清华与同济 Nature 同期聚集生命起初的基因表达调控

Tsinghua and Tongji University all Focus the Regulation of Gene Expression in Early Development in Same Issue

【Nature 系列】在 9 月 22 日的 Nature 上极少见地同时刊登了 3 篇文章都涉及受精后 DNA 结合组蛋白方式的改变和组蛋白分子修饰所产生的变化。

清华大学颉伟研究员

同济大学高绍荣教授

其中 2 篇都是中国科学家的作品，1 篇来自于清华大学，另 1 篇来自于同济大学。这些研究结果都揭示了基因表达的早期调控，分析了精子、卵子和小鼠早期胚胎中三个组蛋白修饰的基因组区域。这些研究在分析的细胞数量上不同，以及 DNA 和相关蛋白（结合在一起称染色质）在分析前如何处理不相同，但都得到了相同的结论。

其一

2016 年 9 月 22 日，清华大学生命科学学院颉伟和医学院那洁研究组在《自然》杂志（Nature）上发表题为《哺乳动物早期发育中组蛋白修饰 H3K4me3 的亲本特异重编程》（Allelic reprogramming of the histone modification H3K4me3 in early mammalian development）的研究论文。论文在世界上首次报道了哺乳动物组蛋白修饰从如何从亲代传递到子代的，以及早期胚胎发育中组蛋白修饰遗传和重编程的模式和分子机制。

组蛋白修饰是否能够从亲代传递到子代，以及如何传递仍是表观遗传学领域长久以来悬而未决的问题。清华大学颉伟组通过优化传统染色质免疫共沉淀（ChIP）技术，结合新型的 DNA 建库技术(TELP)，开发出了一套适用于极低细胞量研究组蛋白修饰的新型技术（STAR ChIP-seq），并成功将其应用在小鼠早期胚胎发育的研究中，揭示了组蛋白修饰在受精前后遗传和重编程的模式和分子调控机制。

研究人员主要报道了 STAR ChIP-seq 技术的开发以及利用 STAR ChIP-seq 研究组蛋白修饰 H3K4me3 从亲代到子代的遗传模式。研究者发现，在受精卵中，精子来源的绝大部分 H3K4me3 可能会被擦除。令人惊奇的是，研究人员意外发现在成熟的卵细胞中 H3K4me3

展现出了一种完全不同于以往任何一种细胞中的富集模式(non-canonical H3K4me3, or ncH3K4me3)。这种非经典 H3K4me3 大量出现在非基因区（intergenic region）。卵子中的这种特殊组蛋白修饰模式在受精后被暂时的保留了下来。在二细胞晚期阶段，随着胚胎早期发育的重要事件—合子基因组激活—的发生，这些来自母本的 H3K4me3 会被迅速的擦除。取而代之的是在来自双亲的基因组上同时建立新的经典的 H3K4me3 模式。最后，研究人员进一步探索了 ncH3K4me3 在卵细胞中的功能并发现与经典 H3K4me3 参与基因激活相反，ncH3K4me3 可能对卵子的基因组沉默是必需的。

其二

2016 年 9 月 22 日，同济大学高绍荣实验室在《Nature》杂志在线发表题为 “Distinct features of H3K4me3 and H3K27me3 chromatin domains in pre-implantation embryos” 的文章。首次从全基因组水平上揭示了小鼠植入前胚胎发育过程中的组蛋白 H3K4me3 和 HK27me3 修饰建立过程，并发现宽的（broad）H3K4me3 修饰在植入前胚胎发育过程中对基因表达调控发挥重要作用。

在本研究中，高绍荣教授研究组利用并改进了最新发表的适用于低起始量细胞的 ULI-NchIP （ultra-low-input micrococcal nuclease-based native ChIP）技术。利用极少量的细胞检测了小鼠植入前胚胎发育各个时期的组蛋白 H3K4me3 和 H3K27me3 修饰变化情况，这两个修饰分别对应基因的激活和沉默，这是目前已知的第一次系统地对小鼠植入前胚胎的组蛋白修饰进行全基因组水平上的检测。

通过分析检测到的数据，他们发现组蛋白 H3K4me3 和 H3K27me3 修饰的建立规律明显不同，H3K4me3 修饰的建立更迅速，并且倾向于建立在 CpG 含量较高且 DNA 甲基化水平较低的启动子区域，而 H3K27me3 修饰的建立比较缓慢，并且倾向于建立在 CpG 含量较低的启动子区域。

