Stable conditions during cell division

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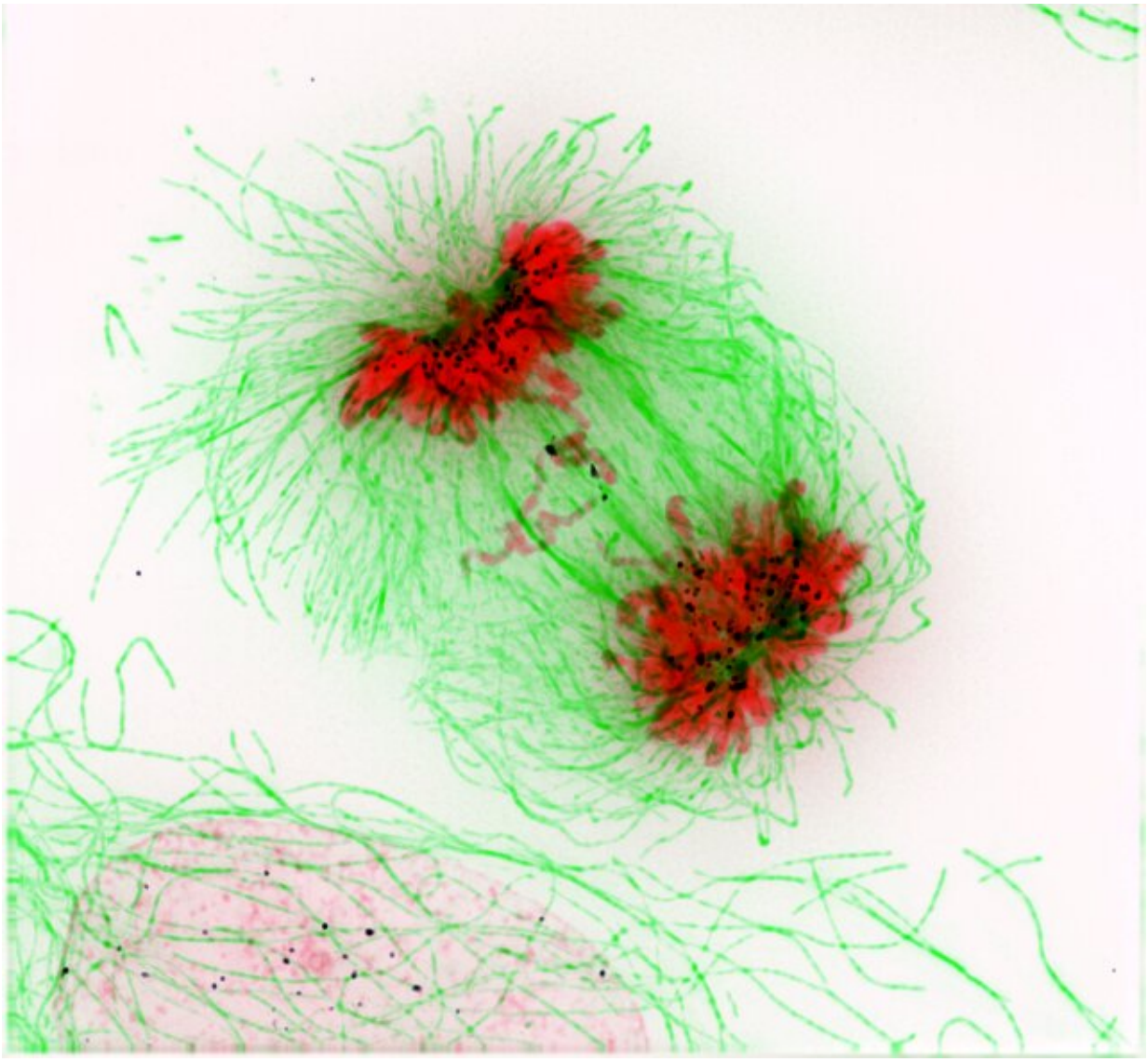

Incomplete seperation of the chromosomes (red) by microtubules (green).
Credit: MPI f. Molecular Physiology

Errors during cell division can trigger the development of cancer. No wonder that this central process is controlled by multiple regulators and guards. Alex Bird's research group at the Max Planck Institute of Molecular Physiology has discovered a hitherto unknown key player and how it provides the necessary stability to the distribution process of the genetic information by repurposing a long-studied factor in cellular trafficking.

Bodies constantly renew their cells. In the digestive tract, cells only live a few days, and skin is renewed once a month. This process is driven by cell division. In the ideal case, two identical daughter cells are created out of one cell. However, the equal division of the genetic information through separation and segregation of the duplicated chromosomes into newly forming daughter cells is very sensitive to errors. If a mistake is left uncorrected, those cells will often die due to lack of genetic information. Even worse, the cells may survive and pass on to the mistake to the following generations. The more errors happen, the more genetic information is garbled, similar to the children's game "telephone." As a result the cells degenerate, potentially leading to uncontrollable cell division and in the worst case to the development of cancer.

To escape this fate the cell has developed a variety of control mechanisms, that among other functions can undo errors during later phases of cell division. Control of chromosome segregation is dependent on the ability of cells to balance the stability of protein tubes (microtubules), which move the chromosomes through the cell. The microtubules form protein filaments that firstly capture chromosomes like the arms of an octopus, arrange them in the center of the cell, and finally separate them equally.

However, binding of the microtubules to the chromosomes is a balancing act: If the microtubules are too fragile, the chromosomes are not

arranged correctly before they are distributed. If the microtubules are too stable, errors made during the capture process cannot be reversed. The team of Alex Bird has discovered a hitherto unknown key regulator of these processes, the protein GTSE1, which promotes microtubule stability. Some cancer cell types that frequently have hyperstable microtubules and missegregate chromosomes are consistently found with elevated levels of GTSE1. Bird and his team were able to show that if the amount of GTSE1 is reduced in these cancer cells, fewer errors occur during the distribution of the chromosomes. On the contrary, increasing in the amount of GTSE1 in normal cells leads to a higher error rate during cell division.

Enigmatic mechanism in cell division solved

With their current research work, the scientists have elucidated how GTSE1 is recruited in the cell to microtubules to stabilize them. Surprisingly, they found that a well-known player in a completely unrelated cell process was the key: the protein Clathrin. Clathrin is important for the transport of fluids or particles from outside the cell into the interior of the cell by forming vesicles. Bird and coworkers show that the specific mechanism by which clathrin is recruited to form vesicles in the cell is repurposed during cell division, where clathrin interacts with microtubules and uses this mechanism to recruit GTSE1 to stabilize microtubules. This work highlights the remarkable way in which evolution provides cells with pathways to repurpose proteins for completely different functions within cells. Furthermore, the molecular insights into the protein interactions and pathways governing microtubule stability and how they are perturbed in cancer could facilitate the development of agents designed to target these processes therapeutically.

"Improper partitioning of chromosomes during cell division contributes to the development of tumours. The high chromosome segregation error

rates common to tumor cells may provide a changing genetic diversity that allows tumours to grow, survive, and resist chemotherapy treatment. This is why it is important to gain a better understanding of the molecular mechanisms by which these errors are induced in tumour cells ," says Alex Bird.

More information: Arnaud Rondelet et al. Clathrin's adaptor interaction sites are repurposed to stabilize microtubules during mitosis, *The Journal of Cell Biology* (2020). DOI: 10.1083/jcb.201907083

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