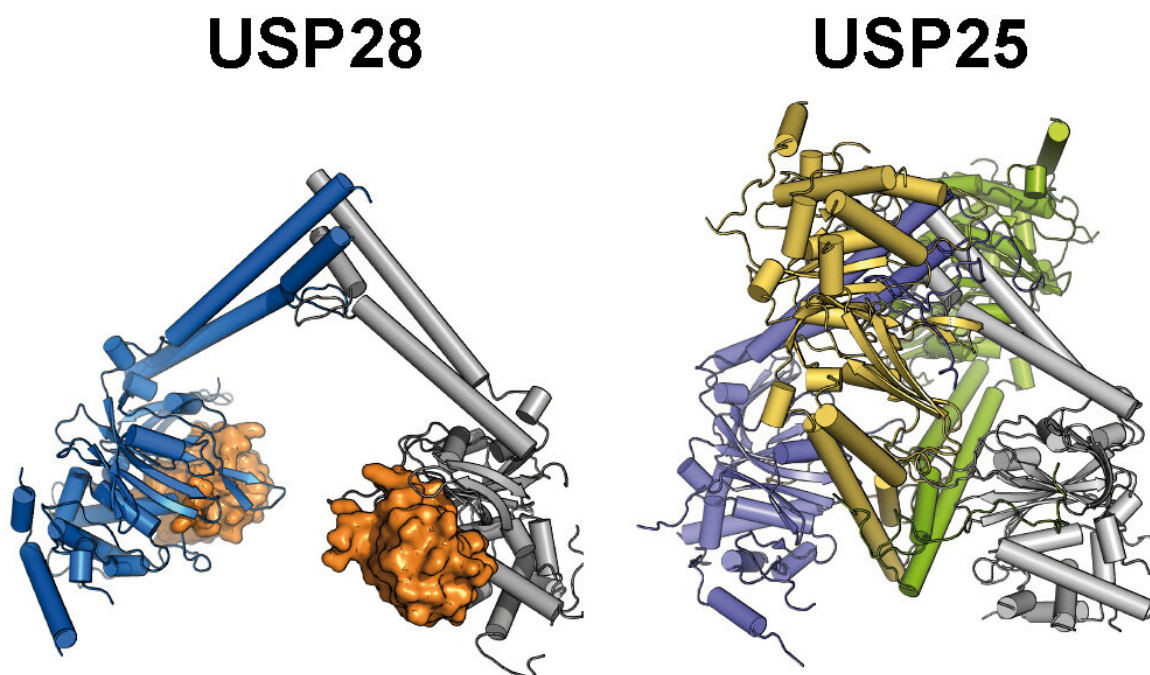


# Tumor-promoting enzymes USP25 and USP28: Substantial differences identified

March 28 2019



Structures of the catalytic domains of USP28 and USP25: USP28 is a constitutively active dimer and can bind and process ubiquitin (orange) at any time. In contrast, USP25 is a tetramer composed of two inter-linked USP28-like dimers (blue / gray and yellow / green) and this arrangement prevents binding of the substrate rendering the enzyme inactive. Credit: Rudolf Virchow Center of experimental biomedicine / University of Wuerzburg

Researchers from the Rudolf Virchow Center of the University of

Würzburg (JMU) have solved the structures of the cancer-promoting enzymes USP25 and USP28, and identified significant differences in their activities. Both enzymes promote the growth of tumors. The results were published in the journal *Molecular Cell* and could benefit towards the development of new, low-side-effects anticancer drugs.

The permanent interplay of protein production and degradation is a major driver of cellular metabolism. A key mechanism of this regulation is the labeling of a proteins with ubiquitin, a small polypeptide that plays important roles in many pathways, but also acts as a signal for protein degradation.

Ubiquitination can be reversed by a group of enzymes, the so-called deubiquitinases, which are able to rescue the proteins. In cancer cells these opposing processes are assumed to be out of balance.

Deubiquitinases have therefore emerged in recent years as promising [drug](#) targets for cancer therapy.

## **Structures of the catalytic domains**

The study focused specifically on the deubiquitinases USP25 and USP28. Both enzymes are important for the progression of various types of tumors. The research of the two structural biologists Dr. Florian Sauer and Theresa Klemm from Prof. Caroline Kisker's group at the Rudolf Virchow Center provides important insights into the structure and function of the two deubiquitinases. Using X-ray crystallography, the group was able to solve the three-dimensional structure of the central catalytic domains of both evolutionarily closely related enzymes and they uncovered similarities as well as crucial differences.

"It was surprising to discover that USP25, despite its structural similarity to USP28, is inactive in the isolated form (in vitro) as well as in cells (in vivo), and that there is a correlation between the oligomeric state and its

activity," says Sauer. The researchers' analysis showed that the inactive USP25 forms a tetramer, a molecular complex of four-subunits. In contrast, USP28 exists as a constitutively active dimer, a molecular complex of two identical subunits. "By inserting alterations, found in [cancer cells](#), we were able to show that the USP25 tetramer dissociates into two USP28-like dimers, thereby abolishing the auto-inhibition of the [enzyme](#)," reports Klemm.

## A new guide for cancer drugs

This knowledge provides the molecular basis for the development of new and highly specific anti-cancer drugs, with a low risk of side-effects. "On the one hand, new approaches have been identified that could, for example, be used to develop tailor-made drugs targeting specifically USP28, thereby preventing inhibition of USP25, which is important for the immune response," says Sauer. "On the other hand, specific targeting of the already per se inhibited USP25 seems feasible by preventing its activation," adds Klemm.

**More information:** Florian Sauer et al, Differential Oligomerization of the Deubiquitinases USP25 and USP28 Regulates Their Activities, *Molecular Cell* (2019). [DOI: 10.1016/j.molcel.2019.02.029](https://doi.org/10.1016/j.molcel.2019.02.029)

Provided by University of Würzburg

Citation: Tumor-promoting enzymes USP25 and USP28: Substantial differences identified (2019, March 28) retrieved 24 April 2024 from <https://phys.org/news/2019-03-tumor-promoting-enzymes-usp25-usp28-substantial.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is

provided for information purposes only.