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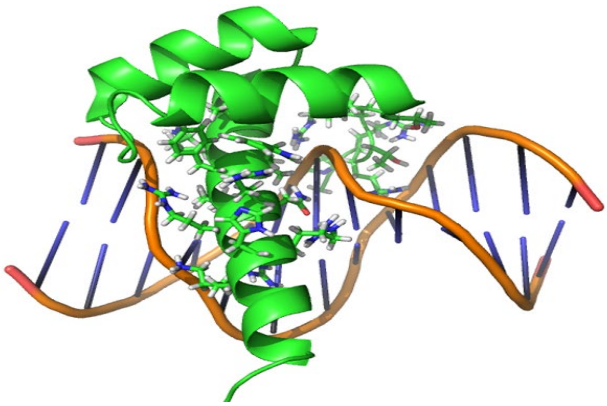
PRESS RELEASE

Not only Transcription Factors

A new study by SISSA suggests that many transcription factors may be involved in more than just turning genes on and off, playing a broader role that extends into the later stages of gene expression, including post-transcriptional regulation.



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Gene regulation has usually been described as a stepwise process. Transcription factors initiate gene expression by switching genes on or off, then other molecules step in to process the RNA and control protein production. But a growing body of evidence suggests that this division of labour may not be as clean as once thought: a new study led by Antonello Mallamaci from SISSA and published in *Neural Regeneration Research* reveals that a substantial share of mammalian transcription factors may physically interact with proteins that govern what happens *after* a gene is transcribed.

This dual activity, observed through systematic data analysis and supported by decades of scattered experimental findings, suggests that gene expression may be governed by more integrated molecular devices and help explain specific patterns observed in developmental and neuronal systems.

Transcription Factors caught in Post-Transcriptional interactions

By mining protein–protein interaction data from a comprehensive public database and applying multiple filtering levels, the authors identified that about 20% of

approximately 1,600 known mammalian transcription factors specifically interact with proteins involved in downstream steps of gene expression. These include regulators of splicing, polyadenylation and the initiation of translation.

“These interactions are not distributed at random,” says Antonello Mallamaci, senior author of the study. “They are statistically enriched for interaction types which involve transcription factors belonging to specific taxa and proteins with well-defined roles in post-transcriptional regulation.”

The authors also revisited over twenty studies published over the last three decades, which independently reported post-transcriptional functions for transcription factors. The first case involved the early developmental regulator Bicoid, localized at the anterior pole of the fruitfly embryo, which binds both *otd*-DNA and *cad*-mRNA and thus controls axis formation. Later examples from vertebrates, such as En1/2, Emx1/2 and Foxg1 (involved in neurogenesis), Zic3, and Esr1 (the estrogen receptor), further confirm that there are experimentally verified examples of proteins having similar dual roles. Moreover, they suggest that these phenomena might be much more widespread than what careful statistical filtering of protein-protein interaction data would indicate.

An evolutionary puzzle: one molecule, two jobs

These results raise questions about how multifunctionality in such proteins could have evolved. They go against the usual model of how new protein functions evolve, where a gene is first duplicated, and then one of the copies gradually takes on a new role while the other keeps doing its original task. In this case, it seems that many transcription factors have taken on extra responsibilities without going through that duplication step.

One possible explanation is that certain genes are especially sensitive to changes in dosage. In case of “triplo-sensitive” genes, producing too much protein, even from a duplicated gene, can be very harmful. As a result, evolution may have favoured the development of multifunctional proteins rather than allowing duplication. This would explain why some transcription factors seem to accumulate additional roles over time: it’s the only way for such a system to gradually evolve without drastically reducing the fitness of the organism.

Another possibility relates to the dynamics of gene expression. In systems like the nervous and immune systems, cells often rely on precise pulses of gene activity rather than steady signals. A protein that influences both transcription and translation might help generate and preserve these more complex patterns — such short bursts of expression followed by sudden shutdown — in a way that’s

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more easily passed down through cell divisions and generations. In fact, a single protein doing multiple jobs might ease the faithful transmission of a non-monotonic pattern, compared to multiple regulators needed to achieve such a pattern.

A third, more speculative idea involves evolutionary reuse. Many transcription factors contain short amino acid sequences rich in arginine and lysine, different from classical RNA-binding domains, however able to bind RNA weakly. Although unable to distinguish mRNAs with diverse sequences, these sequences can allow a protein originally evolved to bind DNA to also interact with RNA. As such, they could ease co-transcriptional transfer of transcription factors bound to a gene to RNA molecules being transcribed from this gene, as experimentally documented for some yeast factors. Over time, this accidental contact between transcription factors and RNA could have been shaped by natural selection into a novel functional regulatory role, effectively recycling the protein's DNA-recognition logic for RNA control.

All three hypotheses will require future specific experimental validation, which the authors plan to carry out in the coming years, but are already supported by statistical patterns and experimental findings in the existing literature.

"We will need further experiments to determine how widespread this phenomenon is and to test whether these interactions have functional consequences in different tissues and contexts" Mallamaci notes "but the fact that the same molecule can end up doing two very different and complex jobs suggests a significant departure from the textbook model of the evolution of transcription factors" Mallamaci notes.

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IMAGE:
Pymol render of Bicoid binding to his consensus site, via Wikimedia Commons

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