CANCER BIOLOGY

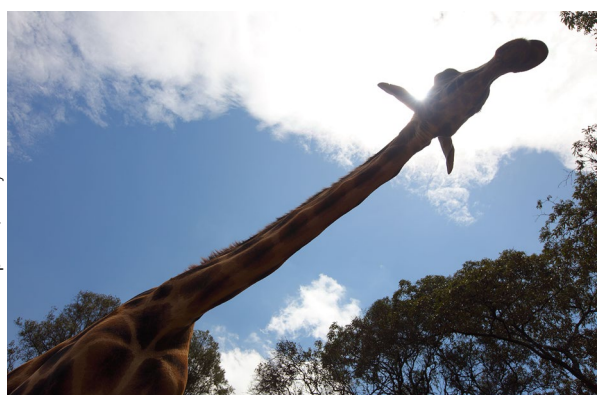
Myc in elongation and repression

> transcription elongation and histone methylation, respectively, mediate gene activation and gene repression by Myc

The oncogene Myc, which is essential in many human cancers, drives tumorigenesis by promoting transcription deregulation, but the underlying mechanisms of its function are not fully understood. Two recent studies reveal how transcription elongation and histone methylation, respectively, mediate gene activation and gene repression by Myc.

The rate of transcription elongation increases at many loci in Myc-driven cancers. The super elongation complex (SEC) phosphorylates RNA polymerase II (Pol II) and releases it from promoter-proximal pausing into productive elongation. To identify compounds that inhibit transcription elongation, Liang et al. performed an in silico screen for small molecules that might disrupt the SEC and subsequently showed that two compounds — KL-1 and KL-2 — inhibit the function of the SEC scaffold proteins AFF1 and AFF4, and thus destabilize SEC and reduce its levels.

Following KL-1 or KL-2 treatment, Pol II occupancy at promoter-proximal regions of SEC-occupied genes increased; a similar increase in Pol II pausing was seen in cells depleted of AFF1 and AFF4. Moreover, labelling of newly transcribed RNA showed a marked reduction in Pol II elongation rates in cells treated with KL-1 or KL-2.



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Myc is required in cancer cells for the overexpression of cell proliferation factors and pre-mRNA splicing factors. Genome-wide expression analyses revealed that many of the Myc target genes (including the *Myc* gene itself) were downregulated following KL-1 or KL-2 treatment, and about two-thirds of these were downregulated also by depleting SEC components.

Next, the authors investigated the effects of KL-1 and KL-2 in Myc-dependent cancer cells. Myc and SEC subunits co-localized on chromatin more in a high-Myc expression cancer cell line than in a corresponding low-Myc expression cancer cell line. Notably, Myc depletion reduced chromatin occupancy of SEC subunits and decreased Pol II elongation rates, suggesting that SEC-dependent transcription elongation is an effector of Myc.

The therapeutic potential of KL-1 and KL-2 was tested in a Myc-dependent cancer mouse model. KL-1 or KL-2 treatment inhibited colony formation in vitro and increased cell apoptosis. In vivo, SEC inhibition delayed tumour development and significantly extended mice survival.

The activity of Myc in cancer cells includes transcription repression of many genes, the mechanism of which is largely unknown. Tu et al. identified the methyltransferase G9a and associated proteins — which catalyse the gene-repressive dimethylation of histone H3 Lys9 (H3K9me2) — as Myc-interacting proteins in human cancer cell lines. The Myc–G9a interaction required the conserved Myc box II region, which is known to be essential for transcription repression and oncogenic transformation by Myc.

G9a is highly expressed in many cancers and this is associated with poor prognosis. Myc was found to induce the gene encoding G9a, and both G9a and H3K9me2 levels decreased following Myc depletion. Conversely, inducing Myc in human non-cancerous epithelial cells increased the binding of G9a to Myc-repressed genes. G9a depletion before Myc induction resulted in a decrease in H3K9me2 levels at Myc-repressed gene promoters and an increase in the levels of histone modifications associated with active transcription. Furthermore, G9a depletion decreased Myc binding and Myc-dependent gene repression, and antagonized Myc-mediated cell cycle activation. Gene derepression was recapitulated using G9a inhibitors, indicating that Myc-target-gene repression is associated with the catalytic activity of G9a.

Two Myc-dependent, basal breast cancer xenograft mouse models were used to assess the effect of G9a inhibition in vivo. Cells expressing inducible G9a-targeting short hairpin RNAs (shRNAs) were subcutaneously injected into mice and shRNA expression was induced following tumour formation. In both xenograft models, expression of Myc–G9a-repressed genes was significantly upregulated and tumour volumes were significantly decreased following G9a depletion.

In summary, the oncogenic function of Myc is mediated by gene activation through SEC and gene repression by G9a. It will be interesting to test whether dual inhibition of both pathways might have a synergistic negative effect on tumours.

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ORIGINAL ARTICLES Liang, K. et al. Targeting processive transcription elongation via SEC disruption for Myc-induced cancer therapy. *Cell* **175**, 766–779 (2018) | Tu, W. B. et al. MYC interacts with the G9a histone methyltransferase to drive transcriptional repression and tumorigenesis. *Cancer Cell* **34**, 579–595 (2018)
FURTHER READING Chen, F. X. et al. Born to run: control of transcription elongation by RNA polymerase II. *Nat. Rev. Mol. Cell Biol.* **19**, 464–478 (2018)