Clever feedback system regulates immune responses

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A newly discovered feedback mechanism in the body is responsible for keeping immune responses from getting out of hand. It works at the level of certain genes, linking the inactivation of those genes to the progress made in transcribing them: This clever mechanism was discovered as part of an Austrian Science Fund FWF project and was recently published in *Molecular Cell Biology*. The discovery offers a completely new approach for future therapies aimed at controlling the immune system.

When microorganisms invade the body, cytokines (proteins that are important in cell signaling) are released that immediately trigger further defence measures. These include the activation and transcription of certain genes, and thus the production of defensive proteins. However, it is important that the body does not produce too many of these proteins, as doing so would result in harm to itself. The protein production is thus curbed in good time. It has long been known that this happens. How it happens, however, was only recently determined – thanks to the work of a team led by the immunobiologist Pavel Kovarik. In a project carried out at the Max. F. Perutz Laboratories and supported by the Austrian Science Fund FWF, the researchers were able to show how this curbing occurs.

Inhibited

To better understand this newly recognized mechanism, it is important to

know that cytokines act on the so-called STAT family of proteins, which act as transcription factors – that is, factors that initiate gene transcription of DNA, and thus the production of proteins. To fulfil this function, the STATs must bind to special DNA sequences, and it is precisely this binding that cytokines promote. In their work, Pavel Kovarik and his team initially focused on the cytokine interferon, which is produced in response to viral infections, and on the regulation of STAT1 activity. Their investigations led to the discovery of a new and surprisingly effective mechanism. The team was able to show that, as the STAT1-induced gene transcription progresses, STAT1 is increasingly unbound from the DNA. Kovarik comments: "This previously unknown feedback mechanism begins very early on in the process of producing defensive proteins and thus permits rapid regulation of an immune response." The project team subsequently observed the same regulation process for STAT2 and STAT3, as well, which is an indication that this mechanism spread early on in the course of evolution.

Clear results

Kovarik was subsequently also able to show that another – already known – STAT1 inactivation process is not crucial to regulating the immune response. This other process is based on a chemical modification of the STAT proteins whereby phosphate groups are removed, resulting in the inactivation of STAT1. "Although this inactivation does, in fact, prevent additional production of defensive proteins, the dissociation of the STAT proteins from the DNA that we discovered is the substantially more effective and thus decisive regulation step", says Kovarik, explaining the findings of his project.

Structural change

Although it is currently not known how the information regarding the

progression of DNA transcription is communicated to the DNA-bound STAT1 – and thus how the unbinding is triggered – Kovarik has a clear idea of how this might occur: "Model calculations and findings from other projects suggest that the progression of the gene transcription affects the DNA structure. This structural change can cause STAT1 to unbind from the DNA."

Point of attack

The newly discovered mechanism for regulating immune responses also opens up completely new possibilities for therapeutic interventions. After all, both immune systems that react too weakly and those that overreact can cause problems – possibly resulting in severe infections or autoimmune diseases. Targeted interventions in the mechanism discovered in the context of this FWF project could hinder this, making optimum use of the body's natural immune response.

More information: "Promoter Occupancy of STAT1 in Interferon Responses Is Regulated by Processive Transcription." *Molecular Cell Biology*, 2015, 35:716 –727. www.ncbi.nlm.nih.gov/pmc/articles/PMC4301719/

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