

論文 / 著書情報
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種別(和文)	論文要旨
Type(English)	Summary

論文要旨

THESIS SUMMARY

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Department of		
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申請学位 (専攻分野):	博士 (Engineering)
Academic Degree Requested	Doctor of
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要旨 (英文 800 語程度)

Thesis Summary (approx.800 English Words)

Introduction

Osteosarcoma (OS) is the most common malignant bone tumor found in both children and adult. OS often causes lung metastasis that is associated with poor prognosis. Although lung metastasis is a major cause of poor prognosis in OS patients, effective therapeutic strategies have not been developed. In order to investigate new therapeutic targets, murine osteosarcoma LM8 sublines with high-metastatic (LM8-H) and low-metastatic (LM8-L) abilities have been established. Confocal fluorescence imaging of lung tissue revealed that LM8-H had significantly higher extravasation ability into lung parenchyma. In addition, LEF1 was found to be an important transcription factor which promotes lung metastasis of LM8-H. Therefore, identification of LEF1 target genes would reveal the mechanisms of high lung metastasis of LM8-H and may provide new treatment strategies for patients with osteosarcoma.

This thesis is composed of five chapters.

Chapter 1: General introduction

General introduction about the background, the role and purpose of the study were described. It also describes the previous studies that was the basis of this study.

Chapter 2: Identification of CYGB as a downstream effector of LEF1

In this Chapter, the study selecting candidate genes involved in lung metastatic ability of LM8 sublines using genome-wide meta-analysis by combining microarray data of the LM8 sublines with the human OS genomic datasets is described. Previous study revealed that transcription factor LEF1 plays an important role in lung metastasis in the LM8 sublines by promoting extravasation ability of LM8-H cell. To identify downstream effectors of LEF1 that are involved in OS lung metastasis, genome-wide meta-analysis was performed. Among of 13 candidate genes, expression level of Cytoglobin (*Cygb*) is well-correlated with expression of LEF1. Transcription factor binding site prediction suggested that LEF1 can directly bind to the promoter region of *Cygb*. In addition, knockout of *Cygb* in LM8-H significantly increased proliferation rate compared to LM8-H whereas overexpressing of CYGB showed the opposite effect. These results are similar to those obtained when the expression level of LEF1 is reduced and overexpressed, respectively. These results suggested that CYGB is a downstream effector of LEF1.

Chapter 3: Analysis of function of CYGB in the extravasation of LM8 sublines

In this Chapter, functions of CYGB in extravasation ability of the LM8 sublines were investigated. CYGB overexpression in LM8-L subline increased the extravasation ability, whereas knocking out the *Cygb* gene in LM8-H cells reduced this ability. These results demonstrate that CYGB is important for extravasation ability of the LM8 sublines. The molecular mechanism by which CYGB plays a role in extravasation into the lung of the LM8 sublines was investigated based on the known function of CYGB such as the regulation of nitric oxide (NO) level and arachidonic acid (AA) productions. The results suggest that CYGB promotes the extravasation ability of the LM8 sublines by mechanism unrelated to NO regulation and AA production.

Chapter 4: Functions of *Cygb* on lung-metastatic ability of LM8 sublines *in vivo*.

In this Chapter, functions of CYGB in lung metastasis were investigated in syngenic mouse model. Knock-out of *Cygb* in LM8-H cells (LM8-H/*Cygb*-KO) significantly decreased extravasation ability of the LM8-H: number and size of LM8-H/*Cygb*-KO foci in the lung were significantly decreased compared to LM8-H foci at 16 days after cancer cell injection into syngenic C3H mice. In addition, LM8-H/*Cygb*-KO significantly increased number of cancer cells trapped within blood vessel of the lung compared to the LM8-H. These results demonstrated that CYGB is a key factor to regulate extravasation of the LM8 sublines. The results uncovered a novel function of CYGB in OS lung metastasis.

Chapter 5: Conclusion remarks and future perspectives

This chapter summarizes the contents of chapters 2 to 4. Furthermore, the prospect of the future is described that the elucidation of the molecular mechanism by which CYGB promotes extravasation may lead to the development of a drug that suppresses lung metastasis of osteosarcoma.

備考：論文要旨は、和文 2000 字と英文 300 語を 1 部ずつ提出するか、もしくは英文 800 語を 1 部提出してください。

Note: Thesis Summary should be submitted in either a copy of 2000 Japanese Characters and 300 Words (English) or 1 copy of 800 Words (English).

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