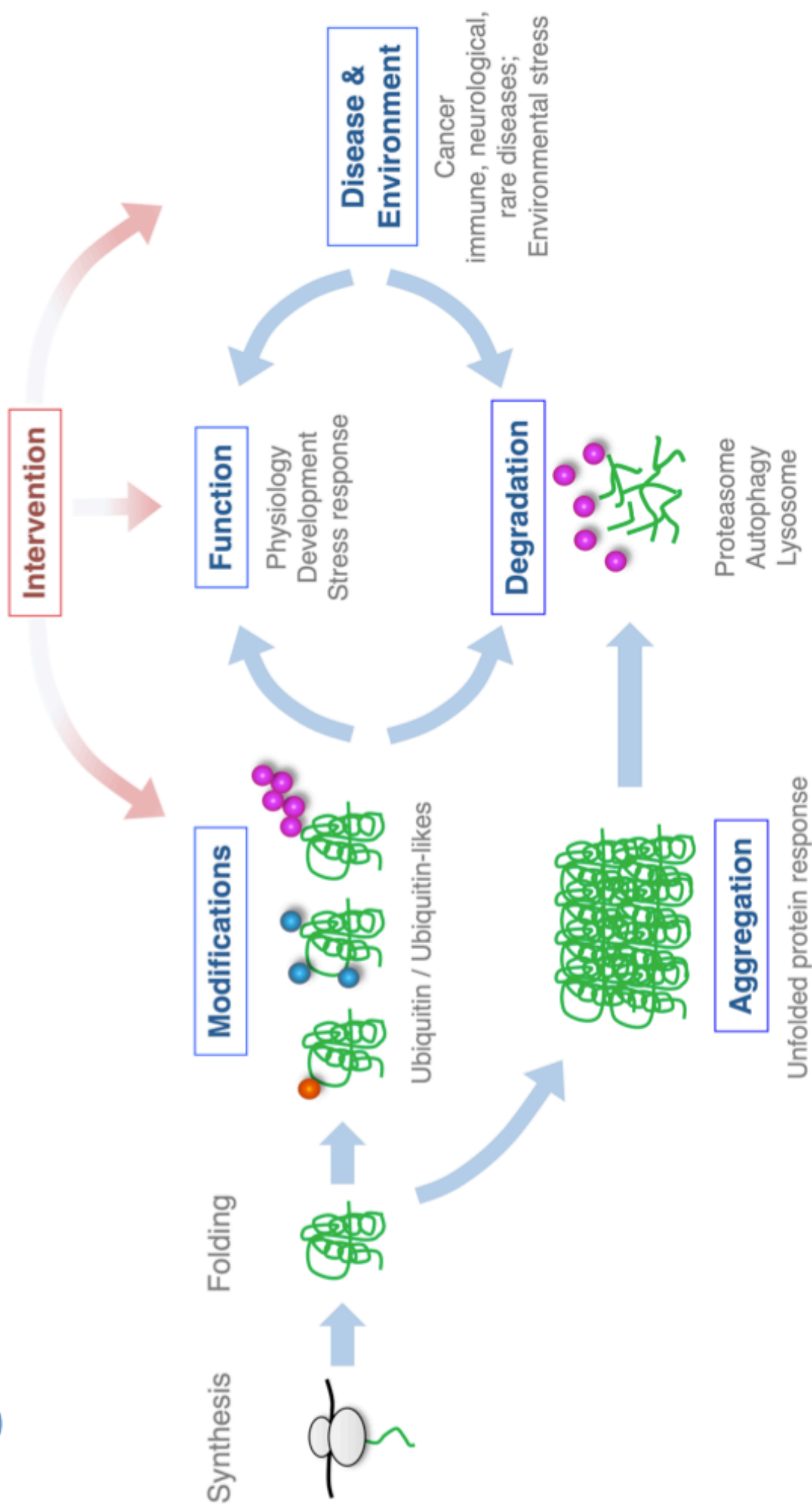
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PROTEOSTASIS

Areas of study



PROTEOSTASIS timeline of activities

Meetings & Conferences (M&C)

Training schools (TS)

Short Term Scientific Missions (STSMs)

