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‘Go back to start’ in the field of meiosis

Researchers have long thought they knew exactly how meiosis, meiosis regulators and the complex that forms between homologous chromosomes during meiosis work. The research group headed by Dr. Andrea Pichler from the Max Planck Institute of Immunobiology and Epigenetics in Freiburg has now discovered a new mechanism that plays an important role in meiosis. The study carried out by Pichler and her colleague Dr. Helene Klug has shown why it is important to look closely at the biochemical mechanisms of meiosis as well as revealing that meiosis regulation in yeast cells differs from that of mammalian cells.

The sumoylated enzyme E2 (red) stimulates the formation of meiotic SUMO chains (yellow).

Yeast and mammalian cells both have to permanently control a number of biological processes. They selectively alter properties of their proteins, such as the activity level or localisation. While transcription factors, to name but one example, can be methylated or phosphorylated by enzymes that attach methyl and phosphate groups to a protein in a single step, the processes of ubiquitination and sumoylation are far more complex. Here not only specific chemical groups, but entire proteins like ubiquitin and SUMO (small ubiquitin-related modifier) are firmly attached to the substrate in a sequential enzyme-dependent reaction. While the addition of ubiquitin to a protein can signal its degradation via the proteasome, the addition of SUMO to a specific protein can have an effect on the regulation of chromatin structure, amongst other things.

Different types of substrate ubiquitination – i.e. the addition of either one or several ubiquitin molecules – affect cellular protein localisation, whether a protein is active or inactive and other processes. The effect the attachment of a SUMO molecule has on the target protein is difficult to predict because it is relatively heterogeneous and many aspects are still poorly understood. What is certain is that sumoylation is mediated by at least two, but in the majority of cases three, enzymes: the first enzyme (E1) activates SUMO and passes it on to a conjugating enzyme (E2). In the final and mostly E3-dependent step, SUMO is attached to the target protein.

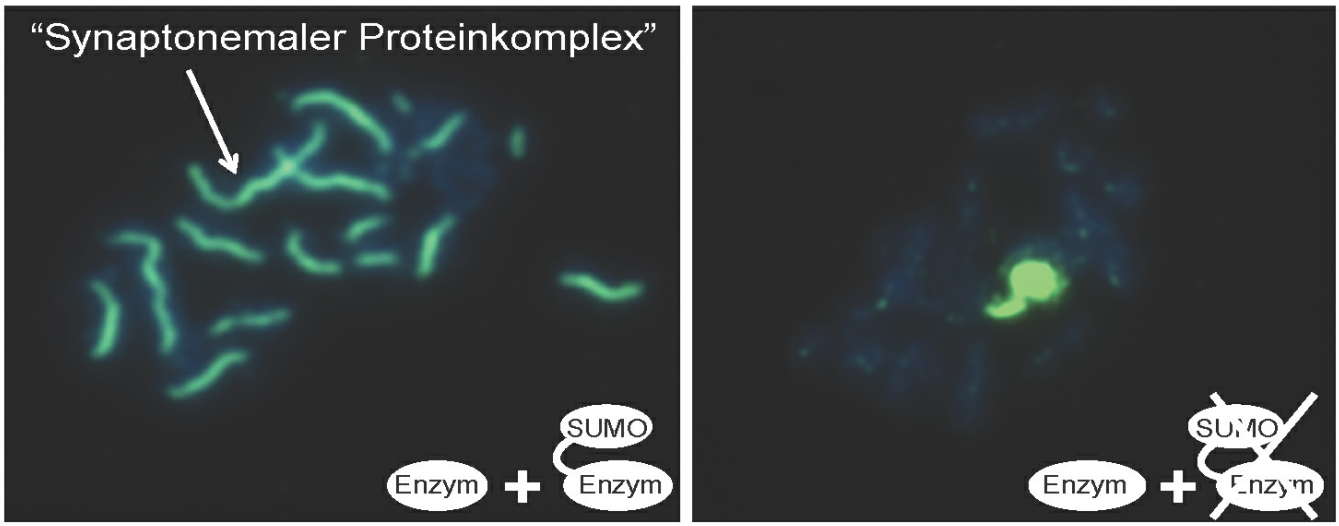
Synaptonemal complex is similar to a zipper

Pichler and her team have discovered that sumoylation plays an important role in meiosis, a key process in sexual reproduction. During meiosis, a protein structure that has been known for 50 years but whose function is not yet fully understood forms between the homologous chromosomes. This protein structure, which is called synaptonemal complex, only exists for a few hours during meiosis and researchers have long speculated about its function.

