Cell Response After DNA Damage: Cell Cycle Arrest And Cell Cycle Transitions

No matter you are the microbe, plant or large animal, you all have cells. But what makes you like this, it is decided by the DNA information. That is to say, the DNA information inside the cells controls all the traits you have. Thus, we really need to understand how important DNA information is as it is a blueprint to give instructions to all the other molecules, like proteins and tell these molecules what work they should do. However, as DNA need to replicate thousands of times every day, it is very hard for it to make sure all details are correct and no mistakes are made. Then, DNA should have its own repair system and solutions when something wrong.

More important, Cells should have ways to sense DNA breaks and let all the other parts in the cell know about this information. In fact, it is very important for cells to notice other parts in the cell that their blueprint – DNA double strands have something wrong. For example, we all know that DNA is the formwork for RNA transcription and translation. If DNA has any mistake, the transcription process will make the wrong RNA strand. Then, the translation process will be wrong as the wrong RNA strand is being used to make proteins. If proteins are wrong, cell structures that are made of proteins will not be functional anymore, some diseases like Parkinson and Huntington will also appear. Based on what we just discuss, we can understand how important for cells to sense DNA breaks, it is also essential for cells to let everyone know about it.

According to Zhou and Allege, the author of “The DNA damage response: putting checkpoints in perspective,” all the organisms should response to the DNA mistakes and disorder through the “damage response pathway.” This response pathway is very helpful as it can not only “regulate known responses,” but also “control additional processes.” For the known responses, they mainly refer to the “cell-cycle arrest” and “program cell death,” and for the additional processes, they may refer to the “activation of DNA repair networks.” In order to have further understood the cell reaction after DNA damage, we should first understand what are the DNA damage response pathway and DNA damage sensors are. Figure 1. This figure comes from the article “The DNA damage response: putting checkpoints in perspective” which is written by Bin-Bing S. Zhou AND Stephen j. Elledge. This figure generally shows the outline of the DNA damage response pathway as it includes signals, sensors, transducers and effectors all four steps. This diagram is coming from the article “The DNA damage response: putting checkpoints in perspective.” Based on this diagram we can see that the DNA damage response pathway is a “signal transduction pathway” as it contains four main steps: signals, sensors, transducers, and effectors. For signals, it includes a lot of things such as replication stress, genomic instability, and cell cycle arrest. All this information tells the cell that there is something wrong in the DNA and sensors can sense the damaged DNA. While for DNA damage sensors, DNA strand breaks can activate them and they are mainly composed of poly polymerase and protein kinase.

According to Will Renthal, the author of “Cancer and the role of cell cycle checkpoints,” a group of four “fission yeast checkpoint proteins, Rad1, Rad9, Hus1, and Rad17” are forming a “checkpoint-sliding clamp.” In addition, Rad26 also be regarded as the DNA damage sensor as it “binds to and is phosphorylated by the Rad3 kinase independently of all other checkpoint

proteins.” Zhou also has a similar idea with Renthal as he/she proposed that these proteins can “loaded into damaged DNA.” For transducers, they are used to transduce the signal that DNA has been damaged or something wrong to the following effectors. According to Renthal, the “activation” of “two kinases” is essential for the “proper transduction of DNA damage” in human cells and they are ATM (Ataxia Telangiectasia Mutated) and ATR (ATM and Rad3 Related). Renthal told us that ATM was found from “a rare mutation” in disease “ataxia telangiectasia” and may cause “chromosomal instability” and “cancer.” Zhou told us that “ATM kinase activity can be activated by DNA damage in vivo.” While in general, both ATM and ATR can be used to phosphorylate some proteins and also act as transducers to send the signal - the DNA is being damaged to the next step, and then the DNA might start to repair itself. Renthal also told us that if the damage is too crucial, they may cause the cell to die. After the signal is being translated to the effectors, the cell will have several reactions. Based on the diagram we can see that the cell cycle transitions might be stopped, the cell may die and undergo apoptosis, the transcription action may change and the DNA might repair itself. In addition, the article “The DNA damage response: putting checkpoints in perspective” also pointed out that the DNA damage response and repair are actually “interacting networks.” That is to say, in order to respond to the DNA damage, the cell may not only die or stop the cell cycle, it may also plan to repair itself. As there are so many different kinds of reactions the cell might have after the DNA damage, it is pretty hard to say what specific result will be for each specific position of DNA strand damage, but all their main goal is to maintain the stability of organisms’ genome. Why does the DNA damage response pathway and checkpoints are so important? Why it is also important for cells to know when to repair and DNA damage and when the damage repair work is done? Although this damage and mistakes may only exist in the microstate, it may directly or indirectly cause the disable and instability for the whole organisms and in the macrostate. For DNA checkpoints, it is a stage in the cell to check and examine whether the cell activity should stop now or keep moving forward (Cell cycle checkpoints). That is to say, if the checkpoints detect the DNA damage or mistake, it will let the cell stop the further work or progress in order to avoid bigger mistakes. Then, it will organize the cell repairing work to make sure all things are on the right track. Another important thing is that cell should not only know when and where to repair, but also aware whether the repair work is done or not.

According to Zhou, if the repair work is finished, a signal for “termination of the response and resumption of the cell cycle” will be generated. Then, the cell will let all progress to keep going and finish all the following work, and the whole flow path is really similar to the factory pipeline operation. By doing all of these work, the cell can make sure all DNA damage can be a response at once, all the mistakes can be fix and the final product will be functional and correct. The cell can also detect the gross fault as soon as possible and it may even let the whole cell die in order to avoid irreversible and devastating consequences. Thus, we can understand how important the whole process is and the reason why scientists pay so many efforts to figure out the DNA response pathway and so many researches are being done in this area for such a long time.

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