

審査の結果の要旨

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This study aims to clarify the molecular mechanism of ectopic hepatoid differentiation in AFP-producing gastric cancer (AFPGC). We have performed RNA-sequencing, ChIP-sequencing, Methylation EPIC BeadChIP array, and ChIP-qPCR to find the following results.

- 1: We analyzed RNA-sequencing data of 215 gastric cancer tissues to identify an AFPGC subgroup showing upregulation of liver-specific genes (e.g., *AFP*, *ALB*, *FGA*, *FGG*, and *ITIH2*) and CEBPA, a significant regulator of terminal hepatocyte differentiation.
- 2: We integrated enhancer-oriented DNA methylation profiling of 178 gastric cancer tissues coupled with the profile of histone modifications and the occupancy profile of four hepatic transcription factors (TFs) of AFP-positive and AFP-negative gastric cancer cell lines. Then, we found that the enhancer regions of liver-specific genes were activated with DNA hypomethylation and hepatic TFs (CEBPA, HNF4A, FOXA1, and FOXA2) occupancy in AFPGC.
- 3: Through analyzing the differentially expressed genes and examining the level of active enhancer marker H3K27ac after siRNA-mediated knockdown of CEBPA using AFPGC cell lines (Fu97 and Takigawa), we found that CEBPA is an essential TF to upregulate liver-specific gene expression through enhancer activation in AFPGC.
- 4: The siRNA-mediated silencing of pluripotent stem cell TF overexpressed in AFPGC, induced the upregulation of CEBPA and its liver-specific targets with CEBPA binding and H3K27 acetylation, and resulted in repressing cell proliferation.

Taken together, this study revealed a core regulatory network of hepatic TFs for ectopic hepatoid differentiation and two associating factors, pluripotent stem cell TF for negatively regulating terminal hepatoid differentiation and controlling cell proliferation, and CEBPA for promoting terminal hepatoid differentiation. Understanding the molecular mechanism of aberrant differentiation can provide new insight into therapeutic approaches against AFPGC.

よって本論文は博士（医学）の学位請求論文として合格と認められる。