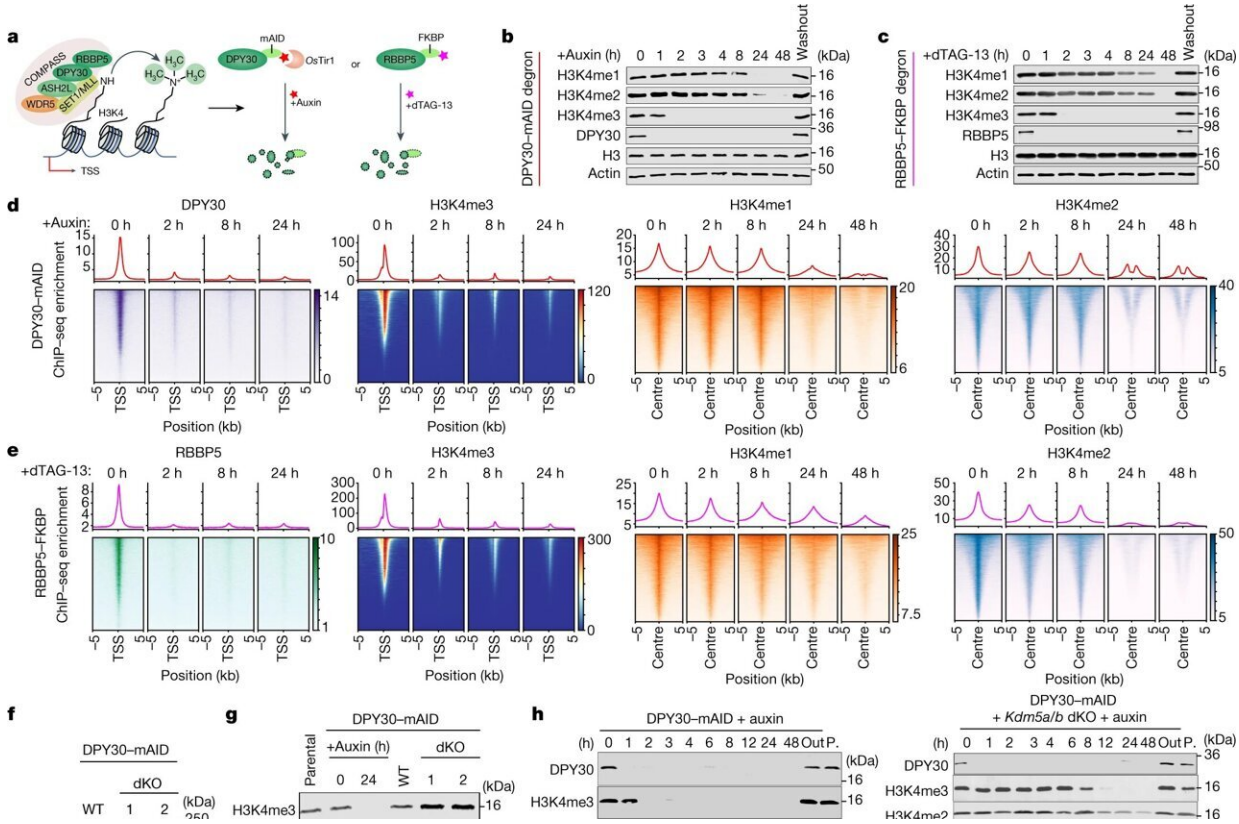
New study unveils epigenetic 'traffic lights' controlling stop and go for gene activity

March 1 2023



Acute depletion of SET1/COMPASS core subunits reveals rapid turnover of H3K4me3. **a**, Schematic of the degron systems for the targeted degradation of DPY30 and RBBP5. **b**,**c**, Immunoblot analysis of DPY30, RBBP5 and H3K4me1–3 levels at the indicated times after treatment with 500 nM auxin (**b**) or 500 nM dTAG-13 (**c**). Washout, degron ligand was washed out for 48 h. **d**,**e**, ChIP–seq heat maps and profiles were generated from control and auxin-treated DPY30–mAID cells (**d**) and dTAG-13-treated RBBP5–FKBP cells (**e**). For DPY30, RBBP5 and H3K4me3 ChIP–seq, the signal was plotted over the TSSs

