PRESS RELEASE

Scientific team discovers protein that protects the cellular nucleus from Alzheimer's disease

Looking at the nucleus of cells to understand Alzheimer's disease. A group of Italian scientists coordinated by Giannino Del Sal has identified a protein, PIN1, which protects the cell nucleus from malformations. The findings have just been published in *Cell Reports* [1].

When the PIN1 protein is absent or present in only small amounts, as happens in the neurons of patients affected by Alzheimer's disease, DNA loses its order, molecules are produced that trigger inflammation and the cells degenerate. The discovery was made by a group of scientists coordinated by Giannino Del Sal, Professor at the University of Trieste, Researcher at IFOM Milan, and Group Leader at ICGEB. The study was also undertaken in collaboration with scientists at SISSA.

The cells of our tissues are subjected to stimuli and stress of different nature to which they respond by modifying and regulating the organisation of the genome and the expression of genes. A crucial mechanism underlying this ability pivots on the PIN1 protein, involved in the decoding of different types of signals that the cell receives, and is therefore implicated in multiple pathophysiological processes. Alterations in its levels are associated with different disease conditions: an increase in PIN1 contributes to the formation of tumours and metastases, while its decrease is observed in neurodegenerative diseases such as Alzheimer's dementia.

Until now, little was known about the molecular mechanisms that in the absence, or with reduced levels, of PIN1, lead to cellular degeneration. The results of the study, published in *Cell Reports*, reveal that PIN1 functions as a guardian of the cell nucleus, preserving its structure and protecting the DNA contained in it from stress of a mechanical nature. Cells are increasingly subjected to stress during aging. The study shows that PIN1 regulates the function of proteins important for preserving the structure of the nucleus and the organisation and anchorage of the genome within. This control allows the nucleus to withstand mechanical stress without altering DNA organisation and gene regulation. During aging, other dysfunctions can lead to significant reductions in PIN1 levels. In neurons, this, in turn, causes malformations of the nucleus, disorganisation of the genome, DNA damage, and production of molecules that trigger inflammatory reactions. These, in turn, and ultimately, lead nerve cells to degeneration.

"Several alterations in the organisation of the genome and in the activity of genes are associated with aging and can lead to DNA damage and inflammation, contributing to cell degeneration" explains Giannino Del Sal, Director of the Laboratory of "Cancer Cell Signalling" at the ICGEB in Trieste, Professor of the University of Trieste, and head of the research program "Signaling, tumour microenvironment and cellular metabolism" at IFOM Milan. "Among these alterations, one in particular is emerging for its particularity and relevance: the activation of mobile genome sequences called transposons, which have the ability to move within the cellular genome damaging the DNA and thus causing further problems. It is precisely the abnormal activation of these mobile elements of the genome that we have observed as the first consequence of the lack or reduction of PIN1 levels." The study was coordinated by prof. Giannino Del Sal with the collaboration of Simona Polo, IFOM and University of Milan, Fabrizio d'Adda di Fagagna, IFOM and CNR-IGM of Pavia and Claudio Tripodo, University of Palermo and IFOM and Remo Sanges and Antonello Mallamaci of Sissa.

Francesco Napoletano, Researcher at the University of Trieste, geneticist biologist expert in Drosophila, first author of the article together with Postdoc Gloria Ferrari Bravo, explains "We understood, studying the drosophila, the fruit fly, that PIN1 is essential to keep these mobile sequences under control, in particular in the presence of mechanical stimuli such as those related to the formation of intracellular aggregates typical of Alzheimer's, and that this

mechanism protects DNA, especially during aging when these stresses are most significant. It involves regulating the very structure of the nucleus with a mechanism preserved by the drosophila to humans." He concludes: "this mechanism is altered in patients suffering from Alzheimer's disease, in whose biological fields we have observed a reduction in PIN1 levels even higher than expected, associated with the abnormal activation of the mobile elements".

Diseases related to aging, such as neurodegenerative diseases and Alzheimer's disease, have an increasingly significant impact from a social and health point of view, given the progressive increase in the average age of the population and the lack of decisive therapies and/or markers useful for diagnosing the disease or predicting its evolution.

"This study," says Del Sal, "has led to the identification of proteins whose function can be pharmacologically modulated to prevent or improve the course of aging diseases such as Alzheimer's. The goal is now to develop molecules that promote its protective function against the cell nucleus and verify its effect in preclinical models of the disease."

"Finally," concludes Del Sal, involved in a collaborative research program supported by the AIRC Foundation for Cancer Research and dedicated to the study of metastases as a "mechanical" disease, "there are other diseases related to aging where mechanical stimuli play a decisive role: tumors. We are actively conducting our research also to better understand the role of PIN1 and the mechanism we have discovered in this context, and the way in which we can exploit it to our advantage to develop new therapeutic strategies".

Reference:

[1] Napoletano, F., Ferrari Bravo, G., Voto, I.A.P., Santin, S., Celora, L., Campaner, E., Dezi, C., Bertossi, A., Valentino, E., Santorsola, M., Rustighi, A., Fajner, V., Maspero, E., Ansaloni, F., Cancila, V., Valenti, C.F., Santo, M., Artimagnella, O.B., Finaurini, S., Gioia, U., Polo, S., Sanges, R., Tripodo, C., Mallamaci, A., Gustincich, S., d'Adda di Fagagna, F., Mantovani, F., Specchia, V., Del Sal, G. 2021. *The prolyl-isomerase PIN1 is essential for nuclear Lamin-B structure and function and protects heterochromatin under mechanical stress.* ***Cell Reports*** 36, 109694, September 14, 2021

Press contacts:

UNIVERSITY OF TRIESTE

Dr. Cristina Perini, Head, Communication and External Relations Staff Unit University of Trieste
cristina.perini@amm.units.it | Tel. +39 040 5583042

IFOM

Elena Bauer, Head of press office and communicationIFOM - the FIRC Institute of Molecular Oncology, Milan
elena.bauer@ifom.eu, Tel. +39 02/574303821 | +39 3387374364

ICGEB

Suzanne Kerbavcic, Head of Communications, Public Information and OutreachInternational Centre for Genetic Engineering and
Biotechnology (ICGEB), Trieste,
kerbav@icgeb.org, Tel: +39-040-3757315 | Mobile: +39-3405971692

Area Science Park

Leo Brattoli
tel. + 39 040 3755221 | mobile + 39 335 1236284
press@areasciencepark.itwww.areasciencepark.it