PRESS RELEASE

CIC bioGUNE researchers discover a molecular recognition mechanism which enables certain proteins of our cells to be recycled and reused

The work, coordinated by the Ikerbasque researcher Aitor Hierro, has been published in Cell, the journal with the highest impact factor in the field of biomedicine and molecular biology

The research describes the recognition mechanism for reusing the divalent metal transporter protein (DMT1) involved in cellular absorption of iron, an essential element for life

For the first time, researchers have managed to resolve the three-dimensional structure of retromer at atomic resolution. The results may have applications to fight against some forms of Alzheimer's and Parkinson's disease

(Bilbao, 5 December 2016). A study conducted jointly by CIC bioGUNE and the National Institutes of Health (NIH) Agency of the United States has discovered a molecular recognition mechanism which enables certain proteins of our cells to be recycled and reused. Study findings point to the existence of a code for the recognition of recycling/ transport signals between cellular compartments.

Recycling has become commonplace in our everyday life, reducing the consumption of resources, saving energy and minimising waste. Likewise, our cells also recycle and reuse their components for the same reasons.

The research findings published in Cell, the journal with the highest impact factor in the field of biomedicine and molecular biology, describe the recognition mechanism for reusing the divalent metal transporter protein (DMT1) involved in cellular absorption of iron, an essential element for life.

The work, coordinated by the Ikerbasque researcher Aitor Hierro, has involved the active participation of six researchers, four of whom are attached to CIC bioGUNE whilst the other two are from the National Institutes of Health (NIH) Agency of the United States. The CIC bioGUNE team consisted of Aitor Hierro himself, María Lucas (first author and postdoctoral researcher), Ander Vidaurrazaga (co-author and research support technician) and Adriana Rojas (co-author and manager of the CIC bioGUNE Crystallography Platform). The research was conducted in collaboration with the team of Dr. Juan Bonifacino at the NIH, where cellular studies confirming the existence of the recycling mechanism were conducted.

Intracellular trafficking pathways are used for recycling and reusing molecules in the cell. Retromer is a complex of proteins responsible for recycling protein channels and

receptors involved in a wide range of physiological processes such as nutrient intake, cell signalling, polarised transport, cell differentiation, immune response and nerve transmission. The physiological relevance of retromer and its involvement in neurodegenerative processes such as Alzheimer and Parkinson's disease has grown exponentially since its discovery over 15 years ago. However, the mechanism for selecting which proteins are to be recycled and their inclusion in vesicles for transportation has remained elusive for many research groups throughout this same period of time.

As Aitor Hierro explains: "Our work sheds some light on the selection mechanism, revealing how coordination between the retromer and SNX3, another cargo protein, promotes the formation of a cavity which, in turn, provides an entry point for the consensus motif present in the protein to be recycled."

To further illustrate the idea, the CIC bioGUNE researcher explains that "the mechanism can be compared to that of a key being inserted in a lock. In this case, the key would be the recycling signal and the keyhole would be made up of the combination of two proteins (retromer and SNX3)". Furthermore, Dr. Hierro points out that "the really groundbreaking aspect of this discovery is the possible existence of a combination code between retromer and other SNX proteins, thereby generating different keyholes for the process of selecting proteins for recycling."

Future applications in neurodegenerative pathologies

The team coordinated by Aitor Hierro is currently working on transferring the knowledge generated through this study to the field of biomedicine. As Dr. Hierro points out: "It has been shown that reduced levels of retromer are associated with pathologies such as Alzheimer and Parkinson's disease. What's more, stabilizing retromer has been found to reduce production of the beta-amyloid peptide associated with Alzheimer both in cellular assays and in mice models, which confirms its potential use as a therapeutic target. The idea is to stabilize the machinery of intercellular recycling to prevent chaos and congestion. We are the only research group in the world to have resolved the three-dimensional structure of retromer at detailed atomic level, which gives us a considerable advantage when looking for compounds which stabilize retromer and which may be patented and assessed as drugs."

Another area of application is in nanomedicine, or more specifically in the administration of therapeutic agents. The effectiveness of a drug during a course of treatment is largely determined by the degree to which it can be sent precisely to where it is required to act. We are often interested not only in sending it to a particular type of cell but also to a specific compartment within that cell. If we knew the routing code for the compartment (or, following the analogy used above, "the keyhole") in question, a specific signal or "key" could feasibly be designed for the drug to gain access to the desired compartment. Systems for the local dispensation of drugs have the advantage of requiring smaller doses, are more effective and reduce side-effects.

The project began six years ago and has been funded by the Regional Basque Government and the National R&D+i Programme. Molecular interactions were analysed under the Molecular Recognition and Host-Pathogen Interactions Programme of CIC bioGUNE. X-ray crystallography was used to resolve the three-dimensional structure of the complex of proteins at atomic resolution. Once the structure was solved, protein-protein interactions were validated using complementary biochemical and biophysical techniques. Finally, molecular recognition patterns were confirmed in vivo using cellular models.

About CIC bioGUNE

The Centre for Cooperative Research in Biosciences (CIC bioGUNE), located in the Bizkaia Technology Park, is a biomedical research organisation conducting cutting-edge research at the interface between structural, molecular and cell biology, with a particular focus on the study of the molecular bases of disease, for use in the development of new diagnostic methods and advanced therapies.