SET Domain–Containing Protein 4 Epigenetically Controls Breast Cancer Stem Cell Quiescence

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Background

Quiescent cancer stem cells (CSC) play an important role in tumorigenesis, relapse, and resistance to chemoradiotherapy. However, the determinants of CSC quiescence and how they sustain themselves to generate tumors and relapse beyond resistance to chemoradiotherapy remains unclear. Utilizing the advantages of ChIP-seq and ATAC-seq, the findings strongly suggest that SET domain–containing protein 4 (SETD4) epigenetically controls breast CSC (BCSC) quiescence by facilitating heterochromatin formation via H4K20me3 catalysis. Single-cell sequence analysis indicates that SETD4^{+} qBCSCs clustered together as a distinct cell type within the heterogeneous BCSC population. These findings provide insights into the mechanism of tumorigenesis and relapse promoted by SETD4-defined quiescent CSCs and have broad implications for clinical therapies.

Research Pipeline

Samples

BCSCs^{SETD4} and BCSCs^{GFP} from the MCF7 cell line

Library Preparation

ChIP-seq library, ATAC-seq library and RNA-seq library

Sequencing Strategy

Illumina platforms, paired-end 150 bp

Bioinformatics Analysis

ChIP-seq and ATAC-seq analysis such as:

- Peak calling for aligned reads
- Differential peak analysis and annotation
- Heatmaps to present the differentiated enriched peaks
- Illustrative read coverage graphs of H4K20me3 pattern analysis across candidate genes

Gene expression and functional analysis

Research Results

1. H4K20me3 enhanced by SETD4 is located at certain promoter regions.

1.1 ChIP-seq was performed to explore epigenetic regulation by H4K20me3 in BCSCs quiescence. Illustrative read coverage graphs of H4K20me3 patterns across candidate genes showed that in BCSCs^{SETD4}, H4K20me3 was typically enriched at some promoter regions but was decreased at the promoter region of TP53 gene (Figure 1).

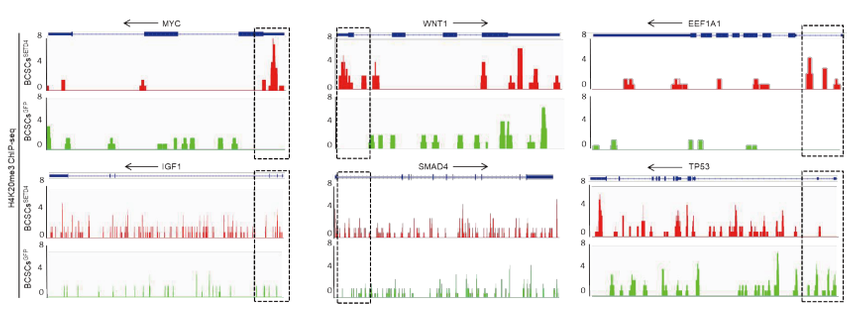

Figure 1. Representative gene read coverage graphs of enriched H4K20me3 distribution by ChIP-seq.

1.2 Weak ATAC-seq signals at some promoters in BCSCs^{SETD4} and stronger signals at the TP53 promoter region were found, which likely explains their gene expression status (Figure 2).

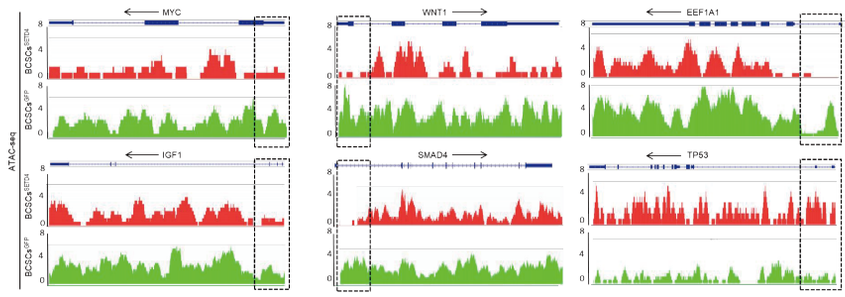

Figure 2. Representative gene read coverage graphs of the chromatin accessibility around the candidate gene by ATAC-seq.

2. SETD4 regulates the expression of a set of genes in the quiescent BCSCs.

RNA sequencing was used to compare the gene expression profiles of BCSCs^{SETD4} and BCSCs^{GFP}. Consistent with our analysis of GO terms and qRT-PCR results, KEGG pathway analysis revealed that genes correlated with cell activation and proliferation were downregulated in BCSCs^{SETD4} (Figure 3).

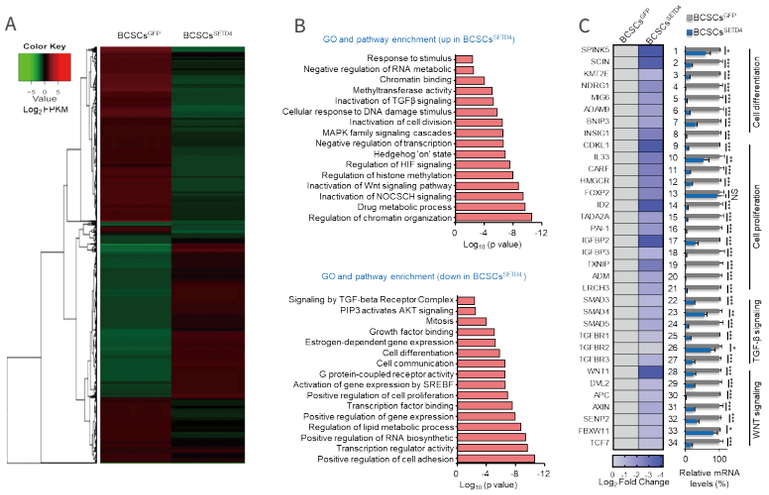

Figure 3. Gene expression analysis of upregulated and downregulated differential expressed genes in BCSCs^{SETD4}.

Conclusions

In this study, our ChIP-seq, ATAC-seq and RNA-seq results indicate that SETD4 promotes cHC formation in qBCSCs and epigenetically regulates the expression of a set of genes by catalyzing the H4K20me3 located at the promoter regions. These findings advance our knowledge about the epigenetic determinants of quiescence in cancer stem cell populations and pave the way for future pharmacologic developments aimed at targeting drug-resistant quiescent stem cells.

Reference

Ye S, Ding Y, Jia W, *et al.* SET Domain–Containing Protein 4 Epigenetically Controls Breast Cancer Stem Cell Quiescence[J]. *Cancer Research,* 2019, 79(18): 4729-4743.

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