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PRESS RELEASE

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Gene expression depends on a constant dialogue between the nucleus and the cytoplasm

Swiss and German scientists discover the unexpected role of a protein complex that is the key to regulate gene expression

Gene expression is the process by which genetic information is used to produce proteins, which are essential for cells to function properly and fulfil their many purposes. It takes place in two distinctive steps: first the transcription, which takes place in the nucleus, then the translation, in the cytoplasm. Control of gene expression is vital for cells to produce the exact proteins that are needed at the right moment. Until now, gene transcription and translation into proteins were thought to be two independent processes. Today, microbiologists at the University of Geneva (UNIGE), Switzerland, and at the European Molecular Biology Laboratory in Heidelberg (Germany) provide additional evidence that these two processes are intrinsically related and show that a protein complex called Ccr4-Not plays a key role in gene expression by acting as a messenger between the nucleus and the cytoplasm. Published in *Cell Reports*, these results shed light on the very mechanisms governing gene expression, a process that controls the life and death of our cells.

Gene expression refers to the biochemical processes through which the information that is stored in our genes is read like an instruction book to produce proteins that will make our cells function properly. Until now, gene expression was thought to take place in two distinctive steps: first transcription, which takes place in the nucleus, then translation, in the cytoplasm. Today, research led by UNIGE and the European Molecular Biology Laboratory shows that transcription and translation are intrinsically related and continuously influence one another. To do so, a very efficient communication within the cell, between the nucleus and the cytoplasm, is essential. This dialogue is made possible by a protein complex called Ccr4-Not, which globally determines the cell translational capacity.

Gene expression: a two-way street

Martine Collart and her team from the UNIGE Faculty of Medicine discovered in 2014 that the Ccr4-Not complex enables the cytoplasm to provide information to the nucleus during translation. Today, they prove that it is a two way-street communication as the nucleus also communicates information to the cytoplasm at all stages of gene expression, thanks to Ccr4-Not. This complex acts as a messenger between the nucleus and the cytoplasm to ensure that both transcription and translation levels are well adapted. It is also able to enhance translation to compensate for transcriptional stress, thus ensuring that gene expression remains well-balanced.

Indeed, there is growing evidence that different levels of gene expression are interconnected to form a network. Constant feedback is the-

refore given by the components of various cellular machineries that act to produce functional proteins. This serves to ensure that gene expression remain stable. Prof. Collart explains the process in details: "During transcription in the nucleus, this complex controls the production of the machinery which produces the proteins in the cytoplasm. Basically, it controls in the nucleus how much proteins can be made as a whole. We were able to show that the Ccr4-Not complex, by connecting the cytoplasm to the nucleus, is a global regulator of gene expression that acts at all steps from gene to protein production." This complex therefore constitutes a major element which allows the cell to react to external events and keep control of its protein production.

"Previously, the nucleus was thought to act as a commanding post, controlling everything that happens within the cell. In 2014, however, we showed that the nucleus is actually influenced by the cytoplasm, where the environmental signals first appear. Our recent research now highlights that Ccr4-Not also regulates the translational capacity of the cells by associating in the nucleus with messenger RNAs, the molecules that convey genetic information from DNA to the ribosome, which then produce proteins. The picture is now complete: gene expression actually depends on a constant dialogue between the nucleus and the cytoplasm and the Ccr4-Not complex is a key player in orchestrating regulatory processes within and in between these different compartments", indicates Zoltan Villanyi, first author of this study.

The Ccr4-Not complex regulator is essential for the development of all animal embryos and is involved in many physiological mechanisms necessary for life, such as heart function, spermatogenesis or lipid metabolism. As this regulator directly controls gene expression, any mutation can have dramatic consequences, from embryonic death to cancer development later in life, as well as various metabolic failures. "Now that we have precisely identified the diversity of steps at which this regulator impacts mRNAs, we can start to study specific targets linked to diseases", stresses Prof. Collart. "It will open new doors to the understanding of the most fundamental cellular mechanisms governing how our genes are expressed, or not."

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