Two sides of a safety switch

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High-profile dioxin victim: Viktor Yushchenko, the former president of the Ukraine, suffered from chloracne, which left his face badly scarred (photo from 2006). Credit: Muumi, Wikimedia commons

Swiss researchers have discovered a new, surprising link between chloracne and a molecule that protects cells against stress: if Nrf2 gets out of control, disfiguring cysts form on the skin.

The images were seen all over the world and stuck in the minds of many: in the autumn of 2004, former President of the Ukraine, Viktor Yushchenko, was poisoned with a high dose of dioxin. Although he survived the attack, the chloracne caused by the poisoning, officially known as MADISH, left him severely disfigured: his face was peppered with numerous cysts, which left deep scars.

Now a team of researchers headed by ETH-Zurich professor Sabine Werner and a senior researcher of her team, Dr. Matthias Schäfer, has stumbled across a link between chloracne and a molecular switch, which causes a comparable skin phenotype in mice after longer and increased activation. The new discovery has just been published in *EMBO Molecular Medicine*.

Interesting candidate

The molecular switch is Nrf2, which the ETH-Zurich researchers have been studying in connection with different skin diseases for some time. Nrf2 is a so-called transcription factor. It activates certain genes that protect cells and help them to survive under stress conditions. The ETH-Zurich scientists had discovered that a moderate activation of Nrf2 protects the skin against UV damage. The molecule activates several genes designed to protect skin cells from aggressive free radicals, which are formed through UV radiation, save them from dying off and prevent damage of the genetic material.

Nrf2 is thus an interesting candidate for use in skincare creams and for cancer prevention. Until now, however, the consequences of prolonged Nrf2 activation in the skin had not been characterized. After all, in a previous study Werner and Schäfer realised that the skin of mice became flaky and was thus potentially damaged upon increased activation of Nrf2.

Striking parallels between mice and humans

For their follow-up study, they used an animal model in which the skin cells of genetically modified mice permanently activated Nrf2. As a result, the animals developed skin changes that were strikingly similar to those in dioxin victims, albeit far less pronounced than in humans. In mice with Nrf2 activation, the sebaceous glands became enlarged and secreted an excessive amount of sebum. The hair follicles were also thickened and callused, which ultimately led to their widening, hair loss and eventually the development of cysts.

Consequently, in a second step the scientists tested tissue samples from MADISH patients and discovered that Nrf2 was evidently activated in their skin, causing a strong expression of the same target proteins as in the mouse model. Therefore, it is very likely that the processes that trigger such abnormal skin changes in mice also take place very similarly in humans.

Lady Luck has a hand

"We only spotted the link between chloracne and the mouse model in the course of our project – purely by chance," says Werner. Originally, the aim had been to understand what takes place in the event of an increased activation of Nrf2 in the skin. Hence, the ETH-Zurich researchers are all the more delighted that they identified a major player in the development of chloracne.

The issue of which molecular mechanisms take place in an early phase of chloracne still remains unexplored. The researchers simply lack the samples from patients, who have suffered from dioxin poisoning, to address this question. Schäfer stresses how difficult it is to get hold of this kind of sample material. "The patients only go to the doctor once the

condition is already quite advanced," he says. "In other words, the early stage goes undetected and is lost."

The two researchers believe, however, that therapeutic targeting of Nrf2 in the case of chloracne is problematic. The cells activate Nrf2 in order to accelerate the detoxification of the body. In the event of dioxin poisoning, slowing down or even stopping the body's response with an intervention against Nrf2 could be fatal. Besides, dioxin is a very long-lived toxin that is stored in the body's fatty tissue. It is no coincidence that precisely the sebaceous glands of the facial skin are changed so severely in the case of MADISH: lipids and thus dioxin are stored in them. Consequently, the researchers consider it more sensible to first examine Nrf2's target genes in more detail, so that the amount of activity of specific proteins that are responsible for the symptoms might potentially be influenced.

More information: Schäfer M et al. Activation of Nrf2 in keratinocytes causes chloracne (MADISH)-like skin disease in mice. 2014 *EMBO Molecular Medicine*, published online 6th February 2014.

Tan NS, Wahli W. The emerging role of Nrf2 in dermatotoxicology. *EMBO Mol. Med.* Published online 6th February 2014.

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