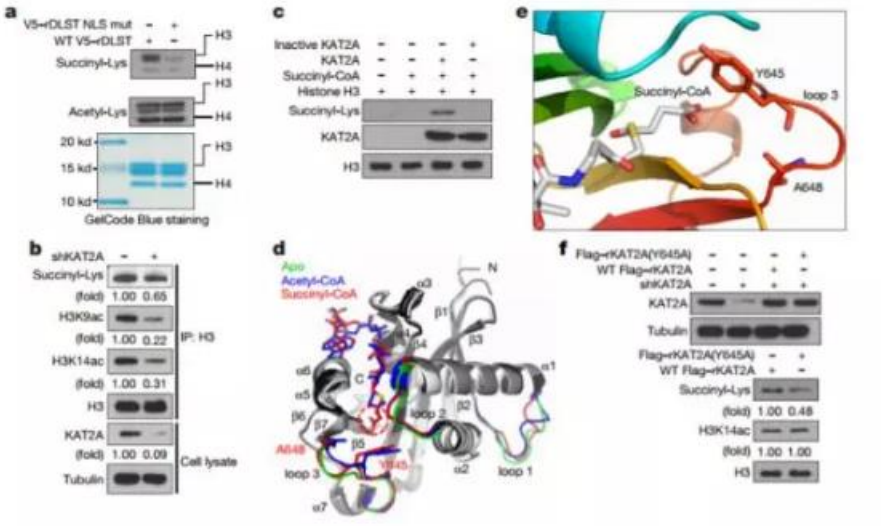
科学家们最新发现组蛋白琥珀酰化修饰的重要机制

Scientists Have Successfully Discovered an Epigenetic Mechanism for Histone Succinylation

12 月 14 日，《Nature》期刊最新发表一篇题为“KAT2A coupled with the α-KGDH complex acts as a histone H3 succinyltransferase”的文章，揭示了组蛋白琥珀酰化修饰的重要机制。

组蛋白修饰对基于染色体的生物学进程而言至关重要，但是组蛋白琥珀酰化的机制和功能却一直没有得到阐明。现在，来自于清华大学生命科学学院的邢东明教授、莱斯大学（Rice University）的陶一之教授和 MD 安德森癌症中心 Zhimin Lu 教授合作，发现了其中的关键细节。

研究发现，细胞核中的 α-酮戊二酸脱氢酶复合物（α-KGDH）能够在基因启动子区域与赖氨酸乙酰基转移酶 2A（KAT2A）蛋白结合，KAT2A 会进一步与琥珀酰辅酶 A（succinyl-CoA）结合，并对组蛋白 H3 进行琥珀酰化。



本研究揭示了 KAT2A 的作用（图片来源：Nature）

如果阻止 α-KGDH 复合体进入细胞核或抑制 KAT2A 蛋白表达，可减少基因表达，从而抑制肿瘤增长。这些结果揭示了组蛋白的一个重要修饰机制。

KAT2A coupled with the α-KGDH complex acts as a histone H3 succinyltransferase

KAT2A 偶联 α-KGDH 复合物可作为组蛋白 H3 琥珀酰转移酶

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Histone modifications, such as the frequently occurring lysine succinylation, are central to the regulation of chromatin-based processes. However, the mechanism and functional consequences of histone succinylation are unknown. Here we show that the α-ketoglutarate dehydrogenase (α-KGDH) complex is localized in the nucleus in human cell lines and binds to lysine acetyltransferase 2A (KAT2A, also known as GCN5) in the promoter regions of genes. We show that succinyl-coenzyme A (succinyl-CoA) binds to KAT2A. The crystal structure of the catalytic domain of KAT2A in complex with succinyl-CoA at 2.3 Å resolution shows that succinyl-CoA binds to a deep cleft of KAT2A with the succinyl moiety pointing towards the end of a flexible loop 3, which adopts different structural conformations in succinyl-CoA-bound and acetyl-CoA-bound forms. Site-directed mutagenesis indicates that tyrosine 645 in this loop has an important role in the selective binding of succinyl-CoA over acetyl-CoA. KAT2A acts as a succinyltransferase and succinylates histone H3 on lysine 79, with a maximum frequency around the transcription start sites of genes. Preventing the α-KGDH complex from entering the nucleus, or expression of KAT2A(Tyr645Ala), reduces gene expression and inhibits tumour cell proliferation and tumour growth. These findings reveal an important mechanism of histone modification and demonstrate that local generation of succinyl-CoA by the nuclear α-KGDH complex coupled with the succinyltransferase activity of KAT2A is instrumental in histone succinylation, tumour cell proliferation, and tumour development.