Protein homeostasis project brings researchers together

Intracellular proteolysis is critical to maintaining cellular homeostasis, and aberrations in this process play a central role in pathologies such as cancers, immune diseases and neurodegenerative conditions. The PROTEOSTASIS project aims to coordinate and integrate the work of research teams from across Europe in this area, as project chair Dr Rosa Barrio explains.

**The process of** intracellular proteolysis is an area of great interest to scientists, with its role in the control of almost all biological processes attracting a huge amount of research attention. The PROTEOSTASIS project, a COST-funded initiative bringing together academic, clinical and industrial partners, will coordinate and integrate the work of research teams from across Europe in this area. “The PROTEOSTASIS project is about research into protein modification by ubiquitin-like proteins and its role in intracellular proteolysis, such as proteasomal degradation and autophagy. It focuses on protein homeostasis within the cell,” explains Dr Rosa Barrio, the project’s scientific coordinator. Protein homeostasis can be thought of as the delicate balance between the production and degradation of proteins. “Ubiquitin, and a family of proteins that are related to it – the ubiquitin-likes – regulate protein homeostasis. We are also looking at a protein degradation process called autophagy,” continues Dr Barrio. “That also depends on proteins that share some characteristics with ubiquitin.”

**Intracellular proteolysis**
The project encompasses both fundamental research into key aspects of intracellular proteolysis and also more translational work, aiming to develop new clinical products. This ultimately is built on a detailed understanding of the intracellular proteolysis process, which is critical for cell homeostasis and in preventing pathologies such as cancers, immune diseases and neurological disorders. “Some neurodegenerative disorders are thought to be caused by an accumulation of proteins that should in fact be degraded. That can cause problems,” explains Dr Barrio. For example, mutations in proteins that handle ubiquitin, such as Parkin or UCH-L1, can lead to certain forms of hereditary Parkinson’s disease; this underlines the wider importance of research into intracellular proteolysis. “If the balance between the production and degradation of proteins is broken it can cause neurological diseases or cancer, among other diseases,” says Dr Barrio.

There is no general rule about the perfect balance between the production, function and degradation of proteins, however. Proteins are one of the main components of cells and are involved in virtually all biological processes. Yet each specific protein is different, and it therefore is difficult to draw general conclusions about their structure and function. “We have not yet identified a general rule about the balance between production, function and degradation in specific proteins, which is why we are studying those processes. In general a synthesized protein will have a characteristic half-life. Normally, when this half-life is too short or too long, it creates problems for the cells,” outlines Dr Barrio. The project brings together researchers from more than 200 laboratories belonging to different companies, universities and research centres, aiming to build a deeper understanding of intracellular proteolysis. “There are many different aspects of research within the PROTEOSTASIS project network,” says Dr Barrio.

**Protein homeostasis** is an essential property to maintain the natural equilibrium within the cell. It involves the synthesis, modification and degradation of the proteins. Proper cellular and organisinal functions depend on protein homeostasis, such as neuronal, immune, development, signaling and proper response to stress.

When this balance is broken diseases like cancer, inflammation or neurodegeneration appear. The different steps in proteins homeostasis are target for therapeutical intervention.
Researchers in the project are looking at the homeostasis of their specific proteins-of-interest, and at how this is modified in certain conditions such as during development, or in a particular pathology.

Based at the Functional Genomics Unit of CIC bioGUNE in the Spanish city of Derio, near Bilbao, Dr Barrio’s lab is pursuing two main lines of research. “We work on a ubiquitin-like protein called SUMO (Small Ubiquitin-like Modifier). It’s a ubiquitin-like protein, and we have been studying how it affects the development of organisms. In my laboratory, we use Drosophila melanogaster, the fruit fly, as a model system, but we also work with human cells. We are interested in how SUMOylation affects some proteins within the cell, and some particular transcription factors that are very important for human development,” she says. Dr Barrio and her colleagues are working in particular on a family of proteins called SALL. “There are links between mutations in the transcription factors that we study in the lab, the SALL proteins, and some hereditary syndromes,” she explains.

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The other side of Dr Barrio’s research is the development of technology and tools for the isolation and study of ubiquitin-like proteins, which points to the wider benefits of this kind of broad-based research collaboration. Even though researchers in PROTEOSTASIS may be working in different fields, they can still benefit from technical advances made in other areas of the project. “That’s the advantage of being part of a network like PROTEOSTASIS – even if you work in a different project to another group, you will have better access to frontline techniques coming from a different field,” points out Dr Barrio. While Dr Barrio works in the isolation or identification of proteins modified by ubiquitin or ubiquitin-lies, she can also be in contact with scientific colleagues working with plants for instance. “This is unrelated to my field, but they might be interested in the approaches I use in the lab,” she continues. “Sharing information is very beneficial, very important. We try to bring the term of the project, which will facilitate communication and knowledge sharing. There is a webpage (www.cost-proteostasis.eu), where important topics of interest and research advances are publicised. “The project is divided in six themes. Laboratories belonging to either of these themes share common scientific interests,” explains Dr Barrio. Fundamental research is integral to PROTEOSTASIS, but Dr Barrio says this can be combined with more translational work, which will form a central part of the future research agenda. “The idea is not that the groups change their focus, but that they find synergies and points of common ground with groups that might have a different orientation,” she says. “For instance, we are structuring the network in smaller groups-of-interest that focus on a particular translational problem. But somebody who is looking into a particular disease might need some basic information on how a protein works, or how the modification of it might affect another protein.”