Investigation of cellular responses to ribosomal protein oxidation during ageing

An increasing number of elderly people suffering from age-related diseases causes a growing burden for the medical healthcare system and society. Many health conditions associated with ageing, such as cancer, cardiovascular diseases or Alzheimer's disease, are linked to complex changes in cellular homeostasis that impair human health. The key to the proper functioning of the organism are proteins that control all the functions of the cells. Thus, in order to maintain cellular balance, each protein must be produced at a specific time and modified accordingly. In addition, existing proteins must be protected from possible damage or efficiently removed from the cell once they have served their purpose.

Proteins are produced in every cell by elaborate and specialized factories called ribosomes. The ribosome itself is a complex made of about 80 different proteins, called ribosomal proteins. Their main role is to construct and maintain the structure of the ribosome, allowing for the flawless production of proteins necessary for the cell to function properly.

During ageing, cellular functions become less efficient and defective proteins accumulate in the cell. These proteins, instead of maintaining the proper functioning of the cell, cause cell destruction and, eventually, its death. Therefore, the cell must react to damage quickly and precisely. Controlling the overall amount of proteins produced by ribosomes is considered one of the processes of cellular response to the generated stress and damage. Limiting the number of newly produced proteins can reduce the burden on various cellular mechanisms, allowing the cell to focus on the removal of the already existing defective proteins. The ribosomes can "shift gears" and prioritize the production of a specific set of proteins that will help the cell counter potential damage and restore homeostasis. Unfortunately, it is still not understood how ribosomes recognize and oppose cellular stress during the inevitable process of ageing.

We hypothesize that some specific ribosomal proteins act as cellular stress sensors during ageing. We have recently identified a set of ribosomal proteins that undergo minor molecular modifications during the early stages of ageing. Thus, within the proposed project, we plan to learn first how changes in these specialized proteins affect the overall production of all proteins, thereby regulating homeostasis. In addition, we will investigate how the selected ribosomal proteins influence the production of a set of specific proteins that can help the cell respond and fight the progression of biological ageing. We anticipate that such selective protein production may be a mean for the cell to delay the age-related damage of various cellular processes and the eventual destruction of ageing cells and the whole organism. Ultimately, we will investigate to what extent such changes in the elementary process of protein production affect the overall health and lifespan of multicellular organisms. The discovery of ways to extend the healthspan is currently one of the most desirable outcomes of scientific research. To understand the basics of the cell's response to the inevitable ageing process, we plan to use two simple model organisms: the baker's yeast *S. cerevisiae* and the small nematode *C. elegans*. Both organisms are well-established models in the study of ageing.

Ribosomes are fundamental structures in every living organism, from bacteria to humans. Therefore, we anticipate that our findings will be generally transferable within various species. Our research will implement the state-of-the-art methodology and combine targeted approaches used in molecular biology and data mining with unbiased large-scale methods. The results of our work will be made publicly available.

Our research plan will not only advance scientific understanding of the principles of biological regulation of ageing but will also provide new mechanisms and possible targets to develop anti-ageing therapies to extend the human healthspan.