How a DNA-damaged cell struggles to divide

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Cells duplicate by division. The division requires that an accurate copy of DNA has been made to ensure the correct passage of genetic material. However, in reality, many factors (such as UV light) are constantly breaking the double strand structure of the DNA molecule. Cells develop a mechanism named checkpoint to find out whether there is DNA damage. When the DNA damage is found in a checkpoint, cells will not divide unless the damage is repaired.

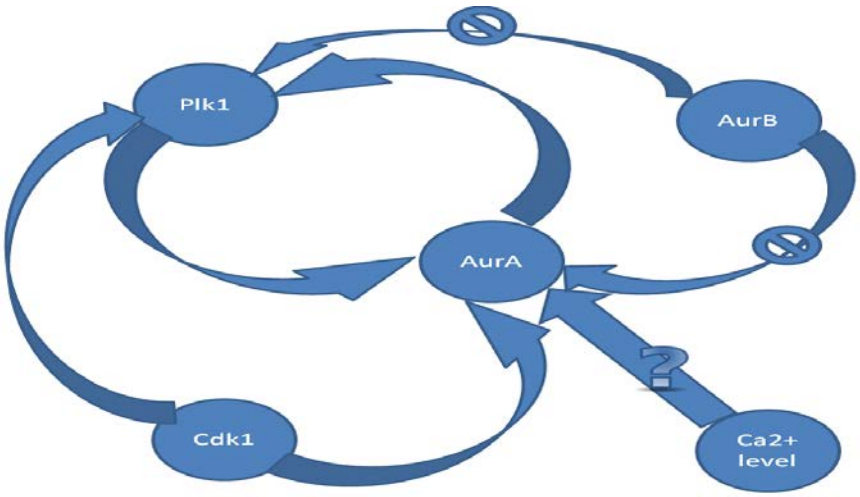
During the whole cell cycle there are three DNA damage checkpoints. Here we focus on the G2 checkpoint, which is where cells are preparing for the coming division. When cells detect DNA damage, they arrest in G2, just before they are about to divide. By using drugs, cells can skip the checkpoint and enter mitosis (a cell divides into two copies), this process is called (induced) checkpoint recovery.

I developed a setup to study the proteins that are involved in checkpoint recovery. Cells were treated with DNA damage drugs and followed by other drug treatments, which brings cells to exit the checkpoint and to divide. The majority of the cell population does not divide. With different drug treatments, many questions for the proteins that regulate division can be answered.

A protein called cyclin dependent kinase 1 (Cdk1) is the most important regulator of division. It binds to cyclin B and forms a complex which activates many essential proteins that promote division. In my study, it can be concluded that the inhibition of Cdk1 activity certainly influences the activity of Polo-like kinase 1 (Plk1, an activator of Cdk1) and Aurora A (AurA, an activator of Plk1). It is shown that between Plk1 and AurA, there is a feedback loop, which means the activation of Plk1 influence AurA, and it results in that AurA activity promotes Plk1 activity.

The molecular structure of Aurora B (AurB) is similar to AurA. These two proteins locate in different positions and also have different functions during cell cycle. My study confirmed that AurB has little effect on AurA activity during checkpoint recovery.

We investigated whether interfering with calcium level can influence AurA activation. The conclusion is that intracellular calcium release (or reduction) may regulate AurA activation, and blocking calcium level certainly causes cell death.



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