

博士論文（要約）

Epigenomic dysregulation in AFP-producing gastric cancer

（AFP 産生胃がんにおけるエピジェノミク異常）

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論文の内容の要旨

論文題目 Epigenomic dysregulation in AFP-producing gastric cancer
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AFP-producing gastric cancer (AFPGC) is a highly malignant subgroup of gastric cancer with the elevation of serum protein or immunohistochemical staining of AFP (α -Fetoprotein). The molecular mechanism and pathological significance of its ectopic hepatoid differentiation remain entirely unclear. We analyzed gene expression data of 215 gastric cancer tissues collected in the International Cancer Genome Consortium (ICGC) project and identified a specific subgroup showing upregulation of liver-specific genes (e.g., *AFP*, *ALB*, *FGA*, *FGG*, and *ITIH2*) and *CEBPA*, a significant regulator of terminal hepatocyte differentiation. Upon integrating enhancer-oriented DNA methylation profiling of 178 gastric cancer tissues coupled with the profile of histone modifications and four hepatic transcription factors (TFs) occupancies of AFP-positive and AFP-negative gastric cancer cell lines, 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. The siRNA-mediated gene silencing demonstrated that *CEBPA* is an essential TF to upregulate liver-specific gene expression through enhancer activation. On the contrary, silencing of *SALL4A*, the longer *SALL4* isoform 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. These results revealed a core regulatory network of hepatic TFs for ectopic hepatoid differentiation and two associating factors, *SALL4A* 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.