

IFOM Fondazione Istituto FIRCA di Oncologia Molecolare

PRESS RELEASE

“SUMO”: THE CHAMPION OF DNA

An international research unveils the molecular mechanism of a novel process which protects our genes from mutations and cancer.

A protein called SUMO shields us from the chromosome alterations that are typical of all the forms of cancer. SUMO (the acronym stands for *Small Ubiquitin-like Modifier*), which is assisted by a number of enzymes, is able to prevent the clustering of “aberrant structures” on the DNA during chromosome replication. In doing so, it hinders the proliferation of damaged cells which could give rise to severe diseases such as tumours and metastases. Its role, dubbed “sumoylation”, has been characterized and described for the first time by an international research effort co-ordinated by IFOM (IFOM - The FIRCA Institute of Molecular Oncology Foundation). Among the teams involved in the research stands the RIKEN Discovery Research Institute in Wako (Japan). The results appear today in the scientific journal *Cell*. The finding sheds light on the operational machinery of one key mechanism in charge of supervising the genome stability, and displays promising therapeutic applications, as it identifies a novel “therapeutic target” that the scientists hope to employ one day in their fight against cancer.

“Tumour cells – explains IFOM Co-Director Marco Foiani, who, together with his colleague Dana Branzei led the research, – are marked by an excess of “DNA recombination”. DNA recombination is a physiological phenomenon that normally occurs when a mother cells splits into two daughter individuals: its genes “shuffle up” and give rise to new genetic combinations, which differ from those in the parental cell. Recombination per se is then a “good event”, which triggers the onset of differences between children and parents.” However, if cells recombine too much, they give rise to a “disordered” DNA and this in turn can have dramatic consequences. “In tumour cells – explains Foiani – the right type of recombination can take place at the wrong time, and, what is worse, excessive and misguided recombination processes are primed.” According to experimental observations, disproportionate recombination is likely to be correlated to all kinds of tumours. “This event – observes Foiani – is particularly evident with some genetic syndromes, such as Bloom’s Syndrome, which give rise to early tumours: in these situations, most chromosomes are involved in the recombination processes.”

To find out what triggers such excessive recombination represents then a “forced route” for scientists such as Foiani and Branzei, whose major scientific interest is genome instability. By carrying out some targeted experiments on yeast cells of *Saccharomyces cerevisiae*, the scientists found out that certain mutations involving SUMO-related genes and SUMO-related enzymes (i.e. involving genes that control “sumoylation”) induce the clustering of “aberrant chromosome structures”, deviant structures that choke up the regular DNA replication process. As a consequence, the recombination process is altered and the genetic damage is spread to the next cellular generations.

“The molecular mechanism is complex – confirms Branzei – but its rationale is quite simple. Try to imagine a road jammed by a car that occludes the lane. If the traffic flow is not immediately restored, all the cars pulling in will get stuck, and the outcome will be a severe traffic jam that stalls the whole circulation. This is just what happens when the sumoylation doesn’t work: ‘cars’ are unable to move and damages cluster up and diffuse.”

The correlation between improper sumoylation and the onset of tumours and metastases has been shown only recently, but no research study had gone beyond the mere experimental evidence. “In many tumours – adds Dana Branzei – the level of sumoylation enzymes is abnormal. This is true for a number of tumours. But, until now, nobody ever looked for mutations in sumoylation genes within

tumours. I am confident that in the next few years we will find many such mutations.” These mutations will represent as many potential therapeutic targets, to be hit by specific drugs in the future anticancer therapies.

Not only this. “Sumoylation – is Branzei’s conclusion – is a very precious protector, which shelters us from the genetic damage that occurs when cells endure a stressful situation, such as during the administration of chemotherapies. If the sumoylation doesn’t work, there is no protection. Understanding the mechanism of sumoylation could therefore help us both to optimize the standard therapies and to select them according to the genetic profile of each patient.”

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