Discovered in plants a mechanism that corrects defects in proteins such as those that cause Alzheimer’s and Parkinson’s Diseases in humans

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Various age-related neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), Alzheimer’s, Huntington’s, and Parkinson’s, are associated with the same basic disorder: the loss of nerve cells capacity to fold their proteins correctly, which causes protein aggregations that form “clumps” that end up generating the cell death (Figure 1). To better understand protein folding let’s visualize folded proteins as a folded paper plane when both have a correct 3D conformation they can accomplish their respective functions, catalyze a reaction, in the case of some proteins or fly in the case of the plane. Incorrect folding cause that proteins lose their normal functions and cause protein aggregations that form “clumps” that end up generating the cell death. Analogously, a paper plane incorrectly folded would not be able to fly and would form a paper ball with other defective paper planes. With this example is easier to understand the conformation or shapes that some proteins acquire (Figure 1).

![Figure 1](image.png)

Figure 1: Some age-related diseases are caused by protein aggregation in nerve cells (blue panel). Schematic representation of protein conformations and visualized as paper planes (yellow and red panels).

Plants, like animals, use proteins to carry out the cellular functions that keep them alive. The protein composition is determined by the information present in the cellular DNA, but to exercise their biological function, the proteins must also be folded in a 3D configuration, like the correctly folded paper plane.
However, in stress situations, such as a sudden increase in temperature, cause missteps in the folding process, thus producing misfolded proteins that have to be either removed or repaired. Otherwise they could cluster and form toxic aggregates.

Chloroplasts are the cellular compartments where the photosynthesis takes place in plant cells. Also, they are responsible for producing many of the nutrients that allow the growth of plants and of animals that ingest them. A big part of this work is carried out by proteins, some of which are very prone to misfold and aggregate, thus losing their function.

Under normal conditions, chloroplasts get rid of these defective proteins by degrading them using the molecular machinery called protease Clp. However, when the accumulation of aggregated proteins exceeds the ability of the Clp protease to remove them, the chloroplasts generate a distress signal that travels to the nucleus of the cell to activate the production of repair proteins, called chaperones. The chaperones, in turn, are transported to the chloroplasts to undo the protein “lumps” and unfold the disaggregated proteins, favoring that they can be folded back correctly and recover their function in a few hours. Based on Figure 1 we can assume that hands correcting the folding defects of our paper plane are the chaperones. These molecular mechanisms are similar to those that work in our nerve cells when misfolded proteins are produced in the mitochondria. In Figure 2 we illustrate this communication between chloroplast and nucleus, in which chloroplast with aggregated proteins send a WhatsApp message to the nucleus, and ask for help. The nucleus receives the message and sends chaperones to eliminate protein aggregation.

Our work was conducted using the model plant Arabidopsis thaliana and published in the journal PLOS Genetics (Llamas et al., 2017). We discovered that the key gene -HsfA2- activates the chaperone synthesis and thus rescues the cell from the toxic effects produced by misfolded protein accumulations. This key gene is also activated when a heat stroke causes problems of protein folding in other cellular compartments. Knowing how plants respond to the challenge of having some of their proteins lose their original structure and function, becoming potentially dangerous, is essential for better crop adaptation to adverse environmental conditions. This challenge is particularly relevant in the current context of climate change.

This research, conducted at Centre for Research in Agricultural Genomics (CRAG), may also help to better understand how protein-misfolding in nervous system diseases start, spread, and aggravate. The result of this research with plants could be transferred to new universal methods to correct the protein misfolding and thus impact the search for solutions to degenerative diseases that, to this day, remain incurable.
Figure 2: Plants use proteins to carry out cellular functions like photosynthesis in chloroplasts (blue panel). In stress situations, such as a sudden increase in temperature, cause protein aggregation and hence chloroplast malfunction. Chloroplast somehow senses the accumulation of aggregated proteins and generates a distress signal (Whatsapp message) that travels into the nucleus of the cell to activate the production of repair proteins, called chaperones. Chaperones disaggregate and unfold the proteins, favoring that they can be folded back correctly and recover their function.

Contributions
Ernesto Llamas, Pablo Pulido, and Manuel Rodriguez-Concepcion wrote the article. Zoila Babot, edited the article. Ernesto Llamas (@eellamas) made the illustrations.

References
E Llamas, P Pulido, and M Rodriguez-Concepcion. Interference with plastome gene expression and Clp protease activity in Arabidopsis triggers a chloroplast unfolded protein response to restore protein home-