The multiplication of cells under close observation

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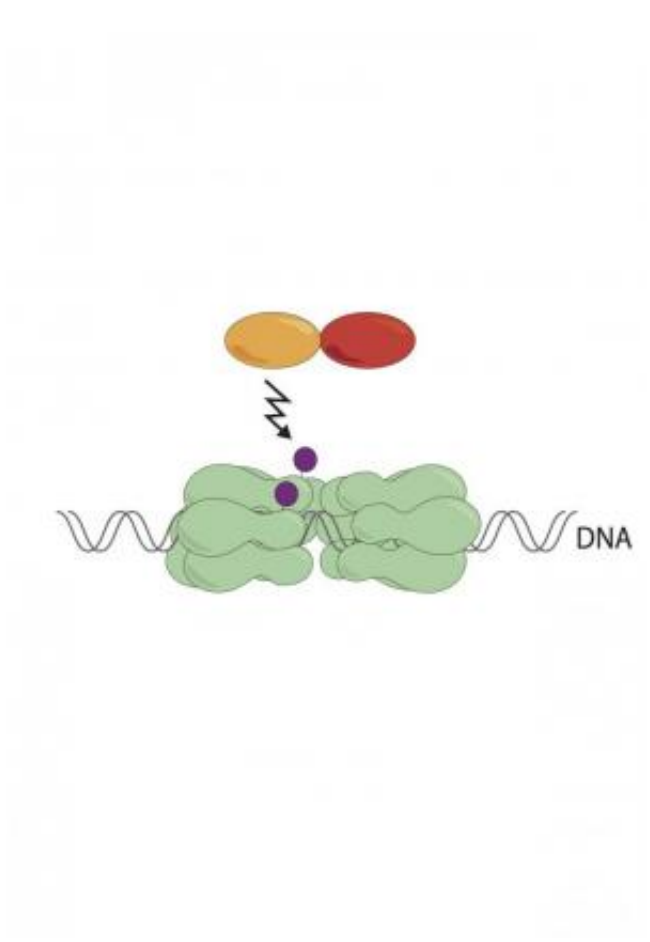

The binding of Rif1 (red) to the PP1 enzyme (orange) inactivates DNA replication by removal of the molecular "tags" (violet) to the replication complex (green). Credit: David Shore, UNIGE

A group from the University of Geneva, Switzerland, discovers a key factor that curbs the undesirable triggering of DNA replication.

Our cells must grow and divide optimally to ensure that our bodies functions properly. It is essential, however, that these processes are carefully controlled in order to prevent unrestrained proliferation that can lead to the formation of tumours. David Shore, a professor at the Faculty of Sciences, University of Geneva (UNIGE), Switzerland, and his team have uncovered a cellular factor that regulates the timing of DNA replication. This molecule, called Rif1, ensures that only a fraction of the origins of DNA replication is activated at specified times of the cell cycle. The researchers' work, published in the journal *Cell Reports*, suggests that Rif1 plays a role in the prevention of "DNA replication stress", a process causing DNA damage that can lead to genome instability.

Each time a cell divides, it must replicate its DNA to provide a copy to the two daughter cells. This process starts at specific regions in the genome, known as "origins of replication". A number of proteins congregate at these sites in an orderly and sequential fashion. However, molecular 'tags' must be added to this protein complex by specific enzymes before replication can initiate.

Maintaining a temporal program for replication initiation

The molecular dialogue leading to the activation of replication origins must be strictly controlled in order to prevent replication from occurring too rapidly, thus overloading the system. "Under normal conditions, there are many more replication origins than are actually used. We suspect that in precancerous cells many of these normally dormant origins are activated inappropriately," notes David Shore, professor in the Department of Molecular Biology of the UNIGE.

Are there safeguards which intervene directly at the level of the origins of replication? This is what the researchers at UNIGE tried to find out by using yeast, a unicellular fungus that is used as a model organism because it functions in many respects like a mammalian cell. "We wanted to determine the possible role of a protein named Rif1 since it was recently implicated in controlling DNA replication in several organisms, including yeast and human

cells", reports Stefano Mattarocci, lead author of the study.

Simply remove the molecular tags

In collaboration with researchers from the Friedrich Miescher Institute of Basel and the Vanderbilt University Medical Center of Nashville (United States), the biologists discovered that Rif1 regulates the timing of DNA replication by acting directly at the level of the origins of replication. "Rif1 recruits a specific enzyme called PP1, which will remove the molecular 'tags' required to start the replication process", explains Maksym Shyian, co-lead author of the article.

The binding of Rif1 to this enzyme curbs the untimely triggering of DNA replication. "These safeguards are probably part of a system that prevents DNA replication stress," reports David Shore. This stress, which is notably induced in pre-cancerous lesions, is characterised by an increased DNA replication rate, which provokes DNA damage and genome instability, major drivers of tumor formation.

Provided by University of Geneva