

Researchers uncover new mechanism of gene regulation involved in tumor progression

January 9 2019

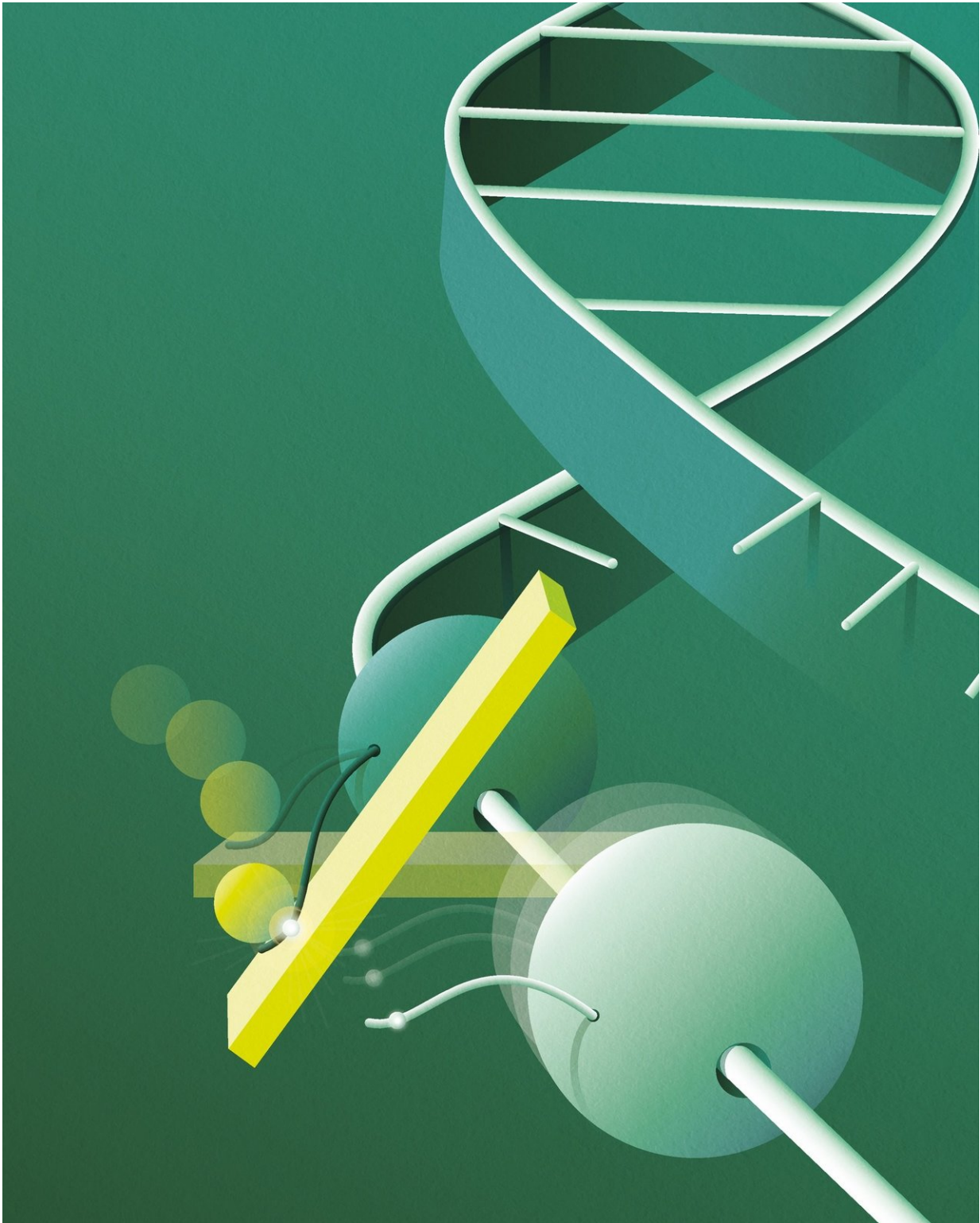


Illustration of arginine citrullination during transcription of a set of genes involved in cell proliferation and tumor progression. Credit: CRG, Iris Joval

Genes contain all the information needed for the functioning of cells, tissues and organs. Gene expression, meaning when and how the genes are read and executed, is thoroughly regulated like an assembly line with several activities happening one after another.

Researchers at the Centre for Genomic Regulation (CRG) in Barcelona, Spain, in collaboration with scientists at the structural bioinformatics group, University Pompeu Fabra (UPF) and department of molecular epigenetics, Helmholtz Center Munich, Germany, have discovered a new step in this assembly line, which controls the expression of some genes with an important role in cancer. "We observed that breast [cancer cells](#) need a particular [modification](#) to express a set of genes required for cellular proliferation and tumour progression," explains Priyanka Sharma, CRG researcher and first author of the paper. "This modification allows the enzyme RNA polymerase II to overcome a pausing barrier and to continue to transcribe these genes." Sharma is a Beatriu de Pinós postdoctoral researcher.

Cancer cells quickly proliferate, so the genes involved in cell division are highly active and highly expressed. Such precise and meticulous machinery requires many molecules to function properly. In this case, when the machinery to express proliferation genes is ready, it still has to wait for a particular modification to start, like a sprinter waiting for the starting gun. Here, the polymerase is ready and set, but still needs a final modification to cross the barrier for transcription.

"Deciphering every single step and all actors involved in this process is an important achievement in terms of fundamental science. We are now able to better understand how an intricate mechanism of gene regulation actually works and this might be a new target for clinical researchers to study novel therapies for certain types of cancer," says Miguel Beato,

CRG group leader and principal investigator in this work.

The work, which has been published in *Molecular Cell*, describes a novel modification of in the Carboxyl terminal domain of RNA Polymerase II, namely the deimination of arginine by the enzyme PADI2, which allows the polymerase to transcribe genes relevant for [cancer](#) cell growth. "Most chemotherapies are oriented to blocking the activity of enzymes, but we know that PADI2 participates in many processes involving the nervous system, immune response and inflammation, among others. Thus, inhibiting PADI2 would have multiple side effects. Our results make it possible to target just the particular action of PADI2 on RNA [polymerase](#) needed for tumour progression without globally blocking the enzyme," explains Beato.

More information: Priyanka Sharma et al, Arginine Citrullination at the C-Terminal Domain Controls RNA Polymerase II Transcription, *Molecular Cell* (2018). [DOI: 10.1016/j.molcel.2018.10.016](https://doi.org/10.1016/j.molcel.2018.10.016)

Provided by Center for Genomic Regulation

Citation: Researchers uncover new mechanism of gene regulation involved in tumor progression (2019, January 9) retrieved 26 April 2024 from <https://phys.org/news/2019-01-uncover-mechanism-gene-involved-tumor.html>

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