徐国良院士揭示胚胎发育关键通路的表观遗传调控机理

Guoliang Xu Reveal the Epigenetic regulation mechanism of the critical pathway in embryogenesis

【Nature 系列】 10 月 27 日，Nature 期刊发表了题为“TET-mediated DNA demethylation controls gastrulation by regulating Lefty–Nodal signalling”的论文，第一次在体内证明了 DNA 甲基化及其氧化修饰在小鼠胚胎发育过程中具有重要功能，揭示了胚胎发育过程中关键信号通路的表观遗传调控机理，为发育生物学提供了新的认识。

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DNA 甲基化在哺乳动物基因组印记和 X 染色体失活等过程中具有非常重要的作用，但 DNA 甲基化及其进一步氧化修饰在小鼠胚胎发育过程中的功能意义还知之甚少。在这一研究中，科学家小组发现，TET 双加氧酶介导的 DNA 去甲基化与 DNMT 介导的甲基化共同作用，通过调控 Lefty-Nodal 信号通路控制小鼠胚胎原肠运动。

具体来说，小鼠中所有 3 个 Tet 基因全部失活会导致原肠胚形成缺陷。而在 Tet 突变背景下，引入 Nodal 单突变等位基因部分修复了缺陷表型。这表明，过度活跃的 Nodal 信号与 Tet 突变引发的原肠胚形成失败有关。

研究指出，Nodal 信号增强可能是因为 Lefty1 和 Lefty2 基因表达水平降低。这两个基因编码了 Nodal 信号的抑制剂。此外，Lefty 基因表达降低还与 DNA 甲基化增强有关。在 Tet 缺陷胚胎中，当 Dnmt3a 和 Dnmt3b 基因被阻断后，Lefty–Nodal 信号和正常形态发生都能够很大程度地被修复。研究还发现，特异性废除双加氧酶活性的 Tet 点突变也能够导致相似的形态和分子异常。

胚胎原肠胚形成是一个高度动态的过程，是发育基本的早期步骤。这一研究证明了平衡和动态的 DNA 甲基化在原肠胚形成中的关键作用。对表观遗传信息调控的研究将有助于了解生长发育与疾病发生发展的分子机理，为维护人类健康，尤其是再生医学的技术开发提供理论依据。

TET-mediated DNA demethylation controls gastrulation by regulating Lefty–Nodal signaling

TET 介导的 DNA 去甲基化通过调节 Lefty–Nodal 信号控制原肠胚的形成

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Abstract

Mammalian genomes undergo epigenetic modifications, including cytosine methylation by DNA methyltransferases (DNMTs). Oxidation of 5-methylcytosine by the Ten-eleven translocation (TET) family of dioxygenases can lead to demethylation. Although cytosine methylation has key roles in several processes such as genomic imprinting and X-chromosome inactivation, the functional significance of cytosine methylation and demethylation in mouse embryogenesis remains to be fully determined. Here we show that inactivation of all three *Tet* genes in mice leads to gastrulation phenotypes, including primitive streak patterning defects in association with impaired maturation of axial mesoderm and failed specification of paraxial mesoderm, mimicking phenotypes in embryos with gain-of-function Nodal signalling. Introduction of a single mutant allele of *Nodal* in the *Tet* mutant background partially restored patterning, suggesting that hyperactive Nodal signalling contributes to the gastrulation failure of *Tet* mutants. Increased Nodal signalling is probably due to diminished expression of the *Lefty1* and *Lefty2* genes, which encode inhibitors of Nodal signalling.

Moreover, reduction in *Lefty* gene expression is linked to elevated DNA methylation, as both Lefty–Nodal signalling and normal morphogenesis are largely restored in *Tet*-deficient embryos when the *Dnmt3a* and *Dnmt3b* genes are disrupted. Additionally, a point mutation in *Tet* that specifically abolishes the dioxygenase activity causes similar morphological and molecular abnormalities as the null mutation. Taken together, our results show that TET-mediated oxidation of 5-methylcytosine modulates Lefty–Nodal signalling by promoting demethylation in opposition to methylation by DNMT3A and DNMT3B. These findings reveal a fundamental epigenetic mechanism featuring dynamic DNA methylation and demethylation crucial to regulation of key signalling pathways in early body plan formation.