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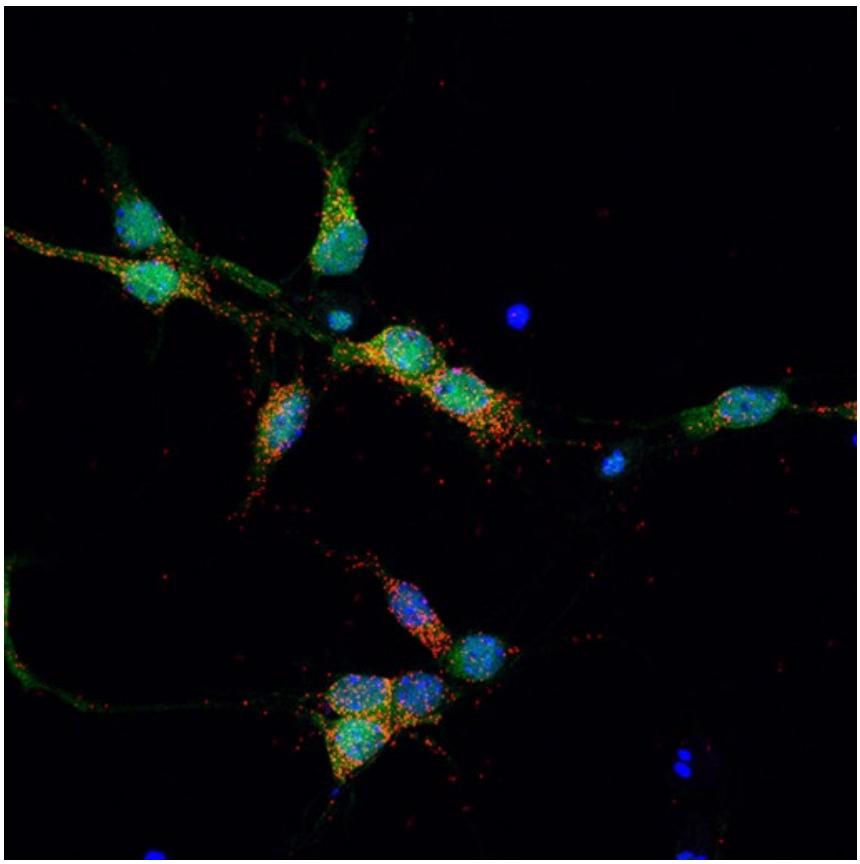
PRESS RELEASE

FOXG1: a SISSA study reveals the dual role of key neurodevelopmental gene

The gene has been found to have a dual function in regulating RNA transcription and translation



Trieste, 17 October 2024

A new study conducted by SISSA's Laboratory of Cerebral Cortex Development and recently published in *BMC Biology* has led to a surprising revelation about the role of the FOXG1 gene: not only does it orchestrate development of the anterior brain by regulating RNA transcription, but its role includes direct regulation of RNA translation, i.e. protein production. This dual function raises interesting questions as to how this mechanism evolved, suggesting that a fine-tuning of FOXG1 gene dosage may have been selected to ensure proper development of the nervous system.

The FOXG1 gene is especially important for generating and patterning the cerebral cortex, the part of the brain that is necessary for such functions as sensory perception and conscious thought. Mutations in this gene can cause FOXG1 syndrome, a rare genetic disorder characterized by structural and functional brain anomalies leading to highly severe behavioural and cognitive symptoms. In this framework, the FOXG1 protein works as a transcriptional regulator, coordinating, activating, and deactivating hundreds of other genes that are necessary for proper brain development.

«The surprise was finding out that FOXG1 is also responsible for the direct regulation of protein synthesis, » says Antonello Mallamaci, director of SISSA's Laboratory of Cerebral Cortex Development. «This is an extremely rare phenomenon, which we were able to prove by following several unrelated clues and with a rigorous analysis of the evidence. »

The discovery of the double role

The first clue was the protein's cellular localisation: not only was it possible to locate this transcription factor in the neuron's nucleus – where it interacts with DNA and 'switches on or off' the various genes – but also in the cytoplasm, including that of axons and dendrites, suggesting additional functionality. Further bioinformatic and structural analyses of FOXG1 also showed that the protein could interact directly with the cell's protein-making machinery in charge of translating mRNA.

«At first, we tried to verify this potential ability to affect not only transcription but also translation, by testing a specific gene – Grin1, which encodes the main subunit of NMDAR, a key receptor. By manipulating the amount of FOXG1 in the cell, we observed significant discrepancies between the levels of Grin1 protein and the corresponding mRNA, proving that these discrepancies originated from a different rate of synthesis (and not degradation) of the protein. We then showed that FOXG1 interacts with the mRNA of Grin1 and with two key factors involved in its translation, » explains Mallamaci.

«Encouraged by this result, and with the help of colleagues from SISSA's Laboratory of Computational Genomics, we then attempted to carry out large-scale analyses, aiming to understand how common translational regulation is. We found out that about 300 genes show a variation in their mRNA-ribosome (i.e. protein factories) recruitment in response to changes in FOXG1 expression. In about half of the cases, the recruitment was stimulated and in the other half it was inhibited. We also verified that FOXG1 interacts with the mRNA of many of these genes and affects the movement of ribosomes along mRNAs. Finally, in a number of selected

cases, we have experimentally verified that FOXG1 level variations lead to tangible changes in the translation rate of these mRNAs. »

The discovery that the FOXG1 gene plays a role in both transcriptional regulation and protein translation raises important questions about the evolution of this complex mechanism. There are currently two main hypotheses that could explain how this dual function developed.

The double role from an evolutionary point of view

In general, the most common mechanism leading to the evolution of a gene's new function is gene duplication: in this way, the original copy continues to perform its original function, while the other can mutate freely, and thus 'experiment' other functions. However, for some crucial genes such as those regulating neurodevelopment, gene duplication may not be a viable option due to the need to calibrate precisely the amount of RNA and protein produced by the gene. This gene dosage-related limitation could be one of the reasons why, in special cases, evolution has 'chosen' a single gene capable of performing a combined function, rather than duplicating and separating roles.

Another possibility is that, by directly affecting both the transcription and translation of certain genes, FOXG1 may facilitate the hereditary transmission of the complex expression profiles that are peculiar to those genes. «This ability to enable a highly-efficient transmission of structured – not necessarily monotonic – spatio-temporal regulation patterns, » says Mallamaci, «could have significant emergent effects, especially in the evolution of neuroplasticity mechanisms underlying cognitive processes. »

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Full paper:
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