論　文　概　要

Thesis Abstract

Thesis title: Role of THG-1-mediated regulation of HIF-1α stability in squamous cell carcinoma

論文題目（THG-1 による HIF-1α 安定性制御の扁平上皮癌における役割）

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目　　的:

Squamous cell carcinoma (SCC) is an epithelial malignancy and show a poor prognosis despite the advances of treatment. Previous results demonstrated that THG-1 (also called TSC22D4) is diffusely and highly expressed in SCCs. Knockdown of THG-1 in TE13 cells (esophageal SCC cell line) reduced cell proliferation, invasion, and tumor formation compared with parental TE13 cells. However, the molecular mechanism of THG-1 functions in tumor is to be determined. In this study we want to investigate the THG-1 molecular function in esophageal squamous cell carcinoma.

対象と方法:

1. The interaction between THG-1 and PHD2 was examined by immunoprecipitation in HEK293T and TE13 cells.
2. The localization of THG-1 and PHD2 was examined by Immunofluorescence staining in HaCaT cells.
3. The HIF-1α stabilization in the presence of THG-1 and PHD2 was examined by western blot analysis in HEK293T cells.
4. The HIF-1α stability in TE13 cells were examined by western blot analysis in 2D and 3D culture condition.

5. The HIF-1α target genes expression were examined by qRT-PCR in 2D and 3D culture condition.

6. The HIF-1α expression in tissue were detected by immunohistochemistry staining.

結　　果:

1. THG-1 physically interacts with PHD2

2. THG-1 regulates HIF-1α by binding with PHD2

3. THG-1 regulates HIF-1α stability in TE13 cells

4. THG-1 increase HIF-1α transcriptional activities

5. THG-1 involved in tumor angiogenesis

考　　察:

In this study, we show that THG-1 functions as a HIF-1α regulator in esophageal squamous cell carcinoma. Oxygen-dependent hydroxylation of HIF-1α by PHD2 is acknowledged degradation pathway that regulates the HIF-1α stability. Our finding is first study that THG-1 interact with PHD2 to protecting HIF-1α from the PHD2-mediated HIF-1α degradation. THG-1 increased levels and transcriptional activities of HIF-1α in TE13 cells under 2D (presence of hypoxic-mimetic agent-$CoCl_2$) and 3D culture condition. Upregulation of HIF-1α target genes involved in cancer progression, invasion, cell survival, glucose metabolism and angiogenesis. It suggest that THG-1 may promote

the tumor growth during regulates HIF-1α. From these finding we can indicate the possibility that small molecule compounds or peptides designed to block the interaction of THG-1 with PHD2 would be a clinical treatment for esophagus squamous cell carcinoma.

結　　論:

THG-1-PHD2 interaction plays a pivotal role in the HIF-1α stabilization and angiogenesis in squamous cell carcinoma development.