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Starting signal for cell division: Molecular switch ensures that cells divide at the right time

About 100 cells divide every second in our body. A key protein in cell division is a protein kinase termed Plk1, because it activates other proteins involved in this process. Plk1 is also overexpressed in many types of cancer. This makes it a promising target for cancer therapies. However, drugs that inhibit Plk1 have often proven ineffective. New findings by researchers led by Peter Lenart and Monica Gobran may help to improve therapeutic approaches. They discovered a previously unknown function of Plk1: It regulates the timely onset of cell division. When the protein is inhibited, cells start dividing many hours later.

Cell division allows a single fertilized egg to develop into a living being, our skin to renew itself, and wounds to heal. Before each cell division, termed mitosis, the genetic information must first be duplicated. This ensures that each chromosome in the cell that is ready to divide receives two copies of genetic information. Once started, cell division normally proceeds through all the stages until two genetically identical daughter cells are formed. During this process, the chromosomes are connected to the poles of the cell with the help of molecular "pulling ropes" – called the spindle apparatus –, aligned next to each other, and finally pulled to the opposite cell poles. The cell is then divided between the spatially separated sets of chromosomes. Erroneous or uncontrolled cell division can have serious consequences, leading to diseases such as cancer.

Plk1 plays a key role in this regulatory process. It activates other proteins involved in cell division by adding a molecular tag, a phosphate group. However, its exact function in the early phase of cell division has been controversial in research. "Previous studies suggested that Plk1 is essential for cells to start dividing at all," says Peter Lenart, who heads the research group Cytoskeletal Dynamics in Oocytes at the Max Planck Institute (MPI) for Multidisciplinary Sciences in Göttingen (Germany).

Right timing of cell division

His group has now discovered that Plk1 is not essential for the start of cell division. "Rather, it acts as a molecular switch to ensure that cells start dividing at the right time. Plk1 is crucial for the correct timing," the cell biologist reports.

When the researchers inhibited Plk1 in living cells, the cells remained in the prophase of mitosis for up to ten hours – this normally only takes about fifteen minutes. In this phase, the cell prepares for cell division by compacting, or "condensing", the chromosomes. "A key moment in the laboratory was when, after many hours, we suddenly observed the chromosomes condensing and the cell continuing its division cycle," says Gobran, first author of the study now published in the scientific magazine EMBO Journal.

A new microscopy assay developed by Gobran made this discovery possible. The PhD student succeeded in imaging hundreds of individual live cells condensing their chromosomes over a period of more than 24 hours during the cell division cycle.

Cells divide differently

The experiments also revealed another finding: Cells divide very individually, even if they belong to the same cell type. “Some cells lag behind in the cell cycle, while others do not even begin to divide.” Individual cells also responded very differently to the inhibited protein, as Lenart adds: “It has been overlooked so far that cell division starts even without Plk1, just later than normal.”

With the help of their colleague Antonio Politi, the researchers were able to reproduce the variable behavior of the cells using mathematical modelling and thus explain how Plk1 acts as a catalyst for the start of cell division.

Prophase can be studied in detail for the first time

In collaboration with the institute’s experts in mass spectrometry as well as data analysis and biostatistics, Henning Urlaub and Juliane Liepe, the team also succeeded in identifying which proteins in the early prophase are labeled with a phosphate group. “With this methodological approach, we now have a technique that allows us to stop cells in prophase before cell division begins. This phase is normally very short and has been difficult to study at the cellular and biochemical level,” Lenart notes.

New approaches for cancer therapy

The researchers’ findings could provide a new approach for future cancer therapies. “In combination with other compounds that prevent mitosis, Plk1 inhibitors could have a greater therapeutic benefit,” says the research group leader.

A next goal of the research group is to understand the role of Plk1 in the specialized division of egg cells, called meiosis. Human egg cells, for example, spend decades in the prophase state.

