Growing and surviving: How proteins regulate the cell cycle

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Cell division is the basis of all life. Even the smallest errors in this complex process can lead to grave diseases like cancer. Certain proteins have to be switched on or off at specific times for proper cell division. Biophysicists and medical biochemists at Martin Luther University Halle-Wittenberg (MLU) have described the underlying mechanism of this process. They report how different signaling pathways in the cell change the structures of proteins, thereby driving the cell division cycle in the right direction at the right time. The researchers present their findings in *Proceedings of the National Academy of Sciences*.

The cell cycle is an extremely complex and precisely defined process. "The parent cell has to double its existing components and then divide into daughter cells. In order to do this, numerous genes have to be switched on and off at very specific times," says biophysicist Professor Jochen Balbach from MLU. The cell cycle is sub-divided into phases. These are controlled by what are known as inhibitor proteins, also called CDK inhibitors. Like a red traffic light, these proteins block transition to the next phase until the cell gives the relevant start signal. The signal to start the next phase of the cell cycle comes from a special enzyme group, the kinases. "Previously, we only knew that the kinases passed on the signal by adding a phosphate group onto the CDK inhibitors. There was no knowledge, however, of which kinases do this, or the underlying molecular mechanism," says Balbach.

Together with the working group led by Professor Mechthild Hatzfeld from the Pathobiochemistry Section of the Medical Faculty of MLU, the

researchers have now described this signaling pathway for the first time. They combined high-resolution magnetic resonance spectroscopy data with methods from cell biology. This meant that the researchers were able to explain the mechanism first in test tubes and then directly in cells . The researchers found that the kinases change the structure of the inhibitor proteins by unfolding them. This process disables the original function of the inhibitor proteins and releases a further blocked kinase that gives the signal for the cell cycle to continue. This local unfolding also triggers the degradation of the inhibitor in the cell, determining the direction in which the progression occurs. The researchers from Halle assume that this mechanism preserved by evolution is the basis of many cellular signal pathways.

More information: Amit Kumar et al, Phosphorylation-induced unfolding regulates p19INK4dduring the human cell cycle, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1719774115

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