“Every biology text book says that the formation of the synaptonemal complex is a crucial event during meiosis,” said Dr. Andrea Pichler from the Max Planck Institute of Immunobiology and Epigenetics in Freiburg. “But we do still not know for sure what its function is.” The complex, which has a ladder-shaped structure where the central element connects the two lateral elements to each other like the rungs of a ladder, is the place where maternal and paternal genetic material is exchanged, thus guaranteeing genetic variation. “The synaptonemal complex looks like a zipper and this is why researchers initially thought it kept the homologous chromosomes together,” explains Dr. Helene Klug from Pichler’s team. “It is also why some of the proteins involved are called zipper proteins.”

Some researchers may not exactly like what Pichler, Klug and her team have recently discovered. The team is specifically focussed on the regulation of the second enzyme (E2) involved in the sumoylation of various metabolic pathways. They have discovered that the E2 enzyme is itself modified by the SUMO protein, stimulates the formation of SUMO chains and plays an important role in the formation of the synaptonemal complex. They were surprised to find that the complex was not as crucial during meiosis as previously thought. They were able to show experimentally that cells in which E2 was not sumoylated were unable to assemble a synaptonemal complex. However, the chromosomes could still pair and exchange genetic information. “This shows that the complex does not play a crucial role during meiosis, at least not to the degree we thought it did,” Pichler says. “As far as the structure of the synaptonemal complex during meiosis is concerned, our

insights are leading to a change of direction in meiosis research."



The synaptonemal complex forms between the homologous chromosomes in the presence of the sumoylated step-2 (E2) enzyme. If E2 cannot be modified with SUMO, the complex is completely absent.
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Uncovering biochemical secrets

The synaptonemal complex has a function, that much is certain. But the question is what is this function. Pichler assumes that a defective synaptonemal complex will eventually give subsequent generations a disadvantage. But quite why is not known. She assumes that the complex restricts the occurrence of crossing-over events, preventing too large a number of parental chromosome fragments from breaking and recombining, something that is always associated with the risk of DNA damage.

It was pure chance that Pichler and Klug made this discovery. However, they find it far more interesting to find out how sumoylation of E2 is regulated. "Some people might think that trying to find answers to such questions is a very dull, biochemical business. But it is only findings like this that help us shed light on what remains secret and start following new paths of enquiry," Pichler says.

Pichler's research is particularly focussed on finding out how SUMO and ubiquitin molecules are attached to target proteins and exploring the consequences of E2 deregulation. As E2 is itself modified by the SUMO protein and thereby alters how it functions and as sumoylation plays a key role in DNA repair, one can safely assume that suboptimal quantities of E2 can lead to DNA mutations, potentially resulting in diseases such as cancer. A correlation between E2 overexpression and certain types of cancer has already been found. Too little E2 potentially has widespread consequences on many downstream processes, many cellular processes can no longer take place; this is because proteins can no longer be sumoylated, a post-translational modification that is required for controlling biological processes.

Of yeasts and mammals

Saccharomyces cerevisiae is a eukaryotic organism and as such is a popular research object. It is far more similar to humans than prokaryotic bacteria. Researchers therefore hope that they will be

able to transfer results gained with yeast to mammals and also draw important conclusions for medical treatment. However, Pichler found that E2 sumoylation differs between yeasts and mammals. In mammals, they found that a single E2 enzyme can also fulfil the function of an E3 ligase. In yeast, the E2 enzyme is inactivated in a complicated mechanism; the inactive E2 enzyme then works with an active E2 enzyme to complete the process of sumoylation. "We were quite surprised that mammalian and yeast sumoylation differed that much, at least as far as E2-SUMO modification is concerned," said Pichler also highlighting that on the other hand she found it quite comforting to see that yeasts and humans are not so similar after all. For Pichler this finding is one more piece of evidence that shows that researchers need to explore the smallest details in their research. "If the molecular mechanisms are not known in detail, researchers tend to draw the wrong conclusions and initially think that such processes are identical in yeasts and mammals. But the enzymes of mammals and yeasts cannot be mixed together, they are not compatible and one cannot simply make what applies to one apply to the other," Pichler says.

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