General Regulatory Factors: guardians of transcription fidelity

As in a literary text, a string of characters do not make a story if punctuation marks and conventions do not tell where to start reading and in which direction. In a recent study published in Molecular Cell, the authors show that Rap1 and other transcription factors called General Regulatory Factors prevent transcription to initiate from inappropriate sites. They function as “guardians” of gene expression fidelity by telling the RNA polymerase where to start transcribing and in which direction.

Transcription originates in regions of the genome that are generally depleted in nucleosomes and are therefore called Nucleosome Depleted Regions (NDRs). NDRs harbor promoters and contain binding sites for transcriptional activators. In many instances transcription is generated in both directions from NDRs even when only one of the transcription events produces a functional RNA. Bi-directional initiation by many promoters generates transcription events producing non-coding RNAs that have no apparent function but that can interfere with the expression of canonical genes and with other DNA-associated processes (e.g. replication). Cells have adopted strategies for limiting non-functional transcription initiation from bi-directional promoters. However, the underlying mechanisms for this control on initiation are only partially understood.

General Regulatory Factors are a class of transcription factors that are responsible for the robust transcription of many highly expressed genes, such as those encoding ribosomal protein, factors involved in glycolysis and snoRNAs (Small nucleolar RNAs). They bind NDRs and have important roles in preventing nucleosomes from invading the NDR, which is hought to negatively affect transcription. However, the mechanisms of transcription activation by these essential proteins remains poorly understood, in spite of many studies in the last thirty years.

In this study the researchers describe a novel mechanism by which a class of transcription factor inhibit non-functional transcription initiation, thus providing a new paradigm for the control of transcription fidelity. The authors depleted these factors and generated high resolution transcription maps to study transcription termination. Surprisingly, they found that depletion of these transcription factors, instead of simply preventing the expression of target genes, as would have been expected, led to massive changes in the position where transcription starts, often leading to the production of
non-coding RNAs. This alters dramatically the *quality* of the genetic message: pretty much as reading a text with capital letters in the middle of sentences (instead of their beginning) and altered spacing between the characters to generate meaningless words. When these proteins are present, they “sit” in the NDR and, together with additional factors, sterically prevent transcriptional initiation from occurring at inappropriate positions or in the wrong direction. In so doing they ensure the fidelity of initiation and gene expression and also suppress a large share of non-coding transcription. In their absence, spurious initiation occurs frequently generating RNAs that have a different coding potential and that are often degraded by post-transcriptional quality control pathways. Thus these factors promote faithful and robust gene expression not only by regulating the usage of a defined transcription initiation site, but by preventing dispersed initiation at many inappropriate sites.

These findings challenge some of the traditional perspectives on gene expression. For instance, they tell us that the mere fact that a gene is transcribed does not necessarily imply that it is expressed: it depends on the *quality* of the RNA produced, in this case where it starts from. And perhaps that transcription can start much more frequently than we used to think: as for hyperactive kids, canalizing RNA polymerases activity to the right targets is a major challenge for achieving the best (gene expression) behavior.

**Legend.** In wild type cells (+GRF) General Regulatory Factors prevent inappropriate transcription initiation and limit non-coding transcription by sterically occluding transcription initiation sites. In their absence (-GRF) transcription initiation of many genes occurs at non
canonical position and generates RNAs that are non-functional or code for truncated proteins. Many non-coding RNAs are also produced in these conditions.

To know more:
General Regulatory Factors Control the Fidelity of Transcription by Restricting Non-coding and Ectopic Initiation.
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