The KRAB-Zinc finger protein ZFP708 mediates epigenetic repression at RMER19B retrotransposons

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Abstract

Global epigenetic reprogramming is vital to purge germ cell-specific epigenetic features to establish the totipotent state of the embryo. This process transpires to be carefully regulated and not an undirected, radical erasure of parental epigenomes. The TRIM28-complex has been shown to be critical in embryonic epigenetic reprogramming by regionally opposing DNA demethylation to preserve vital parental information to be inherited from germline to soma. Yet, the DNA-binding factors guiding this complex to specific targets are largely unknown. Here we uncover and characterize a novel, maternally expressed, TRIM28-interacting KRAB Zinc-finger protein, ZFP708. It recruits the repressive TRIM28-complex to RMER19B retrotransposons to evoke regional heterochromatin formation. ZFP708-binding to these hitherto unknown TRIM28 targets is DNA methylation- and H3K9me3-independent. ZFP708 mutant mice are viable and fertile, yet embryos fail to inherit and maintain DNA methylation at ZFP708-target sites. This can result in activation of RMER19B adjacent genes while ectopic expression of ZFP708 results in transcriptional repression. Finally, we describe the evolutionary conservation of ZFP708 in mice and rats, which is linked to the conserved presence of the targeted RMER19B retrotransposons in these species.

Figure

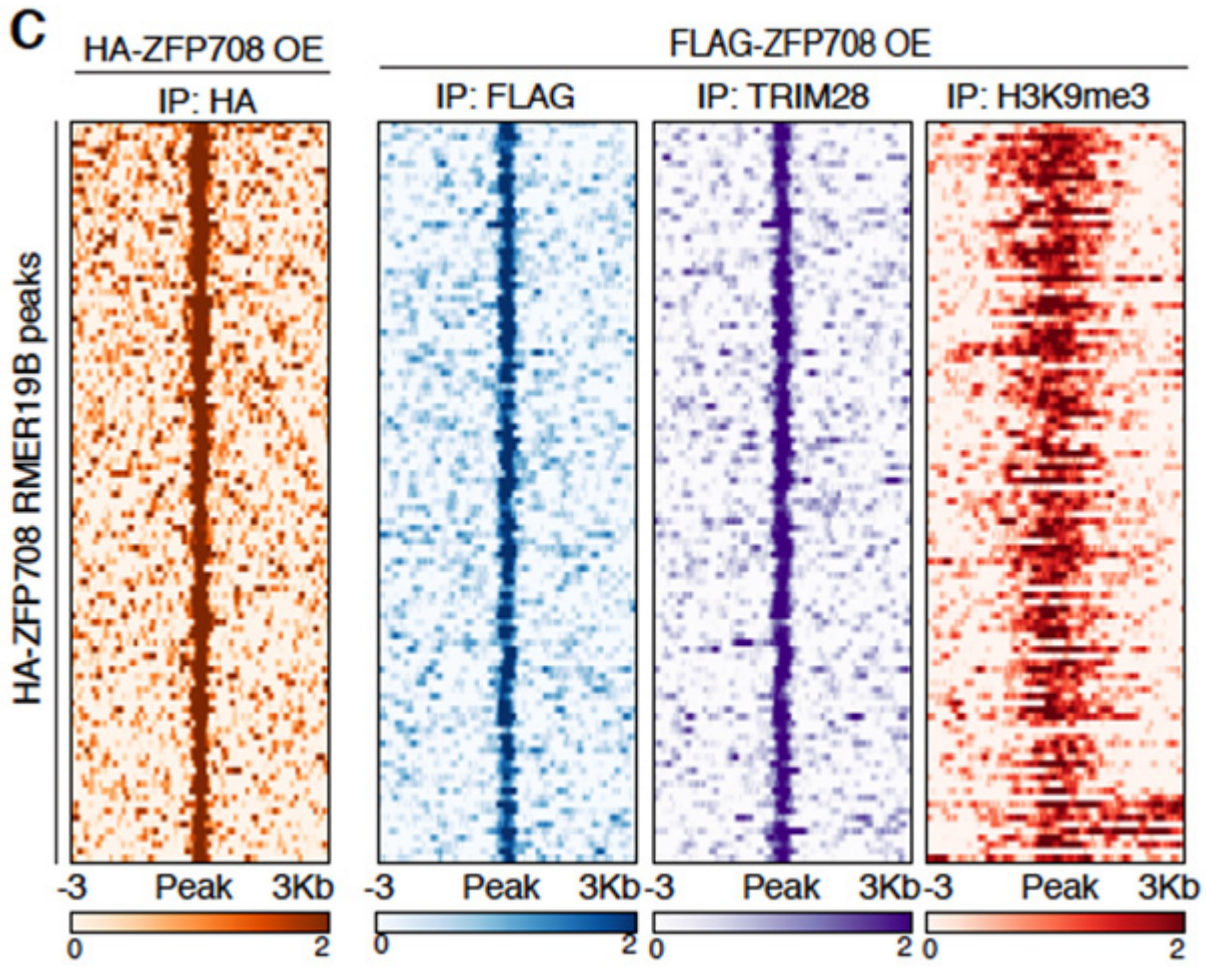

Figure Legend: Heatmaps illustrate binding of ZFP708 to RMER19 retrotransposon insertion sites in the mouse genome, linked recruitment of the TRIM28-repressor complex and consequently H3K9me3 enrichment.