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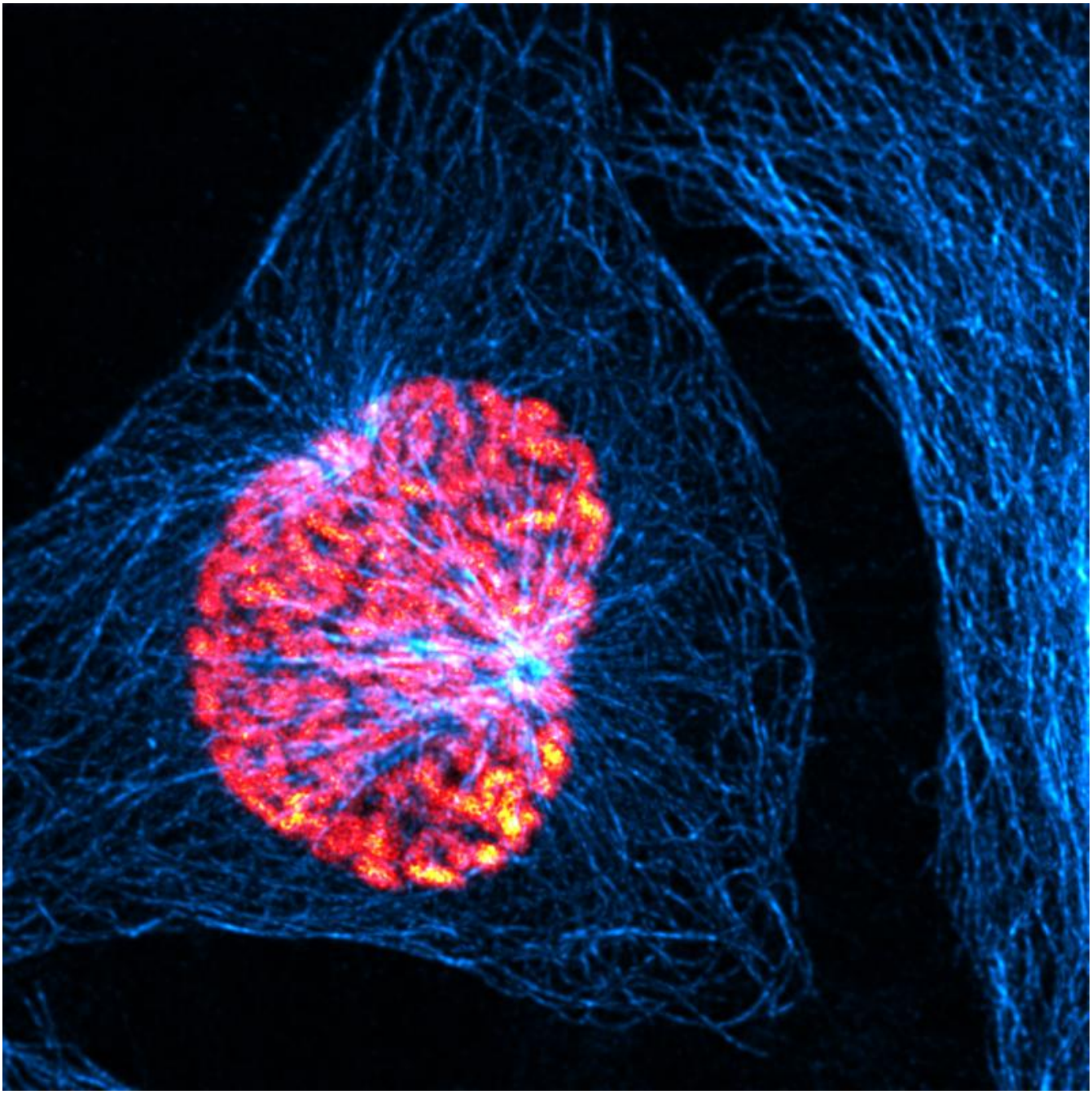
URL zur Pressemitteilung: https://www.mpinat.mpg.de/4973591/pr_2507 – Original press release

URL zur Pressemitteilung: https://www.mpinat.mpg.de/lenart – Website of the Cytoskeletal Dynamics in Oocytes research group, Max Planck Institute for Multidisciplinary Sciences



A cultured human cell (HeLa cell) in prophase. Chromosomes are shown in shades of red, microtubules are marked in blue. 3D image taken with a confocal microscope.
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