論　文　内　容　要　旨

Transcriptional Regulation of VEGFA by the Endoplasmic Reticulum Stress Transducer OASIS in ARPE-19 Cells

（ヒト網膜色素上皮細胞 ARPE-19 における、小胞体ストレス変換分子 OASIS による血管内皮増殖因子 VEGFA の転写制御）

PLoS One, 8: e55155. doi:10.1371/journal.pone.0055155., 2013, in press.

主指導教員：木内　良明教授
（統合健康科学部門 視覚病態学）
副指導教員：近間　泰一郎准教授
（統合健康科学部門 視覚病態学）
副指導教員：今泉　和則教授
（基礎生命科学部門 分子細胞情報学）

宮城　秀考
（医歯薬学総合研究科　創生医科学専攻）

Abstract

Background: Vascular endothelial growth factor-A (VEGFA) is the main mediator of angiogenesis. Angiogenesis plays important roles not only in many physiological processes, but also in the pathophysiology of many diseases. VEGFA is one of the therapeutic targets of treatment for ocular diseases with neovascularization. Therefore, elucidation of the regulatory mechanisms for VEGFA expression is important for the development of pharmaceutical drugs. Recent studies have demonstrated that the unfolded protein response is involved in the transcriptional regulation of VEGFA. However, the precise regulation of VEGFA in the human retina is not fully understood.

Principal Findings: When human retinal pigment epithelial cells, ARPE-19, were exposed to endoplasmic reticulum stressors, VEGFA mRNA was significantly upregulated. The unfolded protein response-related transcription factors XBP1, ATF4, ATF6, and OASIS were expressed in ARPE-19 cells. To determine which transcription factors preferentially contribute to the induction of VEGFA expression after endoplasmic reticulum stress, we carried out reporter assays using an approximately 6-kbp 5'-upstream region of the human VEGFA gene. Among these transcription factors, OASIS acted most effectively on the VEGFA promoter in ARPE-19 cells. Based on data obtained for certain deleted and mutated reporter constructs, we determined that OASIS promoted VEGFA expression by acting on a cyclic AMP-responsive element-like site located at around –500 bp relative to the VEGFA transcription start site. Furthermore, we confirmed that OASIS directly bound to the promoter region containing this site by chromatin immunoprecipitation assays.

Conclusions and Significance: We have demonstrated a novel regulatory mechanism for VEGFA transcription by OASIS in human retinal pigment epithelial cells. Chemical compounds that regulate the binding of OASIS to the promoter region of the VEGFA gene may have potential as therapeutic agents for ocular diseases with neovascularization.