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学位の種類	博士（　人間生物学　）
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審査組織	グローバル教育院
学位論文題目	Function of the interaction between THG-1 and NRBP1 in the esophageal squamous cell carcinoma development （扁平上皮癌の進展における THG-1 と NRBP1 の結合の役割）

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論文の要旨
Abstract of thesis

Esophageal cancer is the sixth leading cause of death by cancer, and eighth most frequentform of cancer in the world. Esophageal squamous cell carcinoma is the most common type ofesophageal cancer in Asian countries. Due to the significant development of anti-cancer drugs inrecent years, esophageal squamous cell carcinoma patients could survive longer, however, with apoor prognosis at advanced stages. In addition, it is difficult for esophagus cancer patients to feel thesymptom at early stage because of absence of diagnostic marker, so most of esophageal cancerpatients were diagnosed at advanced stage with a difficulty in swallowing. The partial esophagealresection following radiation therapy or chemoradiotherapy is the main treatment for esophagealcancer, which can result from an inaccurate prognosis and has, approximately, a 10% five-yearsurvival rate due to severe metastasis – with likely recurrence by chemoradioresistant esophagealcancer cells. Therefore, understanding the biological events and molecular mechanisms ofesophageal squamous cell carcinoma development could propose novel molecular targets, effectivetreatments, and cancer prevention for esophageal squamous cell carcinoma patients.

The dissertation thesis written by Mr. Jongchan Hwan revealed the function of THG-1 in the development of esophageal squamous cellcarcinoma cells. THG-1 is localized in the basal layer of stratified squamous epithelium and ubiquitouslyoverexpressed in squamous cell carcinomas (SCC) by

unknown mechanism. Despite understanding the biological roles of THG-1 for a decade, the function of THG-1 in cancer development has notbeen discovered. It is reported that THG-1 deficient esophageal SCC cells showedthe reduction of cell proliferation, anchorage-independentgrowth and cell migration.

To determinethe molecular mechanism how THG-1 functions in the development of esophageal SCC, the applicantinvestigated THG-1 interacting proteins through proteomics approach. The applicant found that THG-1interacts with several factors regulating cell proliferation, metabolism, and response against themicroenvironmental factors including nuclear receptor binding protein 1 (NRBP1).NRBP1 is a multidomain putative adaptor protein and recent studies demonstrated its tumorsuppressive functions such as negative regulation of β-catenin. The applicant therefore investigated thefunction of the interaction between THG-1 and NRBP1 to identify the role of THG-1 intumorigenesis of SCC. This study conveys the role of THG-1 overexpression in the stimulation ofβ-catenin signaling through antagonizing NRBP1. Additionally, this study first discovered themolecular mechanism how NRBP1 downregulates β-catenin protein and its signaling. Theβ-catenintargeting chemotherapy is promising to cure patients from THG-1 overexpressedesophageal SCC.

審査の要旨
Abstract of assessment result

【批評 Review】

This study found that THG-1 promoted cell proliferation, anchorage-independent growth, and cell migration ability through promotion of β-catenin signaling pathway following the interaction of THG-1 with two LXXLL motifs of NRBP1 which is responsible for the recognition of β-catenin. NRBP1 negatively regulates β-cateninthrough the interaction and ubiquitination as a E3 ligase, and THG-1 interrupts NRBP1- β-catenininteraction and rescue β-catenin protein expression, thereby leading to the activation of β-catenintarget genes and promotion of tumorigenic development of cancer cells.Thus, it is highly expected that drugs controlling β-catenin signaling could be efficacious treatments for esophageal SCC and surely have impact in this field.

【最終試験の結果 Result】

The final examination committee conducted a meeting as a final examination on 28 January, 2020. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

【結論 Conclusion】

Therefore, the final examination committee approved that the applicant is qualified to be awarded a Doctor of Philosophy in Human Biology.