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# Key switch in the immune system regulated by splicing

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The protein MALT1 is an important switch in immune cells and affects their activity. Researchers at Helmholtz Zentrum München report in *Nature Communications* that this activation is not always equally strong. Through alternative splicing, two variants of the protein may arise which have a stronger or weaker effect on the immune system. Understanding this process is important for the pharmacological use of MALT1.

The protein MALT1 (mucosa-associated lymphoid tissue lymphoma translocation protein 1) controls the activation of lymphocytes and thus the immune response following bacterial or viral infections. For this purpose, the protease cleaves other proteins in the cell and is considered a potential target for the treatment of excessive immune responses as observed in autoimmune diseases (e.g. multiple sclerosis) or distinct malignant lymphomas.

To prevent an overshooting MALT1 activity, a team at the Research Unit Cellular Signal Integration (AZS) at Helmholtz Zentrum München is investigating which steps in this signaling chain are feasible for a pharmacological targeting. In the current study, the team led by Prof. Dr. Daniel Krappmann, head of the AZS Research Unit, focused on the two variants MALT1A and MALT1B, which arise through alternative splicing*.

## Stronger activation of T cells

"To our surprise, we showed that MALT1 is regulated by posttranscriptional splicing," said first author Isabel Meininger, a doctoral student at Helmholtz Zentrum München. "Depending on which MALT1 variant is expressed, the immune system activated is more or less," she added.

Specifically, the scientists observed that MALT1A resulted in a stronger stimulation of T cells than MALT1B. According to the study, a molecule called hnRNP U (heterogeneous nuclear ribonucleoprotein U) regulates which of the two isoforms is preferably expressed. If it is present in only small amounts, higher levels of MALT1A are expressed, resulting in stronger activation of the T cells. However, if the quantity of hnRNP U is increased, higher levels of MALT1B are expressed and the response of the T cells is weaker.

"Our findings contribute to a better understanding of the function of MALT1 and enable us to better assess the potential impact of a pharmacological effect on this promising drug candidate," said Krappmann. In previous studies he and his team already identified first pharmacological substances with which the function of MALT1 can be specifically altered. In future studies, the researchers want to confirm in a preclinical model the effects of MALT1 splicing on the immune system and the development of diseases.

*Alternative splicing refers to a process in which a copy of a gene, the pre-mRNA, is spliced differently. Thus, several alternative RNA sequences can be generated that as a consequence lead to different proteins. In the case of MALT1 the variants A and B differ only through the presence of a short sequence that encodes eleven amino acids. If this region is missing, as in the case of MALT1B, this leads to an impaired ability to stimulate T cells.

**More information:** Isabel Meininger et al. Alternative splicing of

MALT1 controls signalling and activation of CD4+ T cells, *Nature Communications* (2016). DOI: 10.1038/NCOMMS11292