Cancer can be treated by blocking central conductor of cell division, study finds

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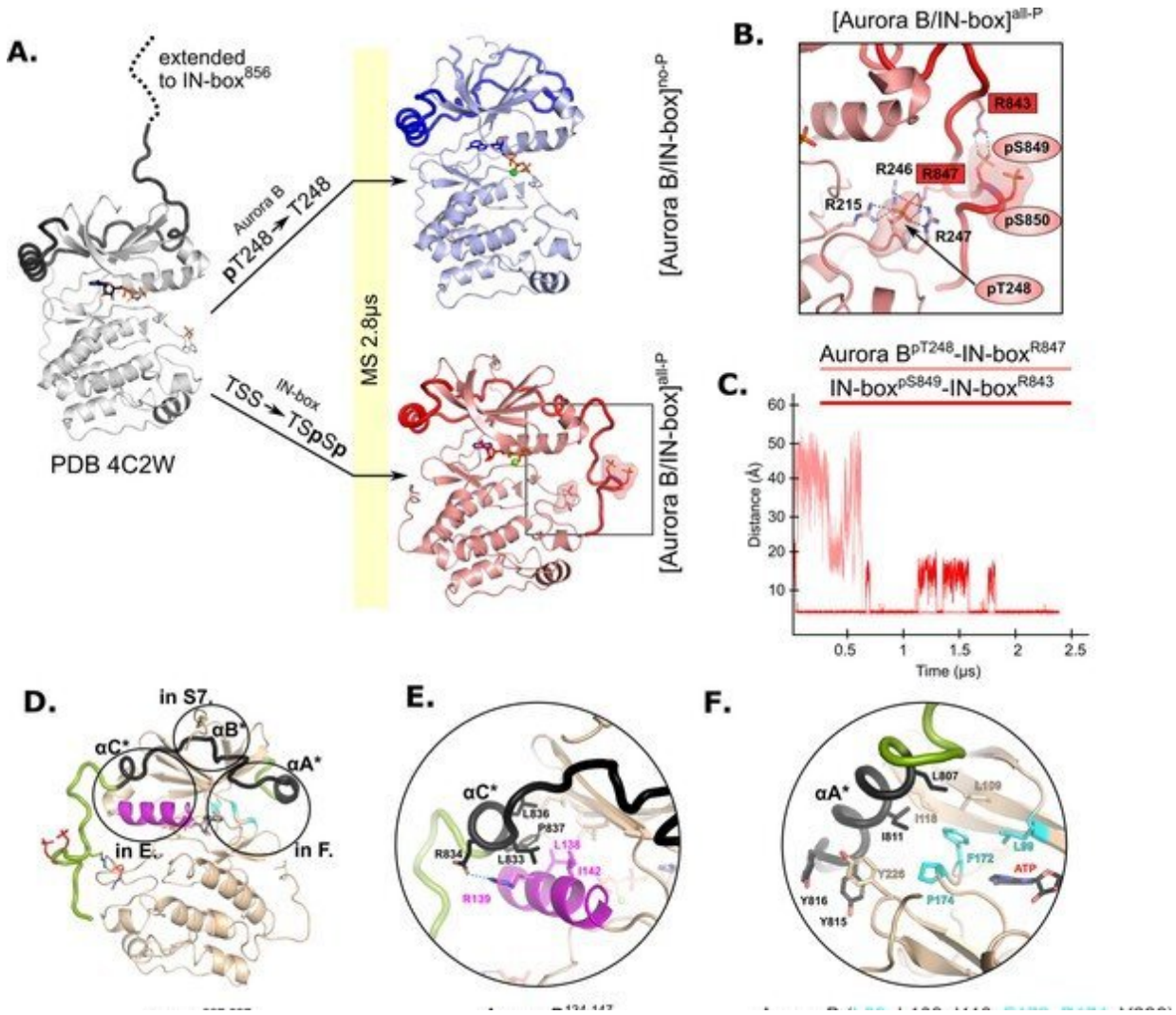

Molecular dynamics (MD) simulation of [Aurora B/IN-box]$^{no-P}$ and [Aurora B/IN-box]$^{all-P}$ reveals large conformational changes in the C-terminal part of IN-box and dynamic coupling between IN-box and the Aurora B catalytic helix.

