A novel DNA damage alarm

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How does our body keep its DNA intact? Researchers at Erasmus MC have just found a new piece of this puzzle. They discovered a novel alarm that cells use to signal DNA damage. "We already knew that DNA damage triggers an alarm in our body cells", says lead researcher Wim Vermeulen. "We have now shown that this alarm is also set off during transcription (expression) of damaged genes." Maria Tresini, Jurgen Marteijn, Wim Vermeulen and other co-workers just published their findings in the leading scientific journal *Nature*.

Cellular metabolic byproducts, chemicals, and radiation such as sunlight continually damage our DNA. Damaged DNA disturbs cellular function and can cause ageing. Moreover, permanent changes in the genetic code (i.e. mutations) can arise when the DNA duplicates before the error is repaired. Mutations may result in cancer. Fortunately, most lesions are quickly repaired by the cell's repair proteins. In addition, the cell turns on a DNA damage alarm when it detects DNA lesions.

DNA damage response

The alarm sets a variety of processes in motion. For instance, it temporarily stops DNA duplication and cell division, preventing errors from being passed on to daughter cells. But DNA damage does not only affect DNA duplication, it also has a great impact on gene transcription (the process that copies DNA into RNA, which is necessary for gene expression). The enzyme that carries out transcription halts when it encounters a UV-induced DNA lesion. Dr Maria Tresini: "Until now, it was unknown whether these transcription problems also trigger the DNA damage response. We discovered that this is indeed the case."

ATM protein

The key actor in the new mechanism is a protein called "ATM". It has long been known that ATM has a central role in DNA damage signal transmission when DNA double strand breaks are formed. "But now we found that the ATM alarm is also triggered by UV-induced transcription halting. ATM then influences alternative splicing of gene transcripts. This leads to the formation of new protein variants that may counteract the negative effects of DNA lesions", says Dr Jurgen Marteijn.

Solving the puzzle

Professor Vermeulen concludes: "This is an important step towards solving the complex puzzle of how cells respond to DNA damage to protect us from ageing and cancer. Our study provides opportunities for possible intervention in these important medical problems in the future."

More information: On the web portal HorizonHealth.eu, they explain how the novel DNA damage alarm works: www.horizonhealth.eu/dna-damage-alarm

The core spliceosome as target and effector of non-canonical ATM signalling, *Nature* (2015) DOI: 10.1038/nature14512

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