Start signal for transcription of stressed genes identified

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Start signal for transcription of stressed genes identified. Credit: Fotolia

What happens when a cell is stressed? In their latest study, Christian Seiser and his team at the Max F. Perutz Laboratories (MFPL) of the University of Vienna and the Medical University of Vienna addressed this question. They identified which genes of the cell are activated under stress, showed that more than half of these genes share the same hallmark and described the molecular mechanism through which it starts the transcription of stress-activated genes. Their results could help to develop therapeutics to treat stress-related disease and have been published in the renowned journal *Genome Research*.

When people talk about stress, they generally refer to feeling the strains of too high burdens at work or in their private life. In biology, the term stress has a broader meaning: discovered and first described in 1936 by Viennese physician and biochemist Hans Selye stress is "a psychological and physical reaction to external stimuli, which the body initially reacts to by mobilizing its defense mechanisms." Triggers for stress, so called stress factors, include not only emotional strain, but also physical factors such as heat, cold, too much sun, infections, injuries, and toxic substances – for example in cigarette smoke.

Stressed genes share a hallmark on histone H3

We all know some of the body's reactions to stress from first hand experience: the heart is pounding, we feel hot or sweaty. But what happens in our cells, the building blocks of the body? Anna Sawicka addressed this question as a PhD student in the lab of Christian Seiser at the Max F. Perutz Laboratories (MFPL) of the Medical University of Vienna. "If cells are stressed, for example with certain chemicals, they immediately activate a specific transcription program. That means that certain genes are activated in a tightly regulated mode, that defines which gene is activated for how long", explains Anna Sawicka. The experiments of the researchers showed that almost half of all the genes that are immediately activated under stress share a hallmark: the protein histone H3 at their promoters, the first part of a gene, is marked with a phosphate residue.

The hallmark of stressed genes is a start signal for transcription

Study leader Christian Seiser says: "It came as a big surprise that we found the same mark at fifty percent of the stress-activated genes. This definitely qualifies it as a hallmark, as we usually find specific marks

only at a small fraction of all histone H3 proteins." Hence, the researcher asked further questions: What genes share this hallmark and what is the function of this mark? To answer these questions Anna Sawicka had to establish two methods that no one else had gotten to work in this context. The former PhD student of the FWF-funded doctoral program "Molecular Mechanisms of Cell Signaling found that the hallmark is mainly present at paused gene. Figuratively speaking, these are genes that are like motor racing cars with a running engine waiting at the start of a race. The phosphate mark then acts as a start signal that immediately upregulates these genes. "The stress signal causes the addition of a phosphate mark to the H3 proteins at the promoter, the regulatory region of a gene. This disables the interaction of H3 with a repressor complex, which blocked transcription up to this point, and stress-regulated genes are activated", explains Anna Sawicka the findings. Christian Seiser sums up the results: "The study has not only identified histone phosphorylation as a hallmark of stress-activated genes, but also the mechanism by which this chromatin mark induces transcription of these genes on a molecular level."

Stress can make you sick

A detailed understanding of the stress reaction on a molecular level could help to develop therapeutics to treat stress-related disease. While Anna Sawicka now works as a Postdoc at the Max Planck Institute in Goettingen, Christian Seiser and his team work to understand the function of the histone mark for long term activation of genes during the stress response. Their first cues hint to a function of the phosphate mark in combination with another histone mark as part of the so-called histone code.

More information: Anna Sawicka, Dominik Hartl, Malgorzata Goiser, Oliver Pusch, Roman R. Stocsits, Ido M. Tamir, Karl Mechtler, Christian Seiser: "H3S28 phosphorylation is a hallmark of the

transcriptional response to cellular stress." *Genome Research* (August 2014) DOI: 10.1101/gr.176255.114

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