PRESS RELEASE

PROTEOMICS SHEDS LIGHT ON DNA'S “DARK MATTER”

It's the least explored region of DNA, of fundamental importance because it is where many solid tumors and genetic diseases such as Down's Syndrome originate: it is the centromere, the structure at the crossroads of chromosomes. For the first time, the structure and composition of this chromosomal region was clarified using sophisticated technologies such as proteomics and electron microscopy . The study was carried out at the FIRC Institute of Molecular Oncology in Milan, and proved that the centromere is protected from genetic damages that may occur during the duplication of chromosomes. This research paves the way for a refinement of chemotherapy treatments.

A little light shines on the "dark matter" of DNA which is the cradle of cancer. It is the centromere, the region of the genome that forms the intersection of the chromosomes: an area so far largely mysterious to scientists, because it is difficult to see. The genetic material there is extremely concentrated, and the sequences highly repetitive.

Thanks to a new integrated approach which combines proteomic technologies with in vivo analysis, researchers were able to shed light on the centromere and its key feature. "When we were able to observe the mechanism, after years of research, there has been a succession of" wow”s in the lab! ": The large amount of unexpected results allowed us to shed light on the region that can be called the dark matter of the genome," said Vincenzo Costanzo, from FIRC Institute of Molecular Oncology in Milan, coordinator of the study. "Half of chromosomal alterations linked to cancer start in the centromere, and our study helps to understand why." The research, published in Nature Cell Biology, analyzes and reconstructs for the first time the structure of this complex area of the chromosome.

And it reveals a hitherto completely unknown aspect: the centromere concentrates most of the DNA repair factors in order to maintain its integrity. This “shield” allows the centromere the luxury of silencing the mechanism which monitors the natural obstacles that the centromeric DNA sequences form during replication. This phenomenon allows the rapid duplication of the centromere, but on the other hand exposes the cells to the risks linked to a malfunctioning of DNA repair.

"The fact that the centromere does not see obstacles of replication but instead relies on DNA repair to remedy the situation was for us the most surprising aspect - says Costanzo. "This mechanism, if on the one hand facilitates the replication of this comples region of chromosome, on the other exposes it to errors that can facilitate tumor formation”. The mechanism has been identified through the use of sophisticated mass spectrometry techniques. "We have succeeded - explains Angela Bachi, head of Functional Proteomics at IFOM - not only in identifying but also in quantifying, for the first time, the protein factors that specifically bind centromeric DNA and provide its shield."

The discovery could have important therapeutic implications. "The majority of chemotherapeutics acts on the mechanisms of cell division and DNA replication" says Costanzo. "Our discovery helps us understand how these therapies work and what could be done to increase their effectiveness."
In addition to cancer, another important pathology that could be analyzed in the light of these data is Down syndrome, which could depend on errors of duplication of the centromere of chromosome 21.
The research was carried out with support from the Italian Association for Cancer Research (AIRC), the European Research Council, Telethon Foundation, the EPIGEN project and the Giovanni Armenise-Harvard Foundation. In particular, the biochemical method that has made the study possible was developed as part of the Career Development Award Grant from the Armenise-Harvard Foundation, that Vincenzo Costanzo won in 2013 and used to open his laboratory on DNA Metabolism at IFOM, after working for over 10 years in the United States and UK.

The study

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