学 位 論 文 内 容 の 要 旨
（Summary of dissertation）

博士の専攻分野の名称　　博士（医　学）　　　　氏 名　迪丽努尔　艾尼瓦尔
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p53 represses the transcription of *snRNA* genes by preventing the formation of little elongation complex

（p53は little elongation complex　の形成を阻害することによって*snRNA*遺伝子の転写を抑制する）

【Background and Objectives】
The regulation of transcription by RNA polymerase II (Pol II) plays a very important role in a variety of cellular functions. ELL/EAF containing little elongation complex (LEC) was identified to be required for the transcription of Pol II-dependent small nuclear RNA (*snRNA*) genes. It was known that tumor suppressor p53 is a specific interactor of ELL inhibits the transcription elongation activity of ELL. Here we provide evidence that p53 inhibits the interaction between EAF/ELL and ICE1 in LEC, so that p53 represses the transcription of Pol II-dependent *snRNA* genes through inhibiting LEC function. Induction of p53 triggered by ultraviolet (UV) decreased the occupancy of ICE1 at the Pol II-dependent *snRNA* genes. Consistent with the results, knockdown of p53 increased both the expression of *snRNA* genes and the occupancy of Pol II and the components of LEC at *snRNA* genes. Our results indicate that p53 interferes with the interaction between ELL/EAF and ICE1 and represses transcription of *snRNA* genes by Pol II.

【Materials and Methods】
In this study HCT116 cells were mainly used for experimental data. We used biochemical methods for example immunoprecipitation (IP), siRNA transfection, western blotting and chromatin IP (ChIP).

【Results】
In our previous work we proved that EAF1 is responsible and directly bound to human mediator subunit Med26-N-terminal domain. In this thesis we included the binding region of EAF1 for Med26-N-terminus domain, which is the C-terminal amino-acid residue from 245 to 268 in human EAF1. We also found out that the EAF

family member protein functions as an adaptor molecule to connect Med26 and LEC. ICE1 (KIAA0947) functions as a core subunit of LEC and interacts with both ICE2 (NARG2) and ELL/EAF. And the C-terminal fragment of ICE1 (1191-2266) is required for the formation of LEC. We here proved that depletion of EAF1 decrease the occupancy of ICE1 at a subset *snRNA* genes. Therefore we proved a model that EAF1 functions as an adaptor molecule connecting LEC and Med26 at a subset of Pol II dependent *snRNA* genes. In this study, we showed that EAF1 is required for the recruitment of ICE1 to a subset of RNA Pol II-dependent *snRNA* genes. We provide a putative model that EAF1 functions as an adaptor molecule connecting LEC and MED26 at a subset of Pol II dependent *snRNA* genes. Our model proposes that p53 interacts with ELL and inhibits the interaction between ELL and ICE1, leading to the repression of the formation of LEC at *snRNA* genes. p53 induced by UV decreased the occupancy of ICE1 at the Pol II-dependent *snRNA* genes. Moreover, p53 repressed the occupancy of not only Pol II but also ICE1 at *snRNA* gene, resulting in downregulation of Pol II-dependent *snRNA* genes. Taken together, p53 likely decreases the transcription of a subset of Pol II-dependent *snRNA* genes via interaction with ELL.

【Discussion】

Our study suggests that tumor suppresser p53 regulates transcription of Pol II-dependent *snRNA* genes through inhibiting LEC function. *Tp53* has been shown to be mutated or lost in more than 50% cancers. Our study proposes a new model that p53 regulates transcription of *snRNA* genes through inhibiting transcription elongation factors such as ELL/EAF and/or LEC and contributes to a new aspect of p53 function in cancer and diseases which associates with dysregulation of *snRNA* genes transcription.

【Conclusion】

Taken together, p53 regulates transcription of Pol II-dependent *snRNA* genes through inhibiting the function of LEC. *p53* genes has been shown to be mutated or lost in more than 50% cancers. Therefore, our study proposes a new model that p53 regulates transcription of *snRNA* genes through inhibiting transcription elongation factors such as ELL/EAF and/or LEC and may contribute to an understanding of diseases which associates with dysregulation of *snRNA* genes transcription.