北师大王占新教授课题组揭示表观遗传调控核心复合物招募到基因组上重要位点的分子机制

The team of Professor Zhanxin Wang in Beijing Normal University reveals the molecular mechanism of epigenetic regulation core complex recruitmented to important loci in the genome

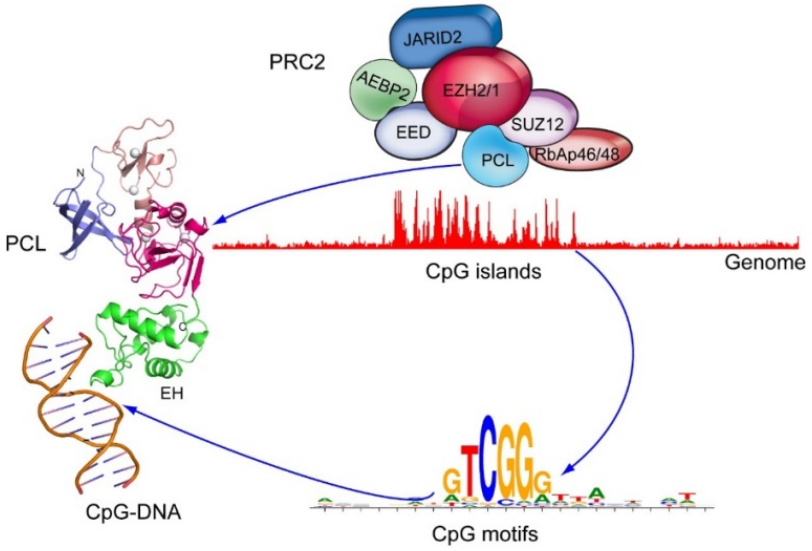
王占新教授

【Nature 系列】2017 年 9 月 14 日，国际顶级学术期刊 Nature（《自然》）刊登了北京师范大学生命科学学院细胞增殖及调控生物学教育部重点实验室王占新教授课题组 发表 的题为“Polycomb-like proteins link the PRC2 complex to CpG islands”的文章，报道了该研究组关于 PCL 家族蛋白调控 PRC2 复合物在染色质上定位的机理研究上的突破性进展。

PCL 家族蛋白是 PRC2 复合物的结合蛋白，该研究首次发现 PCL 家族蛋白的 EH 结构域识别含有非甲基化 CpG 序列的 DNA 元件，并通过结构生物学的方法揭示了 PCL 蛋白家族成员 (PHF1 和 MTF2) 识别这种特定 DNA 元件以及识别含有 H3K36me3 修饰的组蛋白的分子机理。在体内，非甲基化 CpG 序列的 DNA 主要出现在基因组的 CpG 岛上，王占新实验室通过与哈佛大学施扬教授实验室合作，发现在小鼠胚胎干细胞内 PCL 家族蛋白成员通过对基因组上非甲基化 CpG 序列的特异识别，帮助 PRC2 复合物招募到染色质的 CpG 岛上。

该研究首次发现并证实了 PCL 家族蛋白是连接 PRC2 与 CpG 岛的纽带，该工作为 PRC2 复合物在染色质上 CpG 岛特异的招募提供了直接的实验证据，解决了困惑人们多年的关于 PRC2 在染色质上选择性定位的这一重要问题，为进一步理解 PCL 家族蛋白在 PRC2 复合

物中的生理功能，以及靶向与 PRC2 相关疾病开辟了一个全新的思路。



Polycomb-like proteins link the PRC2 complex to CpG islands
多梳蛋白将 PRC2 复合体连接到 CpG 岛

北京师范大学 王占新
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The Polycomb repressive complex 2 (PRC2) mainly mediates transcriptional repression and has essential roles in various biological processes including the maintenance of cell identity and proper differentiation. Polycomb-like (PCL) proteins, such as PHF1, MTF2 and PHF19, are PRC2-associated factors that form sub-complexes with PRC2 core components, and have been proposed to modulate the enzymatic activity of PRC2 or the recruitment of PRC2 to specific genomic loci. Mammalian PRC2-binding sites are enriched in CG content, which correlates with CpG islands that display a low level of DNA methylation. However, the mechanism of PRC2 recruitment to CpG islands is not fully understood. Here we solve the crystal structures of the N-terminal domains of PHF1 and MTF2 with bound CpG-containing DNAs in the presence of H3K36me3-containing histone peptides. We show that the extended homologous regions of both proteins fold into a winged-helix structure, which specifically binds to the unmethylated CpG motif but in a completely different manner from the canonical winged-helix DNA recognition motif. We also show that the PCL extended homologous domains are required for efficient recruitment of PRC2 to CpG island-containing promoters in mouse embryonic stem cells. Our research provides the first, to our knowledge, direct evidence to demonstrate that PCL proteins are crucial for PRC2 recruitment to CpG islands, and further clarifies the roles of these proteins in transcriptional regulation *in vivo*.