Credit: *eLife* (2023). DOI: 10.7554/eLife.85328

Researchers at NCMM have demonstrated the mechanisms behind the activation of Aurora B, a central conductor of cell division. Their findings, now published in *eLife*, can lay the foundations for developing new cancer drugs.

Cell division is a fundamental process for all living things, where one cell divides into two cells. It allows for a human being to grow from a single fertilized egg cell, for wounds to heal, and for dead cells within your body to be replenished with new cells.

By the time you have read this sentence, millions of cells throughout your body have divided.

When a cell divides, it happens through a series of carefully controlled steps, and only when needed. Cancer, on the other hand, is characterized by cells having gained the ability to divide uncontrollably.

"We can say that cancer is a cell division disease. That's why scientists are working to find new cancer treatments that disrupt the process of cell division, so that the cancer cells die instead of dividing," explains Dario Segura-Pena.

At the Center for Molecular Medicine Norway (NCMM), Segura-Pena and colleagues in the Sekulic group have looked closer at an enzyme called Aurora B, which is particularly important for cell division. And what they show can be used as a basis for the development of new cancer treatments.

Aurora B is an enzyme that acts as a conductor of cell division. Aurora B

is activated when the cell is going to divide and makes sure that the different steps are executed correctly and in the right order.

"If we disrupt the activity of Aurora B during cell division, the process will become so chaotic that the cell ends up dying instead of dividing. And that is exactly what we wish to happen to cancer cells," says Segura-Pena.

In their study, Segura-Pena and colleagues show how the activity of Aurora B is turned on and off. The goal is to use this knowledge as a basis for developing new drugs that kill cancer cells by preventing the activation of Aurora B during cell division.

Main author of the study, Dario Segura-Pena (left) together with Nikolina Sekulic (right), head of the research group. Credit: Nikoline L. Rasmussen

A small modification with large effects

Therefore, the researchers looked at the on/off-switch of Aurora B and what happens to the protein structure of Aurora B when it is turned on.

The switch in Aurora B is a tiny molecular modification, called phosphorylation. This involves attaching a small phosphate molecule to the enzyme in order to turn it on.

It's already known that phosphorylation of Aurora B causes a dramatic increase in its activity. But the changes that occur within Aurora B itself upon phosphorylation, was not known before now.

"If we compare the sizes, then the attachment of a small phosphate molecule to Aurora B is like attaching a grain of sand to a tennis ball. We wondered how such a small modification could have such a strong effect on Aurora B activity during cell division," explains Segura-Pena.

To be able to see what happens to Aurora B when it is phosphorylated, the researchers zoomed in on the molecular level.

"Proteins are often depicted as static structures, but the reality is that within our cells they are far from static. They vibrate, almost breathe, and can change their structure to perform different tasks. We have used a method, called HDX-MS, that allows us to see some of these movements in Aurora B, and how they change depending on whether it is turned on or off," says Segura-Pena.

HDX-MS (hydrogen-deuterium exchange mass spectrometry) is a method that makes it possible to analyze the structure and dynamics of a protein. With the help of HDX-MS and computer simulations, the researchers were able to see that the phosphorylation led to a change in the structure of Aurora B. The protein structure went from being chaotic and inactive, to organized, well-structured and synchronized in its motions.

Details can lay the foundations for developing drugs

And it is only when Aurora B is phosphorylated and organized that it can conduct the tasks that lead to cell division.

Knowing how an enzyme looks and functions helps to develop targeted drugs that specifically affect the active part of the enzyme. Therefore, Segura-Pena hopes that their results bring us one step closer to being able to develop cancer treatments that block Aurora B activity and cell division.

"Our findings demonstrate the details around what happens on the structural level when Aurora B is activated. This gives us more avenues for developing new cancer therapies in the future," says Segura-Pena.

More information: Dario Segura-Peña et al, The structural basis of the multi-step allosteric activation of Aurora B kinase, *eLife* (2023). DOI: 10.7554/eLife.85328

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