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A cellular task force to safeguard genome stability

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The maintenance of genome stability is crucial for protecting an organism against the onset of cancer and the study of the mechanisms controlling genome stability represents one of the most promising frontiers in cancer research.

A recent study, published in Nature, now sheds light on a complex regulatory system based on sumoylation and ubiquitination, two important regulatory processes involved in DNA repair and, consequently, the maintenance of genome stability.

he study was conducted by an international team of researchers led by Dana Branzei, Head of the DNA Repair Program at the IFOM Foundation (FIRC Institute of Molecular Oncology) in Milan. DNA repair occurs during the cell cycle, when cells replicate and divide into 2 daughter cells, thus ensuring the correct functioning and survival of the organism. In order for the genetic material to be correctly transmitted to the daughter cells, the genome must be faithfully duplicated, through a process known as DNA replication. During DNA replication, the DNA sequences that make up the two complementary DNA strands are copied. However, it is not unusual that during this replication process DNA lesions occur in one the two DNA strands, caused by the metabolism of the cell itself or by external chemical or physical factors such as ultraviolet radiation. Usually, these lesions are immediately repaired because cells are equipped with extraordinary safeguard systems that protect the genome. Indeed, if a portion of the DNA sequence in one of the two strands is omitted or incorrectly copied during replication, the cell can repair the mistake through a process known as "homologous recombination". This process allows the damaged DNA strand to deviate the replication machinery to the healthy complementary strand, from which the missing genetic information can be extracted. Once the damaged portion has been bypassed, the original replication course is resumed and all signs of the deviation are "eliminated". In this way, replication continues along the initial DNA strands, thus ensuring normal cell cycle progression. The repair system is extremely quick and efficient, but if it goes wrong or if it is not correctly controlled, the repair defect becomes irreversible and may lead to an accumulation of chromosomal alterations. The final outcome is that the stability of the entire genome is jeopardized, predisposing the organism to cancer or rare genetic syndromes, such as the one of Bloom's Syndrome, which is characterized by a high risk of developing cancer, notable in early life. This recombination process is finely regulated and coordinated by sumoylation and ubiquitination: "it was already known that sumoylation and ubiquitination play a role in DNA repair" explained Dana Branzei "however, it was not clear whether, and if so, how, these processes are coordinated in their regulation of enzymes involved in DNA

repair". The study conducted by Dana Branzei takes advantage of a sophisticated experimental approach that allows DNA replication and repair processes to be directly visualized. Using this approach, Branzei and colleagues have discovered that sumoylation and ubiquitination work together in a tight collaboration; the two processes compete with each other to coordinate and control homologous recombination by activating enzymes in charge of DNA repair and guaranteeing that this process occurs correctly. "By directly visualizing the recombination process we were able to observe how the two distinct molecular mechanisms (sumoylation and ubiquitination) are perfectly coordinated in their control of DNA repair." continues Branzei "it is as if they were acting as an emergency task force, whose mission is to safeguard the stability of the genome. Task force members are provided with precise guidelines, based on their specific roles, and their actions are coordinated according to the exact operating modes." For cancer research, this discovery represents a significant advancement of knowledge and offers promising prospects for the identification of novel therapeutic targets for cancer treatment. In particular, the characterization of the enzymes regulated by the DNA repair "task force" may lead to the development of anti-cancer therapies that specifically target tumour cells, without damaging the genomes of healthy cells.

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http://www.innovations-report.de/html/berichte/biowissenschaften_chemie/a_cellular_task_force_safeguard_genome_stability_124605.html