Scientists discover fundamental mechanism that fine-tunes gene expression and is disrupted in cancer

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Wistar's Dr. Alessandro Gardini in his lab. Credit: The Wistar Institute

A team of scientists from The Wistar Institute in Philadelphia and the Peter MacCallum Cancer Center in Melbourne, Australia, discovered a

new checkpoint mechanism that fine-tunes gene transcription. As reported in a study published in *Cell*, a component of the Integrator protein complex tethers the protein phosphatase 2A (PP2A) to the site of transcription, allowing it to stop the activity of the RNA polymerase II enzyme (RNAPII). Disruption of this mechanism leads to unrestricted gene transcription and is implicated in cancer.

The study points to new viable opportunities for therapeutic intervention, demonstrating the anti-cancer effect of a new combination treatment in preclinical models of solid and hematopoietic malignancies.

Gene expression is the first step in the process by which the information encoded by a gene is used to make proteins. Controlling the timing and level of gene expression is crucial for cells to perform their specific functions within an organism, adapt to the surrounding conditions and properly respond to external stimuli.

The team, led by Alessandro Gardini, Ph.D., assistant professor in the Gene Expression & Regulation Program at The Wistar Institute, and Ricky Johnstone, Ph.D., professor, executive director of Cancer Research at the Peter MacCallum Cancer Centre, and head of The Sir Peter MacCallum Department of Oncology at the University of Melbourne, discovered a new checkpoint in the regulation of RNAPII, the enzymes that carries out transcription of DNA into RNA for gene expression.

"Cancer is a consequence of altered gene expression, as turning on or off one or more genes at the wrong time or in the wrong cells can dramatically alter their overall behavior and lead to unrestrained growth," said Gardini. "We describe one of the essential ways through which gene transcription is kept in check."

"We think our discovery provides new insight into how gene expression

is tightly controlled," said Johnstone. "This represents a completely new potential avenue for cancer treatment and our initial studies in mice suggested this could also improve the effect of another emerging treatment approach—CDK9 inhibition—in both blood-based and solid tumours."

Transcription by the RNAPII enzyme takes place in several steps, each tightly controlled through the opposing functions of cyclin-dependent kinases (CDKs), which modify the enzyme by adding phosphate groups to different parts of the protein, and phosphatases that remove those phosphate groups and counteract CDK activity.

The team uncovered the involvement of a phosphatase called Protein Phosphatase 2A (PP2A) in this regulatory balance. Though PP2A performs the majority of phosphatase activities in a cell, this study provides evidence that it also plays a critical role in transcription.

CDK9 is one of the CDKs that activate RNAPII by promoting elongation, the step in which synthesis of a nascent RNA chain continues as RNAPII moves along the DNA template.

The team found that a component of Integrator, a central regulator of transcriptional processes, interacts with the PP2A phosphatase to recruit it to sites of transcription, where it counteracts CDK9 activity, and blocks transcription elongation. PP2A and CDK9 work in tandem to fine-tune the balance between activation and inhibition of transcription.

Then, researchers tested the hypothesis that targeting the PP2A-Integrator-CDK9 axis in cancer by simultaneously blocking CDK9 and activating PP2A could afford therapeutic benefit in mouse models of leukemia and solid cancers. Combining treatment with inhibitors of CDK9 (CDK9i) and small molecule activators of PP2A (SMAPs) killed acute myeloid leukemia cells, driving prolonged therapeutic effect and

significantly longer survival compared to either single agent. Similarly, combination therapy in a solid tumor model demonstrated reduced tumor growth rates and tumor volume, resulting in enhanced overall survival.

Collectively, this study describes a new fundamental mechanism of gene expression regulation and demonstrates that concomitant CDK9 inhibition and PP2A activation results in enhanced anti-cancer effects in preclinical models of both solid and hematopoietic malignancies, opening new avenues for transcription-based anticancer therapy.

More information: Stephin J. Vervoort et al, The PP2A-Integrator-CDK9 axis fine-tunes transcription and can be targeted therapeutically in cancer, *Cell* (2021). DOI: 10.1016/j.cell.2021.04.022

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