研究中最重要的发现是，通过数据的分析，看到虽然 H3K4me3 修饰在 2-细胞时期之后很少出现完全的建立和去除，但是 H3K4me3 信号的宽度却是在不断变化的，并且在早期胚胎的基因组中存在大量宽的（>5kb）H3K4me3 信号。而这种宽的 H3K4me3 信号在细胞系以及普通的体细胞中含量都很低。重要的是，这些宽的 H3K4me3 信号跟基因的高表达以及细胞的发育命运都有很密切的关系，这预示着在早期胚胎中，H3K27me3 等修饰还没有完全建立起来，细胞对基因表达的调控可能有着完全不同的表观遗传调控机制，这其中就包括依靠 H3K4me3 修饰的宽度的变化来调节基因表达。

该研究成果第一次建立起了小鼠植入前胚胎发育过程中的组蛋白 H3K4me3 和 H3K27me3 修饰图谱，并发现了植入前胚胎发育特殊的表观遗传调控机制，该研究为进一步研究植入前胚胎发育以及早期细胞分化的表观遗传调控机制打开了一扇大门。

Allelic reprogramming of the histone modification H3K4me3 in early mammalian development

哺乳动物早期发育中组蛋白修饰 H3K4me3 的亲本特异重编程

清华大学 颉伟 那洁

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Abstract

Histone modifications are fundamental epigenetic regulators that control many crucial cellular processes. However, whether these marks can be passed on from mammalian gametes to the next generation is a long-standing question that remains unanswered. Here, by developing a highly sensitive approach, STAR ChIP–seq, we provide a panoramic view of the landscape of H3K4me3, a histone hallmark for transcription initiation, from developing gametes to post-implantation embryos. We find that upon fertilization, extensive reprogramming occurs on the paternal genome, as H3K4me3 peaks are depleted in zygotes but are readily observed after major zygotic genome activation at the late two-cell stage. On the maternal genome, we unexpectedly find a non-canonical form of H3K4me3 (ncH3K4me3) in full-grown and mature oocytes, which exists as broad peaks at promoters and a large number of distal loci. Such broad H3K4me3 peaks are in contrast to the typical sharp H3K4me3 peaks restricted to CpG-rich regions of promoters. Notably, ncH3K4me3 in oocytes overlaps almost exclusively with partially methylated DNA domains. It is then inherited in pre-implantation embryos, before being erased in the late two-cell embryos, when canonical H3K4me3 starts to be established. The removal of ncH3K4me3 requires zygotic transcription but is independent of DNA replication-mediated passive dilution. Finally, downregulation of H3K4me3 in full-grown oocytes by overexpression of the H3K4me3 demethylase KDM5B is associated with defects in genome silencing. Taken together, these data unveil inheritance and highly dynamic reprogramming of the epigenome in early mammalian development.

Distinct features of H3K4me3 and H3K27me3 chromatin domains in pre-implantation embryos

小鼠植入前胚胎中 H3K4me3 和 HK27me3 染色质域的特征

同济大学 高绍荣

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Abstract

Histone modifications have critical roles in regulating the expression of developmental genes during embryo development in mammals. However, genome-wide analyses of histone modifications in pre-implantation embryos have been impeded by the scarcity of the required materials. Here, by using a small-scale chromatin immunoprecipitation followed by sequencing (ChIP–seq) method, we map the genome-wide profiles of histone H3 lysine 4 trimethylation (H3K4me3) and histone H3 lysine 27 trimethylation (H3K27me3), which are associated with gene activation and repression4, 5, respectively, in mouse pre-implantation embryos. We find that the re-establishment of H3K4me3, especially on promoter regions, occurs much more rapidly than that of H3K27me3 following fertilization, which is consistent with the major wave of zygotic genome activation at the two-cell stage. Furthermore, H3K4me3 and H3K27me3 possess distinct features of sequence preference and dynamics in pre-implantation embryos. Although H3K4me3 modifications occur consistently at transcription start sites, the breadth of the H3K4me3 domain is a highly dynamic feature. Notably, the broad H3K4me3 domain (wider than 5 kb) is associated with higher transcription activity and cell identity not only in pre-implantation development but also in the process of deriving embryonic stem cells from the inner cell mass and trophoblast stem cells from the trophectoderm. Compared to embryonic stem cells, we found that the bivalency (that is, co-occurrence of H3K4me3 and H3K27me3) in early embryos is relatively infrequent and unstable. Taken together, our results provide a genome-wide map of H3K4me3 and H3K27me3 modifications in pre-implantation embryos, facilitating further exploration of the mechanism for epigenetic regulation in early embryos.