Cohesin: a new player in cancer development

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Genome instability is thought to play a pivotal role in the tumorigenic process, and it is considered a hallmark of cancer cells. To ensure genetic identity, the genome must be replicated and segregated prior to the actual division process. Specifically, during M phase, the array of chromosomes must be segregated so that each daughter cell inherits a complete complement: mistakes at this point in the cell cycle can result in cells with deviations from the normal karyotype, which in turn can result in various diseases. The solution to this challenge is sister chromatid cohesion mediated by cohesin whose SMC1A and SMC3, belonging to the Structural Maintenance of Chromosomes protein family, and RAD21 form a tripartite ring structure topologically encircling sister chromatids, according to an embrace model. The fourth subunit, STAG, associates with RAD21.

Increasing evidence suggests that cohesin also participates in many additional biological processes. Indeed, it regulates gene transcription by mediating functional connections between promoters and their distal enhancers in association with the CCCTC-binding factor (CTCF). Cohesin influences gene expression in a cohesion-independent manner and this activity is sensitive to cohesin dosage. In fact, moderate reduction of cohesin levels affects gene transcription without affecting chromosome segregation (1).

In addition to cohesion and gene expression regulation, cohesin promotes DNA repair by homologous recombination and non-homologous end joining, and controls fork replication speed. Following DNA damage, cohesin accumulates in a large 50-kb domain that surrounds the damage site and SMC1A-SMC3 are phosphorylated. Cohesin’s ability to establish cohesion de novo is essential for DNA damage repair and we found that fork stalling induced an increase in SMC1A synthesis levels (2). These findings suggest that increased cohesin and its accumulation can stabilize the broken sites, acting as scaffolding to improve the recruitment of DNA repair machinery.

Germline mutations in cohesin and its regulators are responsible for Cornelia de Lange syndrome, a rare developmental disease characterized by chromosome aberrations and aneuploidies, precocious sister chromatid separation and sensitivity to genotoxic drugs (3,4).

The recent finding that human cancer cells carry mutations in cohesin genes further supports the notion that the cohesin pathway is involved in genome instability and cancer. Mutations in genes belonging to the cohesin pathway have been recently identified in human cancers, including acute myeloid leukemia, bladder cancer, and colorectal cancer (5). There are many potential functional effects of cohesin mutations on human cells, including increased susceptibility to DNA damage, triggering of genomic instability and aneuploidy, alterations in chromatin organization leading to replication stress and/or changes in gene expression. Altogether, these observations indicate the need to look at the relationship cohesin-cancer with new eyes. The main objective of our project, granted by the Italian Association for Cancer Research (AIRC), is to gain further insight into the role of the cohesin pathway in genome stability maintenance and cancer development.

References:

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