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Polycomb-targeted TF genes remain active despite promoter hypermethylation in colorectal cancer

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DNA methylation is a key epigenetic regulator often disrupted in cancer, yet how promoter methylation dynamics translate into transcriptional changes during cancer progression remains incompletely understood. Here, we employed targeted bisulfite sequencing and RNA-seq on paired tumor and non-tumor tissues from 80 Korean colorectal cancer (CRC) patients to map promoter methylation and gene expression dynamics. Promoters with high baseline methylation in non-tumor tissues tended to become hypomethylated in tumors, while those with low baseline methylation underwent partial hypermethylation. However, these changes did not consistently correlate with gene silencing or activation. Strikingly, promoters marked by Polycomb (PcG^+) in non-tumor tissue were prone to hypermethylation yet often remained transcriptionally active in tumors, a paradox most prominent in transcription factor (TF) genes. In contrast, hypermethylation in PcG^- promoters was more consistently associated with transcriptional repression. Our findings suggest that epigenetic plasticity at PcG^+ TF gene promoters can override the typically repressive effects of DNA methylation, potentially enabling tumors to maintain or enhance the expression of key regulatory genes. This highlights the importance of PcG occupancy in shaping the functional consequences of methylation changes during colorectal tumorigenesis, warranting deeper investigation into how these epigenetic adaptations drive cancer progression.