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Press release **For immediate release**

HKU Biologists Discover Alternative Systems that Help Cells Control Genes

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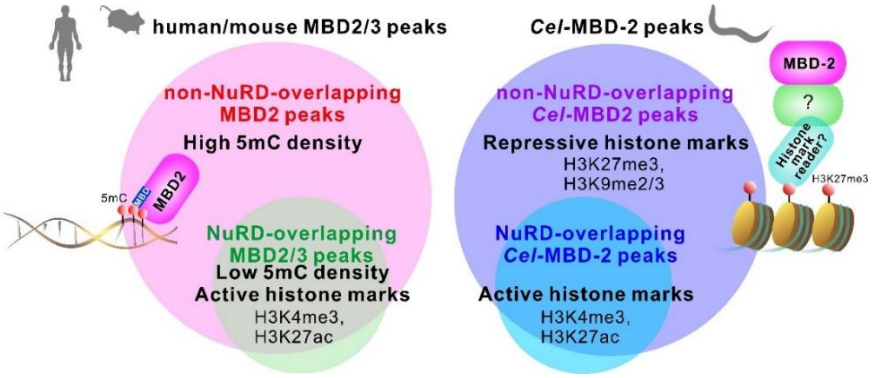

Figure 1. Dual binding patterns of MBD proteins in mammals and in C. elegans.

In mammals (left), previous studies show that most MBD3 binding sites overlap with MBD2 and the Nucleosome Remodeling and Deacetylase (NuRD) complex, while MBD2 also independently occupies additional regions enriched with DNA methylation (5-methylcytosine, 5mC).

In Caenorhabditis elegans (C. elegans) (right), which lacks DNA methylation, MBD-2 (Cel-MBD-2) displays a dual binding pattern as in mammalian MBD2, despite lacking a methyl-binding domain. The majority of Cel-MBD-2 binds to genomic regions enriched with repressive histone modifications, such as H3K27me3 and H3K9me2/3, independently of NuRD. This model illustrates how MBD-2 can be guided by different epigenetic signals when DNA methylation is absent. (Image credit: Tsui, et al., 2026. Nature Communications)

Researchers at the School of Biological Sciences of The University of Hong Kong (HKU) have uncovered how eukaryotic cells can control gene activity even after losing one of their major gene-regulatory systems during evolution. By studying a microscopic soil-living roundworm, the team revealed how an alternative, conserved epigenetic mechanism can take over when a common one is missing. The study has just been published in the interdisciplinary scientific journal *Nature Communications*. The findings provide new insights into how gene regulation adapts through evolution and may help scientists better understand disease mechanisms involving massive gene dysregulation, such as cancers, neurological disorders and autoimmune diseases.

Cells must carefully control which genes are turned on and which are turned off throughout development to function properly. While the DNA sequence provides the genetic blueprint, gene expression is also regulated by epigenetic mechanisms — regulatory systems that influence when genes are turned on without changing the genetic code. This allows different cell types, such as nerve cells and muscle cells, to share the same DNA while behaving very differently.

One common way cells control gene activity is through DNA methylation, in which a small chemical label, the methyl group, is added to cytosine, a specific base on DNA, forming 5-methylcytosine (5mC), to signal that certain genes should be kept switched off. 5mC is a key epigenetic mark in many animals and plants. However, some organisms, including the microscopic roundworm *C. elegans*, have lost DNA methylation multiple times during evolution. For a long time, scientists did not fully understand how these organisms could still regulate their genes properly without this major epigenetic system.

In this study, Dr Emily Hok Ning TSUI, a Postdoctoral Fellow at the School of Biological Sciences at HKU, working in the laboratories of Professor Karen Wing Yee YUEN and Professor Chaogu ZHENG, together with Dr Charmaine Yan Yu WONG, also in the YUEN Lab, showed that when DNA methylation is absent, cells can switch to an alternative epigenetic mechanism. Instead of relying on chemical labels on DNA, cells use various histone modifications — different post-translational chemical marks on histone proteins, the packaging proteins in which DNA is wrapped around inside the cell.

The researchers focused on a protein called MBD-2 (methyl-CpG-binding domain protein 2), which in many animals recognises 5mC-marked DNA and helps silence or activate genes. Surprisingly, even though *C. elegans* lacks DNA methylation and 5mC, its version of MBD-2 remains essential.

The HKU team found that in *C. elegans*, MBD-2 no longer reads DNA methylation signals. Instead, it is localised to genes in association with specific repressive histone marks, particularly H3K27me3, a histone modification known to be associated with gene silencing.

When MBD-2 was deleted, the worms became infertile and developed severe physical defects. A large number of genes were no longer properly regulated, demonstrating that MBD-2 remains a key regulator of gene activity, even in the absence of DNA methylation.

These findings reveal that epigenetic regulation is highly adaptable. When one gene-control system is lost, organisms can adapt to read different signals and maintain precise control in gene expression.

“While scientists already know histone modifications and DNA methylation are highly interconnected and crosstalk with each other, this study in *C. elegans* showcases the functional conservation of the gene-regulatory NuRD complex on one hand, but also the plasticity and adaptability of epigenetic mechanisms in eukaryotes on the other hand,” said Professor Karen YUEN.

This work may help scientists better understand the causes of human diseases, such as cancers, autism and inflammation, in which aberrant DNA methylation disrupts the regulation of many genes at the same time. Understanding how different epigenetic mechanisms can compensate for one another may also facilitate the development of alternative therapeutic approaches.

For more details, please refer to the journal paper: https://www.nature.com/articles/s41467-026-68592-0

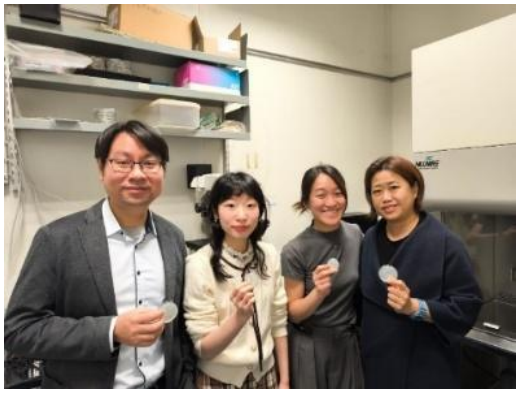

Figure 2. The research team at the School of Biological Sciences. From the left: Professor Chaogu ZHENG, Dr Emily Hok Ning TSUI, Dr Charmaine Yan Yu WONG and Professor Karen Wing Yee YUEN.

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