FONDAZIONE ISTITUTO FIRC DI ONCOLOGIA MOLECOLARE

UNIVERSITÀ DEGLI STUDI DI MILANO

Press release

Identified a protein that senses the mechanical vibrations of the cells and controls cellular plasticity.

A step forward in the understanding of metastasis and stem cells

This interdisciplinary research effort, conducted by IFOM and the University of Milan, in collaboration with the National University of Singapore and the Danish Cancer Society Research Center in Copenhagen, has identified the ATR protein, known for its role as DNA defender and tumor suppressor, as the engine of cellular plasticity. This completely unexpected role has important implications for the understanding of metastasis and stem cells. The discovery published today in Cell, was made in the IFOM laboratories in Milan by combining advanced microscopy with mechanical engineering and electrophysiology techniques.

Cellular plasticity: cells use it as a defense mechanism and for migration; however, the molecular aspects behind this characteristic are still largely a mystery. Research published today in Cell and conducted at IFOM (FIRC Institute of Molecular Oncology) and the University of Milan, in collaboration with the Mechanobiology Institute at the National University of Singapore, and the Danish Cancer Society Research Centre in Copenhagen, has just identified the protein that gives cells the gift of plasticity.

The protagonist of this discovery is the ATR protein, already known for its crucial role as a damage sensor in DNA repair processes and, therefore in tumor suppression. In fact, ATR is the alarm that warns of DNA damage and activates p53, known as "guardian of the genome" because of its role in preserving genomic stability by preventing mutations and therefore cancer.

But research conducted using engineering techniques and published today in Cell reveals a completely new role for ATR: "Having worked on ATR for many years - says Marco Foiani, head of the Genomic Integrity Program at IFOM in Milan and coordinator of this research - we have always had the impression that it might have functions in the cell under normal conditions, even in the absence of DNA damage. Applying these engineering techniques, we noticed that whenever cells undergo mechanical stress, either from inside the nucleus or from outside of the cell membrane, ATR senses the mechanical vibrations and immediately becomes activated and moves to the nuclear membranes. This provides the cell with plasticity to protect it from the stress." Thus, ATR would have a major role in modulating cellular plasticity, an important capacity both in the response to mechanical stress and during migration, for example during metastasis. Cancer cells adopt various strategies to invade distant tissues. They can completely deform themselves, including their nuclei, in order to pass through the narrowest interstices. This capacity likely depends on ATR, which paradoxically could play dual roles as a tumor suppressor that protects from cancer and, at the same time, as a driver of tumor spreading by facilitating metastasis.

But there is more. The research reveals another unexpected aspect, which could have further implications for cancer research: we know that stem cells have a high level of plasticity that

they gradually lose as they differentiate. Stem cells have a very high threshold for ATR activation, and many scientists suspect that this is the source of relapse after chemotherapy. However, it is not yet clear why. "What emerges from our study - says Foiani - is that a cause-and-effect relationship between ATR and stem cell plasticity is highly likely. We are taking this aspect further by studying ATR in the context of cell differentiation.
The key to this study was a change of perspective in the method of scientific research: "We posed a question that is unusual in Biology - says Foiani – that is, we did not ask only about the 'what', 'why' and 'when' of the molecular process controlled by ATR, but especially the 'how much', focusing on quantification of the biological processes by measuring the forces involved. This is the experimentally innovative aspect of the research, and to accomplish it we assembled a truly interdisciplinary team: Jiri Bartek at the Danish Cancer Society's Research Centre in Copenhagen, a cancer expert with expertise seemingly distant from our own; electrophysiologists, such as our colleague Michele Mazzanti at the University of Milan, and mechanobiologists such as GV Shivashankar, head of the new research group that we started in Singapore, in collaboration with the National University of Singapore. We have developed sophisticated technological approaches in our laboratories that combine our advanced microscopy techniques with their miniaturized systems for inducing mechanical stress. Thus this result - says Foiani - is the product of a collaboration between truly diverse disciplines: for years IFOM has advocated interdisciplinarity as an indispensable value on the frontier of research."

But what exactly is done to the cells under the microscope? From the description given by Amit Kumar, researcher at IFOM for about 5 years now and first author of the study, it is more reminiscent of a workout at the gym, than a hi-tech laboratory experiment. "We pluck them with tweezers, we stretch them with suction cups using the patch clamp technique, or we compress them with a piston in the compressive load system to deform them and create tension in the chromatin within the cell nucleus. What you instantly visualize at the microscope are processes that occur within seconds. This allowed us to observe dynamically the molecular activity of ATR and its crucial role in cellular plasticity."

In the future, the goal is to broaden our research both in the area of metastasis and in cellular differentiation to look at the application of possible therapies.

'We are very excited about this collaborative project, and the truly paradigm-shifting discovery to be published in the Cell article', says Jiri Bartek. 'Among the far-reaching implications of this new concept for biomedicine is its relevance for early organismal development (embryogenesis) that involves a lot of active cell migration, and possibly even the major aging-associated health problems such as cardiovascular diseases.'

This six-year study was made possible thanks to support from, among others, the Ministry of Education, the European Community, the Italian Association for Cancer Research, Telethon and the European Centre for Nanomedicine, created in 2009 to promote research projects with an interdisciplinary perspective, drawing on the transversal skills of scientists active in different disciplines.

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IFOM-MBI partnership in the fight against cancer

In May 2014, a new partnership was formed between the Mechanobiology Institute (MBI), Singapore, and the FIRC Institute of Molecular Oncology (IFOM), Italy, that will see the establishment of a 'Joint Research Laboratory', to be headed by Prof GV Shivashankar, deputy-director of the MBI.

This partnership aims to develop a multi- disciplinary approach to cancer research, where traditional biology is further enhanced by technologies and methods developed in fields such as mathematics, physics, engineering and computational biology. The Joint Research Laboratory will focus on understanding the molecular mechanisms that drive tumor formation and development.

Through the MBI-IFOM partnership, further studies into the mechanisms that control nuclear dynamics andprotein synthesis will be possible. Mathematical modelling and computer simulations will help predict the effect of mechanical stress on protein synthesis while cells will continue to be grown on surfaces designed to mimic those found in the body, such as bone, muscle or cartilage. By adopting a multidisciplinary approach to its research, the Joint Research Laboratory will be well placed to assess the effect of stretching or compressive forces on regulating cancer specific signaling pathways and protein synthesis.