Cell Reports

CellPress
OPEN ACCESS

Preview

Louder for longer: Myc amplifies gene expression by extended transcriptional bursting

Dan Lu,[1] Ashwini Jambhekar,[1] and Galit Lahav[1,*]
[1]Department of Systems Biology, Blavatnik Institute at Harvard Medical School, Boston, MA 02115, USA
*Correspondence: galit@hms.harvard.edu
https://doi.org/10.1016/j.celrep.2022.110470

Transcription is a complex, dynamic process. Using live single-cell measurements, Patange et al. show, in a recent issue of *Cell Reports*, that elevated levels of the transcription factor MYC enhance target gene RNA production by increasing the duration but not frequency of transcriptional bursts.

Transcription factors regulate the timing and magnitude of gene expression. Recent advancements in live single-cell imaging have questioned the conventional static view of transcription-factor quantity as a measure of activity, a view that was mainly derived from large-scale sequencing studies. Instead, they have brought to light a dynamic process regulated by interactions with co-factors and leading to episodic RNA transcription. This phenomenon, known as transcriptional bursting, can be regulated by altering the duration of bursts (ON time) or their frequency (the interval between bursts; OFF time).

Patange and colleagues study the transcriptional kinetics and mechanisms by which Myc, an oncogenic transcription factor, activates its target genes (Patange et al., 2022). The authors constructed an optogenetic MYC protein whose nuclear localization, and thus activity, is photoinducible in human cells. The acute effects of MYC on transcription bursting were measured by smFISH in fixed cells and by MS2-tagging of RNA in live cells. Their results reveal that elevated levels of MYC ubiquitously increase the duration of transcriptional bursts without affecting their frequency. Furthermore, the authors find that MYC modulates the residence time of other HALO-tagged core transcriptional factors at promoters. The authors suggest that the changes in burst duration probably result from changes in the residence time of transcriptional machinery, and they show that the increased bursting durations are more pronounced for target genes with basally lower expression.

Transcription bursting kinetics have been studied across different systems and organisms. For example, steroid receptors were shown to exclusively modulate burst frequency in response to changes in hormonal ligand dose (Larson et al., 2013). The tumor suppressor p53 does not affect the frequency or the duration of transcriptional bursts, but rather influences the probability of bursting (Hafner et al., 2020). Exclusive modulation of burst duration, on the other hand, has not been experimentally reported before. Myc's mechanism of function therefore adds a new, unique mode to the existing range of transcriptional-bursting regulation. However, a detailed mechanistic understanding of what regulates the burst properties of a transcription factor remains elusive. Patange et al. provide new insights into this question by suggesting that, at least for MYC, prolonged burst duration might result from changes in the binding of other core transcription machinery (Figure 1). Similar mechanisms might play a role in controlling and modulating transcriptional bursts in other systems.

What benefits are conferred by different types of burst modulation? It might seem, at first glance, that regardless of the specific type of modulation – increased duration or increased frequency – both would ultimately lead to greater ON times. However, when accounting for downstream determinants, such as RNA degradation rates or complexities in regulatory network motifs (Alon, 2007), it becomes clear that different forms of input dynamics could result in vastly distinct outputs. Controlling signal outputs through modulation of dynamics is by no means a new concept; multiple studies have shown this for the dynamics of various transcription factors (Purvis and Lahav, 2013), albeit at longer time scales compared to transcriptional bursting. Nevertheless, similar principles can be extended to transcriptional bursting and indeed, models of frequency modulation predict sensitive and rapid control of gene regulation (Li et al., 2018). What might then be gained by modulating transcription burst durations? Short burst duration is more selective, allowing only quickly transcribed RNAs to accumulate, whereas longer burst durations may increase the probability of slowly transcribed RNAs accumulating. In the case of Myc, it is not clear how essential modulating burst duration is for facilitating the growth and proliferation responses that Myc coordinates. Future work in this area would be informative for understanding how the molecular mechanisms of transcriptional regulation translate into physiological responses. Mathematical modeling might also assist in evaluating the impact of adjusting various bursting parameters (e.g., duration, frequency) on the accumulation of different genes.

Two previous, influential studies defined MYC as a global amplifier of gene expression (Lin et al., 2012; Nie et al., 2012); based on these findings, together with the new findings from Patange et al. that show that it prolongs the duration of RNA transcriptional bursting, MYC now appears to be an amplifier of gene expression that is louder for longer. However, it is not fully straightforward to reconcile some of the new findings by Patange et al. with those of the previous studies (Lin et al., 2012; Nie et al., 2012). For instance, in the global amplifier view, MYC amplification of targets is

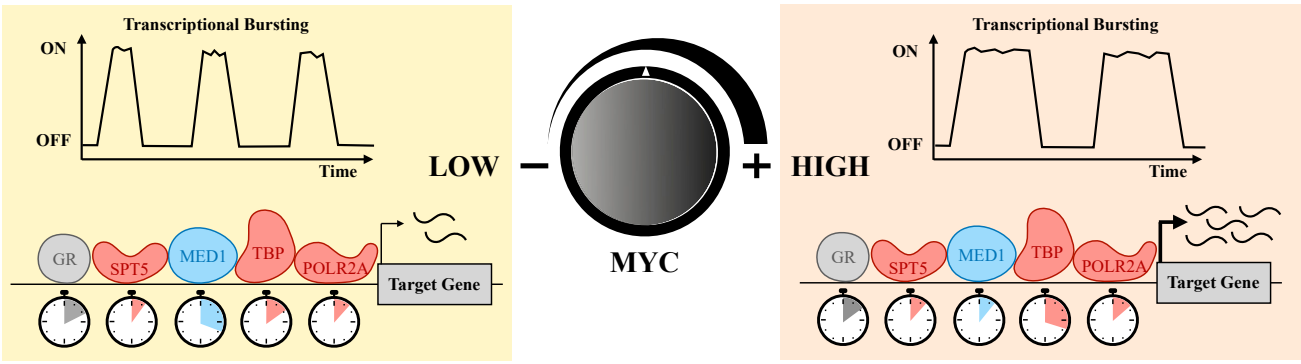

Figure 1. Elevated MYC enhances gene expression through increasing transcription burst duration and changing dwell times of transcriptional machinery components

