Stem cells: Tuning the death sentence

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In this week's issue of *Science Signaling* (22 January, 2013), Danen and colleagues of the Division of Toxicology of LACDR report novel insights into the question how stem cells decide to commit suicide when their DNA is damaged.

It is known that damaged DNA, especially in stem cells can lead to accumulation of potentially dangerous mutations that may be a source for cancer. To prevent this, evolution has provided our cells with the ability to recognize damaged DNA and to rapidly respond to it. This so-called "DNA damage response" activates repair mechanisms, and, if damage is too severe to repair, turns on a cascade of events leading to cell death.

All cells in our body are constantly experiencing small injuries in their DNA, for instance due to UV light or chemicals. It is important that cells first try to repair damaged DNA and only decide to commit suicide if damage is beyond repair. If suicide signals would be turned on too fast, stem cells in our tissues might be depleted causing premature aging. The discovery published in this week's *Science Signaling* is a new mechanism that acts as a break on the suicide signals.

In collaboration with colleagues from the Department of Toxicogenetics of the LUMC and from the University of Copenhagen, Danen et al. have been able to integrate several large-scale analyses to unravel the events that make up the DNA damage response. Genome-wide changes in gene activity and protein modifications, as well as genome-wide "gene silencing" screens were integrated with bioinformatics tools to create

signaling networks. This was possible through extensive collaboration within the NGI-funded, "Netherlands Toxicogenomics Center".

The signaling networks point to novel methods to recognize chemicals or drugs that activate a DNA damage response and hence, might be dangerous for human exposure. At the same time, the networks provide new clues for why cancer cells are often able to avoid activation of suicide signals when exposed to radiotherapy or chemotherapy. The publication in *Science Signaling* is one of the outcomes of this project; additional publications will come out this year.

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