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Insider News

Rigid and fragile chromosomes: the double-edged sword of tumour cells

A new mechanism giving rise to DNA fragility has been identified in malignant cells. This fragility is one of the tumour's strong points, through which the integrity of the genome is dramatically compromised. Thanks to this accomplishment, though, it could become a point of attack for targeting cancer with its own weapon. The discovery was made by a team of scientists from IFOM in Milan led by Marco Foiani, in collaboration with the University of Milan, and will be published today in the journal *Cell*.

That cancer is a disease caused by multiple alterations accumulated in the genome has long been known.

It is as if the DNA of each cell were constantly under attack: Various agents and situations both internal and external to the organism may compromise stability, pushing the cell inexorably towards a tumour fate. In order to defend itself, the cell has a sort of molecular taskforce that detects and repairs DNA damage and protects the organism from the onset of tumours.

The game of genome incorruptibility, however, is not played only on this field. A new element is now emerging from the study coordinated by Marco Foiani, Scientific Director of IFOM (Istituto FIRC di Oncologia Molecolare) and Professor of Molecular Biology at the University of Milan (Departments of Biomolecular Science and Biotechnology), published today in the journal Cell. DNA integrity is also a matter of the plasticity of the molecule.

The surveillance system (an actual checkpoint) that the cell has in order to confront the dangers in which its genome finds itself must not only insure that the genetic material is correctly copied before cell division and does not contain damage, but also serves a crucial function that until now was unknown: to render DNA plastic to avoid that dangerous tension accumulates in the molecule of life due to the numerous activities for which it is the nerve centre.

When this does not occur, such as in tumours where these systems have failed, the price to pay is very high: DNA becomes rigid and incredibly fragile.

"That the DNA of tumour cells is extremely fragile has been known for years", says Foiani, "what we did not understand was the reason for this fragility". The team of researchers coordinated by the scientist found the missing piece of this complex puzzle by studying two fundamental processes of cellular life: the copying or replication of DNA and its transcription. The first has the aim of faithfully transmitting the genetic inheritance to the daughter cells that are generated when a cell divides and proliferates. The second is a fundamental

step to translating the information contained in the genome into action, thus allowing the accomplishment of the specific functions of each cell within the organism.
At times these two processes may occur simultaneously on the same stretch of DNA. Therefore, intense traffic is generated on the tracks of the double helix in the form of molecular convoys involved in the various operations associated with the two processes. The collateral effect of all of this is physical stress to the molecule, which is twisted, coiled and super coiled, unwound and separated into its two complementary strands or restrained in particular zones of the cell nucleus. During such manoeuvres, accidents and destructive collisions may occur.
Therefore, paradoxically crucial moments such as replication and transcription represent a danger to the integrity of the DNA double helix.
Particularly delicate is the moment in which the replication process involves stretches of DNA that, in order to be transcribed, are anchored at particular points of the envelope surrounding the cellular nucleus, housing the chromosomes. At these points the processes going from transcription to translation of the genetic message are favoured. However, they serve as traps for DNA that is about to be replicated, because here it is as if the double helix is shackled on one side and twisted on the other. Therefore, the anchoring imposes a strong rigidity, predisposing the genetic material to dangerous breakage.
By focusing attention on this specific phase, the researchers discovered that the healthy cell is able to finely orchestrate replication and transcription. It confronts the associated risks by employing the proteins of its surveillance systems in the previously known processes for detection and repair of DNA damage, additionally in a function that has not been described until now: modifying the structures of the anchoring points to liberate the DNA from these traps, thus releasing the tension, reducing its rigidity and increasing its plasticity.
According to the hypothesis of the scientists, the checkpoint proteins, acting as seismographs, would register the mechanical vibrations of the DNA molecule and would go into action when solicitations are detected.
The discovery allows an understanding of a fundamental aspect of tumour biology. "In the situation in which, the cells contain defects in the surveillance systems" explains Rodrigo Bermejo, collaborator of Foiani, "the clash between replication and transcription generates an unresolved rigidity in the chromosome, which may degenerate leading to DNA breakage. Therefore, the main difference between a normal cell and a tumour cell in which the checkpoint is altered is that in the tumour cell the DNA is much more rigid, therefore more fragile and predisposed to breakage. In the tumour cell without surveillance systems" - the scientist continues "the situation is increaingly dramatic considering the frenetic and uncontrolled rhythm with which it proliferates and therefore replicates its DNA and considering the fact that an upheaval of the transcription programs is superimposed on all of this.
Such DNA fragility in tumour cells represents a deadly weapon since it offers

the possibility of continuously generating new genetic anomalies potentially allowing the cells to acquire more aggressive characteristics.
This is a double edge sword, however, because it also makes them more vulnerable. "Now that we know that rigidity is a crucial aspect of the fragility of tumour cell chromosomes – explains Foiani - we could think about exploiting this characteristic and, based on the acquired knowledge, design new strategies to target tumours. For example we could exasperate it to the point of making the DNA so fragile that it causes its destruction, resulting in the death of the diseased cells". And he concludes: "There are already drugs in clinical trials that work in this way and others could be developed".

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