Ready, go!

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The Super Elongation Complex (SEC) activates stalled RNA polymerase II in response to developmental and environmental cues. Credit: Courtesy of Dr. Ali Shalitifard, Stowers Institute for Medical Research with permission of CSHL press.

Just like orchestra musicians waiting for their cue, RNA polymerase II molecules are poised at the start site of many developmentally controlled genes, waiting for the "Go!"- signal to read their part of the genomic symphony. An assembly of transcription elongation factors known as Super Elongation Complex, or SEC for short, helps paused RNA polymerases to come online and start transcribing the gene ahead, found researchers at the Stowers Institute for Medical Research.

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study not only assigns a new role to the SEC, but also emphasizes the importance of transcription elongation control for the rapid induction of genes in response to developmental and environmental cues.

"Our findings indicated that SEC facilitates the coordinated and controlled induction of genes that are active during the early developmental stages," says Ali Shilatifard, Ph.D., investigator and the study's senior author. "Having preloaded Pol II and general transcription factors reduces the number of steps required for productive transcription and allows cells to respond quickly to internal and external signals."

Transcriptional control by RNA polymerase II (Pol II) is a tightly orchestrated, multistep process that requires the concerted action of a large number of players to successfully transcribe the full length of genes. For many years, the initiation of transcription—the assembly of the basal transcription machinery at the start site—was considered the rate-limiting step. "We know now that the elongation step is a major node for the regulation of gene expression," says Shilatifard. "In fact, we have shown that mislocated elongation factors are the cause for pathogenesis of infant acute lymphoblastic and mixed lineage leukemia."

Mixed lineage leukemia is caused by a chromosomal translocation of the gene named MLL, resulting in its fusion to a seemingly random collection of other genes. Although the translocation partners don't share any obvious similarities, they all create potent leukemia-causing hybrid genes. In an earlier study, Chengqi Lin, a graduate student in Shilatifard's lab and first author on the current study, had identified the novel Super Elongation Complex (SEC) as the common denominator shared by all MLL-fusion proteins.

"We found that several frequent translocation partners of MLL are part of a super elongation complex that can activate paused Pol II. The accidental activation of developmentally regulated genes could explain

how leukemia arises as a result of MLL translocations," explains Lin. "However, the function of SEC in our cells is not to give us leukemia, but rather to regulate transcription of developmentally regulated genes, and therefore, we tried to learn more about the normal biological function of SEC."

They started talking to co-author Robb Krumlauf, the Scientific Director of the Stowers Institute, who has long been interested in Hox genes. Expressed early during development, Hox genes are key regulators of an organism's basic body plan. Instead of being scattered about the genome randomly they congregate into tight clusters on several chromosomes. A previous collaborative study between Krumlauf's and Shilatifard's laboratories demonstrated that Hox gene expression is differentially regulated by MLL. "In light of the functional links between MLL and SEC emerging from Shilatifard's lab it made sense to study the induction of Hox genes in murine embryonic stem cells, as model system to learn more about SEC and its role during early development," recalls Krumlauf.

"Hox genes are not only rapidly turned on in differentiating ES cells but because precise regulation of their gene expression is so important to coordinating normal development, they seem to use every known mechanism in the book," says Krumlauf. "Rather than studying 40 different genes to search for a relevant use of a regulatory mechanism you can often look at the Hox clusters and uncover relevant examples. This makes them a great model system to learn more about the fundamentals of controlling gene expression."

After initial experiments revealed that SEC is frequently present at highly transcribed regions, Lin in Shilatifard's lab and Bony De Kumar in Krumlauf's lab zoomed in on the Hox gene clusters in murine embryonic stem cells. Although both Hoxa1 and Hoxb1 were rapidly induced after treating the cells with retinoic acid, only Hoxa1 was

occupied and engaged by paused Pol II. "They are the first genes to be activated within their respective clusters but Hoxa1 is a little bit faster than Hoxb1," Krumlauf's says, "which Lin showed is likely the result of the presence of preloaded Pol II on Hoxa1."

When he expanded his analysis to the whole genome, Lin was able to identify a set of rapidly induced genes that contain paused Pol II. Many of them also recruit SEC in a fairly synchronous and uniform manner to the treatment with retinoic acid, which signals embryonic stem cells to turn on early developmental genes.

One notable exception among the first responders was the gene Cyp26a1, which encodes a cytochrome P450 that metabolizes retinoic acid and is essential for development. Although it lacks preloaded Pol II it is rapidly induced and still needed SEC for its rapid activation. "Not only did it come up extremely fast but it was also induced to much higher levels than the other very early retinoic acid-induced genes containing Pol II," observed Lin.

"Paused Pol II may not be strictly necessary for rapid induction, but rather facilitate coordinated and controlled induction," says Shilatifard. "Having preloaded Pol II and general transcription factors reduces the number of steps required for productive transcription and could result in a more equivalent and uniform way to induce gene expression."

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