

PRESS RELEASE

CHROMOSOME LASSOING: A NEW KEY MECHANISM IN CELL DIVISION

Scientists at the IFOM-IEO Campus have revealed the function of a protein that is indispensable for passing on an accurate copy of the genome from mother to daughter cells. This study, published in Cell, opens up new avenues of research to reduce the toxicity of chemotherapy in the treatment of cancer.

The protein can be compared to a cowboy's lasso: it catches chromosomes and ties them to a transitory structure assembled during cell division. Once they have been neatly tied up, the chromosomes await the end of replication to be equally distributed between the two daughter cells. But if the lasso doesn't catch them, chromosomes end up being randomly scattered, with potentially disastrous genetic effects: should cells survive this, they receive the wrong genetic inheritance, with dire consequences. The structure and function of this chromosomal lasso were discovered in Milan, at the IFOM-IEO Campus (that hosts the laboratories of the FIRC Institute of Molecular Oncology Foundation – IFOM – and of the European Institute of Oncology – IEO) and these findings have just been published in the prestigious scientific journal, *Cell*. “We've been studying a molecule called Ndc80 – explains Andrea Musacchio, principal author of the study, and head of a research group in the Department of Experimental Oncology (IEO). This protein is a key player necessary for the correct distribution of genetic inheritance. Ndc80 could potentially be used as a target for new drugs that would have fewer toxic side-effects than current drugs, such as paclitaxel (originally called taxol), which mainly act as inhibitors of cell replication.” The operative word here is ‘mainly’. Although many drugs used in traditional chemotherapy act on molecular targets that are involved in the duplication of cells (during a phase known as ‘mitosis’), these targets also have other cellular functions. Ndc80, on the other hand, performs its job only during mitosis. So, by blocking Ndc80, the only cells that would be affected would be the dividing ones. Any other cells would be unaffected. Musacchio and his colleagues (together with co-author Peter De Wulf and his research team) are already testing a number of substances that might be able to block the action of Ndc80. The published findings were a truly international effort involving research groups from England and the USA; much of the work was made possible thanks to financial support from the Italian Association for Cancer Research (AIRC).

Mitosis and chemotherapy treatment for cancer

“We've been studying the mechanisms that regulate accurate genome duplication for many years now – explains Musacchio. Our hope is to discover new, less toxic drugs for chemotherapy. Cancer cells grow at a much faster rate than normal cells and traditional chemotherapy drugs, like paclitaxel, block this cell division process. The efficacy of these drugs depends on differences in the growth rates of normal and cancer cells. This means that paclitaxel is toxic for all cells undergoing mitosis; however, since most mitotic cells in cancer patients are actually cancer cells, it follows that this drug will do most of its damage in cancer cells. The problem is that paclitaxel acts on proteins that are essential not only for cells to divide, but also for other phases of the cell cycle. This means that the drug has significant associated toxicity, something we would rather avoid. We had hypothesized that Ndc80 was only active during cell division, which is why we thought it might be an interesting target to study. And our results proved us right. We discovered that Ndc80 acts as a kind of molecular lasso that tethers chromosomes to the mitotic spindle, a molecular structure that only forms during mitosis. Ndc80 straps chromosomes

firmly onto the spindle until the dividing cells separate; after this stage, it is of no more use to the cell. So, if we interfere with Ndc80, we can significantly reduce the so-called 'toxicity window'." Any drug that inhibits the function of Ndc80 would therefore be much more tumor-specific than currently available treatments. "Peter De Wulf and I – continues Musacchio – have already flagged some interesting molecules. Our *in vitro* work now needs to be validated *in vivo*, first in laboratory models, and then in standard clinical trials."

Changing strategy: from therapeutic targets to therapeutic drugs

Musacchio and colleagues have made an important step forward in understanding the molecular workings of normal and cancer cells. This work is the starting point for the development of new drugs. But, as this scientist points out, the expertise needed to achieve this latter step is sorely lacking in Italian academic research environments. "The development of new drugs – explains Musacchio – depends on the mutual interaction of Chemists and Biologists. Italian academic research still hasn't capitalized on this, and academia limits itself to the identification of therapeutic targets. While this is a necessary and important step, the development of new drugs is left in the hands of the large pharmaceutical companies."

This situation is unacceptable. Italian academic research (which is, by definition free, and not profit-led) can – and should – also focus on screening for molecules that can interact with newly-identified targets to inhibit them. To add insult to injury, such compounds are often neglected by pharmaceutical companies, when they do not fall within their production strategies. Musacchio and De Wulf's strategy in their hunt for molecules that can inhibit Ndc80, exemplifies what needs to be done. But, unfortunately, their approach is not commonly adopted in Italy, and the gap between basic and translational or applied research grows ever wider. Musacchio uses a vivid metaphor to describe the situation: "We discover mountains to climb, but we don't have the equipment needed to guarantee the success of our expeditions". We shouldn't underestimate the value of the collections of compounds hidden away in academic chemistry laboratories; these could be made publicly available. Musacchio concludes: "A contribution of this kind would be invaluable for international research and a crowning achievement for our Nation".

An international collaboration

The findings are the result of a collaborative effort between the IFOM-IEO Campus and the University of North Carolina (USA), Colorado State University (USA), the Sir William Dunn School of Pathology (UK), the Wellcome Trust Centre for Cell Biology at the University of Edinburgh (UK) and the University of London (UK). The research was funded not only by AIRC, but also by the International Association for Cancer Research, the Telethon Foundation and the Italian Ministry of Health.

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