The ON duration of transcriptional bursts is shorter under low MYC (left panel) compared to high MYC (right panel), whereas the OFF time remains similar (ON and OFF phases not drawn to scale). Changes in burst dynamics are accompanied by changes in dwell times of core transcriptional machinery. Under basal conditions, transcriptional machinery factors exhibit different dwell times, as shown by the timers (in seconds). MYC overexpression uniquely modulates the dwell time of each factor shown. The gene-specific transcription factor glucocorticoid receptor (GR) shows undetectable changes in dwell time (gray) when MYC level is elevated. Factors whose dwell times increase (red) are SPT5, a co-factor of the elongation factor subunit; TBP, a component of the pre-initiation complex TATA-binding protein; and POLR2A, the large subunit of RNA-polymerase-II. MED1, a Mediator complex subunit, shows decreased dwell time (blue) upon MYC overexpression. Taken together, elevated MYC enhances the RNA output of its target genes.

logarithmic, primarily enhancing transcription of already highly active genes. By contrast, using a select panel of genes, Patange et al. observe that bursting duration is preferentially enhanced for target genes with lower basal expression. A critical question is raised as to whether it is the initially highly or lowly expressed genes that, upon increased induction, confer the oncogenic and transformative properties of MYC. The answer to this question would profoundly influence our understanding of how the frequently deregulated and elevated MYC found in cancers promotes tumorigenesis. Finally, the authors detect MYC-mediated alterations in the dwell times of other core transcription machinery, and they suggest that elevated MYC predominantly affects pre-initiation complex assembly and polymerase pause release times during transcription. These conclusions align with some previous studies (Rahl et al., 2010), yet differ from others, suggesting prominent effects on transcription elongation (Lin et al., 2012; Nie et al., 2012). To what extent these differences are cell-context-dependent is unclear, but regardless, the results provide potential avenues to selectively target specific interaction partners of MYC for cancer therapeutic benefits.

Without doubt, this article highlights the utility of novel experimental techniques, including optogenetics and quantitative live-cell imaging, to investigate mechanistic details of gene-expression regulation, unveiling greater diversities and complexities of transcription while posing new conundrums in Myc biology. It is bewildering to think that our understanding of transcription, which was represented by a simple arrow adjoining DNA to RNA a few decades ago, is now a complex, dynamic process with many unanswered questions just beginning to be addressed.

DECLARATION OF INTERESTS

The authors declare no competing interests.

REFERENCES

Alon, U. (2007). Network motifs: theory and experimental approaches. Nat. Rev. Genet. *8*, 450–461. https://doi.org/10.1038/nrg2102.

Hafner, A., Reyes, J., Stewart-Ornstein, J., Tsabar, M., Jambhekar, A., and Lahav, G. (2020). Quantifying the Central Dogma in the p53 Pathway in Live Single Cells. Cell Syst. *10*, 495–505.e4. https://doi.org/10.1016/j.cels.2020.05.001.

Larson, D.R., Fritzsch, C., Sun, L., Meng, X., Lawrence, D.S., and Singer, R.H. (2013). Direct observation of frequency modulated transcription in single cells using light activation. eLife *2*, e00750. https://doi.org/10.7554/eLife.00750.

Li, C., Cesbron, F., Oehler, M., Brunner, M., and Höfer, T. (2018). Frequency Modulation of Transcriptional Bursting Enables Sensitive and Rapid Gene Regulation. Cell Syst. *6*, 409–423.e11. https://doi.org/10.1016/j.cels.2018.01.012.

Lin, C.Y., Lovén, J., Rahl, P.B., Paranal, R.M., Burge, C.B., Bradner, J.E., Lee, T.I., and Young, R.A. (2012). Transcriptional amplification in tumor cells with elevated c-Myc. Cell *151*, 56–67. https://doi.org/10.1016/j.cell.2012.08.026.

Nie, Z., Hu, G., Wei, G., Cui, K., Yamane, A., Resch, W., Wang, R., Green, D.R., Tessarollo, L., Casellas, R., et al. (2012). c-Myc is a universal amplifier of expressed genes in lymphocytes and embryonic stem cells. Cell *151*, 68–79. https://doi.org/10.1016/j.cell.2012.08.033.

Patange, S., Ball, D.A., Wan, Y., Karpova, T.S., Girvan, M., Levens, D., and Larson, D.R. (2022). MYC amplifies gene expression through global changes in transcription factor dynamics. Cell Rep. *38*, 110292. https://doi.org/10.1016/j.celrep.2021.110292.

Purvis, J.E., and Lahav, G. (2013). Encoding and decoding cellular information through signaling dynamics. Cell *152*, 945–956. https://doi.org/10.1016/j.cell.2013.02.005.

Rahl, P.B., Lin, C.Y., Seila, A.C., Flynn, R.A., McCuine, S., Burge, C.B., Sharp, P.A., and Young, R.A. (2010). c-Myc regulates transcriptional pause release. Cell *141*, 432–445. https://doi.org/10.1016/j.cell.2010.03.030.