'Tom Sawyer' regulatory protein initiates gene transcription in a hit-and-run mechanism

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A team of genome scientists has identified a "hit-and-run" mechanism that allows regulatory proteins in the nucleus to adopt a "Tom Sawyer" behavior when it comes to the work of initiating gene activation.

Their research, which appears in the *Proceedings of the National Academy of Sciences*, focuses on transcription factors—proteins that orchestrate the flow of genetic information from DNA to messenger RNA (mRNA). Their results show how transcription factors (TFs) activate mRNA synthesis of a gene, and leave the scene – in a model termed "hit-and-run" transcription.

"Much like Mark Twain's Tom Sawyer who begins to paint Aunt Polly's fence, and then convinces others that they are privileged join in, before leaving to relax, this pioneer transcription factor binds to a gene promoter to initiate transcription and then leaves, recruiting its friends to continue work it started," explains New York University Biology Professor Coruzzi, the study's senior author.

The transcription factor under study is crucial to activating genes needed to respond to nitrogen, a nutrient signal that is the rate-limiting element in plant growth.

Thus, in addition to uncovering a new mechanism of "hit-and-run" transcription, the discovery has potential practical applications to

improving nitrogen responses in crop plants.

The discovery points to the possibility of re-engineering plants in ways that increase their efficiency in acquiring and assimilating nitrate, a primary source of energy that is contained in fertilizer. By reducing the amount of nitrate-based fertilizers, growers can lower the health risks associated with fertilizer runoff into ground waters.

The study, funded by the National Institutes of Health, also included researchers from Cold Spring Harbor Laboratories and France's National Center for Scientific Research (CNRS), focuses on specific changes to Gene Regulatory Networks (GRNs).

GRNs—the "circuit boards" that dictate how the genes in living organisms interact to propagate responses to signals in their environment—are of particular interest to genomics researchers in the new field of Systems Biology, which aims to understand of how genes work together as a system. In this example, understanding how nitrogen signals are conducted through the genetic circuit board could point to ways to create more environmentally sustainable plants and crops.

Coruzzi's laboratory has focused on how to change this genetic circuit board so that plants can more efficiently take in nitrate fertilizer, thus reducing the amount necessary for crop yield.

Specifically, they have examined how transcription factors (TFs) function in a dynamic way inside nuclei of cells to bind to DNA and regulate gene expression.

TFs are of prime interest to biologists because they help dictate which genes are expressed in each cell of an organism. However, gauging their role has often stymied scientists. TFs' interactions with DNA are transient, often lasting only a few minutes, and are typically missed as

current techniques to measure them take up to 30 minutes to execute, making it difficult to fully capture and measure highly transient associations of a TF and its gene target.

In the *PNAS* study, the researchers devised a new method that took only one minute to complete, allowing them to accurately capture early events and previously elusive TF activity. They also devised a way to identify direct targets of a TF based solely on a functional read-out of TF-induced changes in gene expression, even in the absence of detectable TF binding. This enabled them to spot direct gene targets of a TF even in cases where TF binding lasts for only nanoseconds.

This method allowed the researchers to uncover new dynamic and transient interactions between TFs and targets that have previously eluded detection across yeast, plants, and animals.

Using their newly developed method, the researchers uncovered genome-wide evidence for a hit-and run transcription model – first proposed in the 1980's. This model proposes that a TF first initiates transcription of a target gene by binding to the DNA (the Hit), then detaches from DNA (the Run), while transcription occurs without its assistance—thereby revealing its "Tom Sawyer" nature.

Once this process begins, the pioneer TF then moves on to another gene target, enabling it to rapidly and catalytically activate a large set of genes in response to a signal.

More information: Hit-and-run transcriptional control by bZIP1 mediates rapid nutrient signaling in Arabidopsis , *PNAS*: www.pnas.org/cgi/doi/10.1073/pnas.1404657111