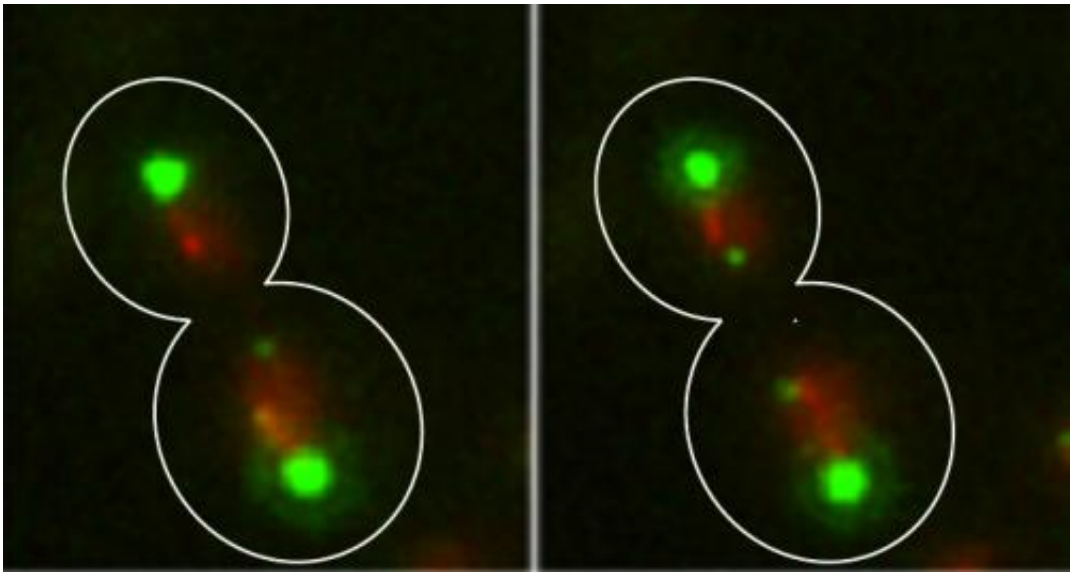
Unraveling cell division

September 16 2014



CRG researchers shed new light on mitosis. The study published in the *Journal of Cell Biology* describes how Topo 2 disentangles DNA molecules and is essential for proper cell division

At this very moment thousands of our body's cells are duplicating and dividing. This is the mechanism by which the body repairs damaged tissues and regenerates others like skin and hair. It involves a fairly complex process known as "mitosis", during which the cell duplicates its genetic material and separates it into two identical halves, which are then split apart. It is crucially important that this process works well each and

every time it takes place, as otherwise it could give rise to mutations that might trigger diseases such as cancer.

Work published today in the *Journal of Cell Biology* and carried out by a team of researchers from the Centre for Genomic Regulation (CRG) sheds new and revealing light on this complex mechanism. In a study using yeast, they have discovered that an enzyme known to be vital for chromosome separation, topoisomerase 2 (Topo 2), is active for much longer than was previously thought; they have also observed that chromosome length is decisive in determining the amount of time this protein works for.

Untangling chromosomes

When a cell prepares to divide, it duplicates its DNA and compacts it into pairs of identical chromosomes. However these duplicated chromosomes are twisted around each other, as if they were a tangled up pair of earphones. Before the cell is split into two, each half must receive one copy of each replicated chromosome; it is thus essential that chromosome pairs unknot or untangle properly. Otherwise, they will not be able to separate during cell division, and the DNA within could be cut or divided badly, which might lead to cell death or harmful mutations – and possibly cancer.

"To solve this problem the cell has two options: either to patiently disentangle the chromosomes, as one unties messed up cables; or to cut them up and put them back together again. For cables, especially if they are earphones wires, perhaps cutting them is not a good idea, but chromosomes are so long that there is really no other option. And this is what the cell does using Topo 2", explains Manuel Mendoza, head of the Coordination of Cytokinesis with Chromosome Segregation group at the CRG.

Topo 2 is, therefore, a molecule responsible for cutting DNA knots between replicated DNA molecules, untangling the pairs of chromosomes and closing up the cuts afterwards, so that each member of the pair of chromosomes can migrate to the opposite side of the cell as it splits in half. This role of Topo 2 has been known for some time, but it was believed that it acted quickly and equally on all chromosomes. However, Mendoza and his team suggest that this hypothesis was wrong.

The team of researchers from the CRG wanted to know if chromosome length influenced this enzyme's action at all. In principle, if the number of entanglements between the chromosomes in each cell is the same, independently of whether the chromosomes are long or short, then the time Topo2 needs to untwine them should always be the same too.

However, they have found that in cells with chromosomes that are longer than normal, Topo2 needs an extra amount of "help" to undo the knots, suggesting it has to be active for longer. To continue with the previous metaphor, apparently this molecule needs –although it is not known why- for the cables of the two earphones to be stretched until the first knot is under tension: this is when Topo2 begins to untie it. And it does this in order, knot by knot, starting with the closest to the end of the earphones and ending with the farthest away.

The "help" which Topo2 receives comes from the microtubules, a type of tiny wire that makes up part of the mitotic spindle, a structure similar to a rugby ball that is created when the cell begins the process of duplication and division. The microtubules are anchored to the chromosomes at a precise point (the centromere) and pull them apart so that one copy goes to each side of the cell. This way when it splits apart, each half will contain the same genetic information.

Mendoza explains that "surprisingly, we saw that the longer a chromosome is, the more time it takes the enzyme to unknot it

completely. And we believe we understand why. As the speed at which these microtubules pull chromosomes apart is constant, when the chromosome is short, all the tangles or knots rapidly come under tension. On the other hand, if it is long, it will take more time for tension to spread through the whole chromosome", and, therefore, Topo 2 will finish to untangle them later. To understand this process better, just imagine someone trying to pick up and wrap a long rope.

According to the results of this study, the long chromosomes need more time to be disentangled than the short ones. And this untangling only occurs when the microtubules begin to stretch the chromosomes, in the period of mitosis known as 'anaphase'. Right up to this moment, Topo2 continues doing its job.

Understanding all the players in the precise mechanism of cell division helps us understand one of the most complex and repetitive processes in any organism. The correct functioning of cell division is key to the survival of every cell and, by extension, of all living beings.

More information: Titos et al., Chromosome length and periuclear attachment constrain resolution of DNA intertwines. The *Journal of Cell Biology* (2014), doi.org/10.1083/jcb.201404039

Provided by Center for Genomic Regulation