様式３

論　文　内　容　の　要　旨

〔　題　　名　〕 LATS2 positively regulates repressive epigenetic integrity via Polycomb repressive complex 2
（LATS2はPolycomb repressive complex 2を介して抑制性エピゲノムを制御する）

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LATS2 (large tumor suppressor 2), a pivotal Ser/Thr kinase of the Hippo signaling pathway, plays important roles in many biological processes. LATS2 and its homolog LATS1 function in many tumor-suppressive signals, including some that involve canonical Hippo signaling and others that are Hippo-independent. On the other hand, because *Lats2* knockout (KO) mice exhibit embryonic lethality due to a defect in neurogenesis, whereas *Lats1* KO mice do not, it is likely that LATS2 has essential functions that it does not share with LATS1. Furthermore, a recent study reported that Lats2 is indispensable for maintenance of stemness in murine embryonic stem cells. Therefore, elucidation of novel non-canonical signals of LATS2 would improve our understanding of the role of this protein in normal development and tumorigenesis. In this thesis, I demonstrate that *LATS2* KO causes dysregulation of Polycomb repressive complex 2 (PRC2), followed by reduction of tri-methylation of histone H3 at K27 (H3K27me3) levels in both mouse and human cells. Chromatin-modifying activities involved in the generation of appropriate epigenetic landscapes by PRC2 play an essential role in development and tumorigenesis. However, the spatiotemporal mechanisms by which PRC2 generates diverse epigenomes in specific tissue or cellular contexts remain poorly understood

To profile the effect of *LATS2* KO on the epigenome and transcriptome in human cells, I constructed a new *LATS2* KO HeLa-S3 cell line using TAL-effector nuclease (TALEN) technology. Omics analyses of this HeLa-S3 line and mouse embryonic fibroblasts revealed that *LATS2* depletion causes induction of genes involved in development, especially neurogenesis, in a manner that is partially independent of canonical Hippo signals. LATS2 binds to EZH2, a component of PRC2 on chromatin and can phosphorylate EZH2 *in vivo* and *in vitro*. LATS2 positively regulates histone methyltransferase activity of EZH2 in a kinase dependent fashion. Dysregulation of PRC2 also interferes with the normal pattern of the H3K4me3 modification, further reinforcing the failure of PRC2. This LATS2-dependent H3K27me3 module correlates with a dedifferentiated state in the nervous system. Indeed, in glioblastoma multiforme, LATS2-high tumors are associated with poor prognosis accompanied by silencing of PRC2 targets. Overall, these results suggest that LATS2, a known tumor suppressor, may coordinate oncogenic epigenetic signatures in specific tissues via PRC2. Therefore, these findings provide insights into the oncogenic role of LATS2 in specific contexts, as well as its importance in regulation of epigenome-associated signals in normal development and tumorigenesis.

様式７

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、がん抑制遺伝子LATS2の新規な細胞機能の解明を目指し、昨今注目を集めているゲノム編集技術と、次世代シークエンサーを用いた網羅的解析技術を効果的に組み合わせたアプローチを試みた。その結果、LATS2は抑制性のエピジェネティック制御機構であるポリコーム抑制複合体２（PRC2）をリン酸化することで、その機能を正に制御することを見出した。また、既存の網羅的解析データを有効に再利用した解析により、このLATS2－PRC2軸の神経系の未分化性維持やがん化との強い相関を明らかにした。本研究ではLATS2の新規機能の解明に留まらず、既知がん抑制遺伝子でもエピゲノムの制御を介して、細胞の脱分化方向のシグナルを担う可能性や、PRC2の組織特異的な上流のリン酸化シグナルについても新たな示唆をもたらすものであり、本論文は学位に値するものと認める。