Slow down to get ahead

To ensure that protein production in our cells runs smoothly, the protein complex NAC slows down the rate of protein synthesis right at the start. An international research team with significant involvement of Konstanz biologists has now discovered what underlies this previously unknown function of NAC.

Proteins are among the most important molecular building blocks of life. They are chains of amino acids assembled in our cells by ribosomes, the molecular "protein factories" of our bodies. The genetic code of our genome serves as a blueprint, guiding the step-by-step translation into a specific sequence of amino acids that defines each protein. But that's not all: To perform their vital functions in the cell, proteins must be modified – in some cases already during their synthesis – then fold into their functional, three-dimensional structure and finally reach their designated location in the cell. Just like a real factory, protein production requires specific adjustments and complex logistics in addition to the basic assembly.

The protein complex NAC (nascent polypeptide-associated complex) plays a key role in controlling and regulating processes within our cells. In previous work, Konstanz researchers around Elke Deuerling and Martin Gamerdinger, together with international colleagues, were able to reveal some of the molecular mechanisms underlying the functional complexity of NAC. In their current study, which has just been published in the scientific journal Nature, they delve deeper into the secrets of the versatile molecular player NAC, uncovering a previously unknown interaction mode of the protein complex. They show that NAC slows down the very early stages of protein formation to ensure a smooth and orderly production process.

Early interaction

To get a better understanding of the study findings, it is worth taking a closer look at the molecular details. "We already knew where NAC binds to the 'protein factories' – namely near the ribosomal tunnel. This is the point where the newly synthesized proteins emerge from the ribosome", explains Deuerling. "There, NAC brings the growing amino acid chains into contact, as needed, with various components of the cell's biochemical toolbox, which then carry out, for example, specific modifications of the proteins or direct their transport to particular destinations."

In their latest study, the researchers wanted to obtain as complete a picture as possible of the functions of the NAC protein complex. First, they investigated which proteins the complex interacts with during its formation and at what point in time. They found that NAC interacts with a very broad spectrum of proteins – thousands in fact – each destined for diverse cellular locations and performing a wide array of functions. In addition, they identified three different phases of interaction: a very early phase, in which the nascent protein is less than 30 amino acids long, a middle phase with a chain length of around 50-60 amino acids, and a comparatively late phase, in which the growing amino acid chain has already more than 80 amino acids.

"The early interaction between NAC and the nascent protein was a particular surprise for us. Once the chain reaches 50 amino acids and more, the growing protein begins to extend beyond the tunnel, allowing NAC to interact from the outside. To do so with significantly shorter amino acid chains, however, NAC has to reach into the ribosomal tunnel with one of its "arms". We did not really know that this interaction option exists", says Deuerling.

"Where" determines "when"

The researchers also found that there is a correlation between the destination of the emerging proteins and the time of interaction with NAC. For example, proteins destined for the cell's membrane network – the endoplasmic reticulum – interact with NAC especially in the early and middle phases. In the middle phase, the protein complex promotes the targeted transport of proteins carrying the corresponding signal sequence to the endoplasmic reticulum.

But what happens during the previously unknown early interaction? The study results show that the interaction with NAC inside the ribosomal tunnel leads to a slowdown in the growth of the nascent proteins. "By regulating the growth rate, NAC ensures that protein synthesis runs smoothly. It optimizes the movement of ribosomes along the genetic blueprints, reduces the risk of collision and coordinates subsequent folding and logistics processes", summarizes Gamerdinger.

With the discovery of this additional function of NAC, the picture of the protein complex as a multifunctional control and regulatory hub during protein synthesis becomes even clearer, reaffirming its fundamental role in maintaining the proper functioning of our cells.

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Further information

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