(TSS ± 5 kb) of protein-coding genes. For H3K4me1 and H3K4me2 ChIP–seq, the signal was plotted over their center peaks (peak center ± 5 kb), which are called from steady-state mES cells. Sites were sorted by the ChIP–seq signals at 0 h. **f**, Immunoblot analysis of KDM5A and KDM5B in DPY30–mAID cells and two independently isolated dKO cell lines. β-Actin was used as the loading control. **g**, Immunoblot analysis of H3K4me3 and H3K4me1 levels in DPY30–mAID, control and *Kdm5a/b*-dKO cells. Histone H3 was used as the loading control. **h**, Immunoblot analysis of DPY30, H3K4me1–3, KDM5A and KDM5B at the indicated times after auxin treatment. Out, degron ligand was washed out for 48 h; P, parental cells. **i**, H3K4me3 ChIP–seq heat maps in DPY30–mAID *Kdm5a/b*-dKO cells. The signal was plotted over the TSSs (TSS ± 5 kb) of protein-coding genes. Rows are sorted by decreasing ChIP–seq occupancy in the auxin 0 h cells. Credit: *Nature* (2023). DOI: 10.1038/s41586-023-05780-8

A major new study in the journal *Nature* reveals a 'traffic light' mechanism controlling genetic activity within cells—a system which could potentially be targeted by cancer drugs already in development.

The research describes how 'epigenetic' changes to the structure of DNA can act as a stop-go signal in determining whether a gene should be read.

Unlike our genetic make-up, which is well understood, the world of epigenetics is still largely unexplored and referred to as the 'dark matter' of the genome.

But the new findings answer a fundamental and longstanding question—how epigenetic proteins regulate the processes of transcription and gene expression, through which our genes are read and translated into proteins.

Scientists at The Institute of Cancer Research, London, reveal how a key

epigenetic signal called H3K4me3—determines when and how DNA should be read and translated into proteins within our cells.

The study shows that H3K4me3 ensures genes are transcribed and activated at the right time in a controlled manner, like a set of traffic lights regulating the flow of cars on a busy road. Understanding how it functions in normal cells can also shed new light on the development of cancer—and the role played by a breakdown in the regulation of gene activity.

It has been known for more than 20 years that the enzymes placing H3K4me3, a chemical tag added to DNA, are crucial for normal cell development, as well as being linked to leukemia, breast, bowel and pancreatic cancers. But, until now, scientists lacked an understanding of what the chemical tag does, despite many years of research.

The new 'textbook discovery', as described by the researchers, transforms our understanding of:

- how epigenetic proteins help regulate cell development and can be involved in cancer
- how the process of gene expression—decoding DNA into functional proteins used by our body—is regulated
- how blocking epigenetic proteins could affect both normal and cancer cells.

The long-term hope is that this new understanding could lead to a new class of cancer treatments that target epigenetic 'traffic lights' to block the activity of genes that may be fueling cancer.

Epigenetics affects gene activity, or expression, without changing the underlying genetic code—for example, by adding or removing chemical tags or modifications to DNA or proteins that the DNA is wrapped

around, called histones. Chemical modifications such as H3K4me3 (tri-methylation of histone H3 lysine 4) can turn genes on or off, and are often altered in cancer.

Using mouse stem cells and sophisticated genetic and biochemical experiments in the lab, researchers found that the H3K4me3 modification is essential for regulating how and when our genes are expressed.

The team found that H3K4me3 acts like a traffic light at a busy intersection. By regulating the flow of RNA polymerase II—a protein complex that reads and decodes DNA—H3K4me3 determines when gene expression should start and the speed at which it runs.

When it gives the green light, H3K4me3 allows RNA polymerase II to move along DNA, transcribing it into RNA as it moves. But without H3K4me3, RNA polymerase II gets stuck at specific points on the DNA, creating a hold-up and slowing down transcription.

Previous results have suggested that disrupting or changing H3K4me3 levels in cells is important for cancer development and affects response to treatment.

Study leader Professor Kristian Helin, Chief Executive of The Institute of Cancer Research, London, and a world leader in the study of epigenetics, said, "Our study offers a fundamental new understanding of epigenetics, a very exciting and still largely underexplored area of cancer research. We have solved a 20-year-old puzzle by discovering how a well-known epigenetic modification controls gene expression. Because the enzymes determining the level of H3K4me3 in the cell frequently are found mutated in cancer, our studies could have implications for understanding and treating cancer."

"This is what I call 'textbook' science—the aspiration of many scientists, including myself, to solve fundamental questions so that our discoveries go into textbooks. Even the most cutting-edge treatments for patients are built on the foundations of fundamental scientific discoveries like this one. It is only thanks to basic understanding of how or genes and cells work, and what can go wrong with them, that we can create the cancer treatments of the future."

"Drugs targeting these 'traffic lights', or epigenetic modifications, such as H3K4me3, are already being developed—and it is possible that they could one day become an effective way of treating cancer patients. This is an exciting new avenue for cancer research, and we believe our findings will pave the way for more effective development of these epigenetic drugs."

More information: Kristian Helin, H3K4me3 regulates RNA polymerase II promoter-proximal pause-release, *Nature* (2023). DOI: 10.1038/s41586-023-05780-8.
www.nature.com/articles/s41586-023-05780-8

Provided by Institute of Cancer Research