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Thesis Title

A transposon screen identifies enhancement of NF-κB pathway as a mechanism of resistance to eribulin

（トランスポゾンで同定された NF- κB 経路活性化による乳癌のエリブリン耐性メカニズム）

Thesis Summary

Eribulin mesylate (eribulin) is an efficient microtubule inhibitor that is used for patients with metastatic breast cancer. However, breast cancer can develop resistance to eribulin. This resistance mechanism needs to be elucidated. A Transposon Mutagenesis Screen was conducted using a pPB-SB-CMV-puro-SD plasmid and pCMV-PBase transposase. *TAB2*, which is part of the Nuclear factor-κB (NF-κB) pathway, was identified as a candidate eribulin-resistant gene. Using an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay and flow cytometry, we found that *TAB2* down-regulation resulted in significantly lower cell viability and higher cytotoxicity of cells treated with eribulin, while *TAB2* up-regulation showed opposite results. Similarly, combination of NF-κB inhibitors (BAY-117082 and QNZ [quinazoline derivative]) with eribulin showed significantly lower cell viability and higher drug cytotoxicity than single agent treatment with eribulin. QNZ induced similar effects when combined with TAB2 up-regulation in MCF7 cells. Furthermore, combination of BAY-117082 with eribulin induced greater regression of MDA-MB-231 tumors compared to eribulin monotherapy *in vivo*. Collectively, these results consistently illustrated that the NF-κB pathway increases resistance to eribulin in breast cancer models. Moreover, these results support the use of a combination strategy of eribulin with NF-κB inhibitors, and provide evidence that Transposon Mutagenesis Screens are capable of identifying drug-resistant genes.