



Title	Fam60a/Tera is a metazoan specific mSin3A interactor that is implicated in TET1 acti
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## 論文内容の要旨

### [題名]

*Fam60a/Tera* is a metazoan specific mSin3A interactor that is implicated in TET1 activity

(*Fam60a/Tera* は後生動物特異的なmSin3A結合因子でありTET1活性に関与する)

学位申請者 鍋島 了

The methylation of cytosine residues is a heritable epigenetic mark, involved in parasite DNA silencing and gene regulation. In this research, I showed that Fam60a/Tera is a component of mSin3A/HDAC complex and is implicated in DNA demethylase activity.

To know the molecular function of Fam60a/Tera, first I performed a binding partner screening. As a result, the mSin3A/HDAC co-repressor complex was identified as a binding partner of Fam60a/Tera. mSin3A/HDAC co-repressor complex works as a gene repressor when recruited to DNA by binding to transcription factors, modified histone binding factors or methylated CpG binding proteins. Most of *Fam60a/Tera*<sup>-/-</sup> embryos are embryonic lethal. Some of them exhibit various morphological phenotypes, such as growth retardation, cardiac defects, neural tube defects, and placental defects. Fam60a/Tera localizes to gene promoter regions in the genomic DNA just like mSin3A and Fam60a/Tera target genes are mainly up-regulated in *Fam60a/Tera*<sup>-/-</sup> embryos. These data indicate the Fam60a/Tera have an enhancing effect to repressor activity of mSin3A/HDAC co-repressor complex during embryogenesis. Fam60a protein conservation suggests that Fam60a is associated with DNA methylation and when co-overexpressed with TET1, Fam60a could suppress TET1 activity in a culture cell.

Bisulfite sequence analysis on a Fam60a target gene promoter shows reduction of DNA methylation level in E9.5 *Fam60a*<sup>-/-</sup> embryo. However the reduction of DNA methylation was not observed in E7.5-E8.5 *Fam60a/Tera*<sup>-/-</sup> embryos, indicating that aberrant DNA demethylation occur in Fam60a/Tera-/- embryos. Finally increased TET1 and mSin3A recruitment to the target gene promoter was observed in Fam60a depleted ES cells. These data suggest that Fam60a is metazoan specific mSin3A interactor and is implicated in TET1 activity.

## 論文審査の結果の要旨及び担当者

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## 論文審査の結果の要旨

申請者は転写因子Oct3/4下流因子として同定されたFam60a/Teraの機能解析を、マウス胚で行った。その結果、Fam60a/TeraがmSin3A/HDAC複合体の因子であること、Fam60a/Tera欠損胚は胎生中期に全身性の形態異常を示すことを明らかにした。また、ChIP-seqやRNA-seqといったゲノムワイドな解析によりFam60a/Teraが遺伝子の転写開始点にリクルートされ、さらに遺伝子発現に対して抑制的に働く傾向があることを示した。mSin3A関連因子の中でも、mSin3A結合因子であるTET1 DNA脱メチル化酵素に対するFam60a/Teraの効果を調べた。Fam60a/TeraはTET1の持つ酵素活性を抑制し、Fam60a/Tera欠損胚では、DNA脱メチル化がFam60a/Tera標的遺伝子の転写開始点付近で亢進していることを明らかにした。これらの結果は新規因子Fam60a/TeraはmSin3A複合体の結合タンパク質であり、TETによる転写制御に関与することを示している。申請者は学位の授与に値するものと認める。