How cells tolerate DNA damage -- start signal for cell survival program identified

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Cancer researchers of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, have gained new insights into how cells react to DNA damage. Dr. Michael Stilmann, Dr. Michael Hinz and Professor Claus Scheidereit have shown that the protein PARP-1, which detects DNA damage within seconds, activates the transcription factor NF-kappaB, a well-known regulator of gene expression. NF-kappaB triggers a survival program, which blocks programmed cell death. The activation of NF-kappaB is thought to be one of the potential causes for tumor cell resistance to chemo and radiation therapy.

The DNA of each human cell is damaged many times every day. DNA lesions can be caused by ultraviolet radiation, errors in cell division, DNA-damaging chemicals or intracellular metabolic products. Damaged chromosomal DNA can ultimately be the cause for serious diseases, such as cancer.

However, cells have developed complex systems that recognize DNA lesions within seconds and ensure that the damage will be repaired. In case of massive DNA damage, the affected cell can be destroyed by initiating apoptosis (programmed cell death).

Apoptosis is a cellular program which drives defective cells to commit suicide, thus protecting the organism as a whole. Another regulator of gene expression, the transcription factor p53 - also known as the "guardian of the genome" - has a key function in the activation of programmed cell death. But p53 is not always successful in switching on

the protective program.

NF-kappaB opposes the function of p53, in turn activating a survival program which protects the damaged cells from destruction. The activation of this program by NF-kappaB is considered to be one of the possible causes for resistance of tumor cells to chemo or radiation therapy.

The transcription factor NF-kappaB not only regulates cell survival programs, it also plays an important role in the immune system and in inflammatory processes. NF-kappaB can be switched on by a number of extracellular and intracellular stimuli.

Such stimulation alters the activity of protein-regulated signaling pathways, which ultimately activate NF-kappaB. The process of signal transduction initiated by external physiological stimuli has been well characterized in recent years.

However, it was not understood how NF-kappaB is switched on by DNA damage. MDC researchers have now succeeded in illuminating this particular signaling pathway.

Professor Scheidereit and his colleagues Dr. Stilmann and Dr. Hinz discovered that the DNA damage detector PARP-1 plays a key role in the activation of NF-kappaB. PARP-1 recognizes sites of DNA damage within seconds and then attracts several proteins, which are important for this signaling pathway, to form a complex in the cell nucleus.

Due to subsequent chemical changes in the complexed proteins, signals are generated, which then trigger NF-kappaB activation. "We have thus identified the start signal for NF-kappaB activation", Dr. Stilmann and Dr. Hinz explained.

Now the researchers want to investigate further components of this signal transmission cascade and their interaction. "For medical research it is of enormous significance to understand these signaling pathways. This is based on the hope to identify targets for the development of drugs, which allow to switch off the survival factor NF-kappaB in cancer diseases in a context-specific manner."

Already now, clinical trials are in progress worldwide with various, not yet approved substances, which target and inhibit PARP-1 and which have gained much attention from the scientific community. In the context of these studies, experts consider the work of the MDC researchers to be of special significance.

Professor Scheidereit and his collaborators have been working for many years on NF-kappaB. Some years ago they were able to show that NF-kappaB plays a key role in tumor cell survival in Hodgkin's lymphoma, a common lymph gland cancer.

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