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その他のタイトル	子宮体癌と卵巣癌において抗アポトーシスタンパクを制御する新規分子標的治療薬の探索
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博士論文（要約）

Exploring novel molecularly-targeted therapies which modulate anti-apoptotic proteins in endometrial and ovarian cancers

（子宮体癌と卵巣癌において抗アポトーシスタンパクを制御する新規分子標的治療薬の探索）

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This study was performed to explore novel molecularly- targeted therapeutic options which could modulate antiapoptotic proteins in endometrial and ovarian carcinomas. The incidence of endometrial carcinoma is rising in most parts of the world, and mortality rates due to ovarian carcinoma are still unacceptably high. The study focused on "survivin", an antiapoptotic protein and a member of IAP (inhibitor of apoptosis) family which is highly expressed in most of the human cancers, but almost completely undetectable in normal terminally differentiated cells.

To investigate the role of survivin in apoptosis-based therapies for endometrial and ovarian carcinomas, the prognostic significance of the expression of a survivin gene-*BIRC5* was evaluated in endometrial carcinoma clinical samples. A panel of sixteen endometrial cancer cell lines and ten ovarian cancer cell lines derived from different histology were analyzed. Cells were either untreated or treated with a survivin suppressant- Y155 (sepantronium bromide), kaempferol (natural dietary flavonoid) or celecoxib (COX-2 inhibitor), and antitumor effect were analyzed. At some point, hormone-receptor positive Ishikawa and HEC-265 endometrial cancer cell lines were treated with estradiol before analysis to gain insight of its role in ERα (estrogen receptor-alpha)/ survivin signaling.

In this study, the following results were observed;

Higher expression levels of *BIRC5* gene were associated with poor progression-free survival (PFS) (p= 0.006) and showed a strong tendency towards poor overall survival (OS) (p= 0.06) as evaluated by Kaplan-Meier survival analysis and a log-rank test. A multivariate analysis showed that high expression of *BIRC5* gene is an independent poor prognostic factor in endometrial carcinoma (HR= 1.97, 95% CI = 1.29–4.5, p= 0.045). Survivin protein was highly upregulated in over 87% of endometrial carcinoma cell lines. Survivin suppressant-YM155 successfully suppressed the growth of all analyzed endometrial carcinoma cell lines at IC_{50} values ranging from 14nM to 150nM. YM155 also induced significantly sub-G1 cell population (p< 0.001) and apoptotic cell death (p< 0.001). Further evaluation revealed that YM155 suppresses survivin, induces cleaved caspase-7 and cleaved PARP (poly (ADP-ribose) polymerase). Knockdown of *BIRC5* gene by siRNAs caused similar effects. Kaempferol suppressed the growth Ishikawa and HEC-265 endometrial carcinoma cell lines at IC_{50} values of 83μM and 65μM respectively. It also induced sub-G1 and G2/M cell populations in a cell cycle (p< 0.05) and apoptosis (p<0.001). Estradiol induced nuclear co-expression of ERα and survivin, an effect which was inhibited by kaempferol. Kaempferol also suppressed survivin and Bcl-2, and induced p53 and induction of cleaved PARP. Celecoxib

suppressed growth of ovarian carcinoma cells at IC_{50} values ranging from 17μM to 45μM, induced sub-G1 ($p< 0.01$), suppressed the expression of survivin and significantly induced an apoptotic cell death in all ten analyzed cell lines ($p< 0.01$).

In conclusion, this study has found for the very first time that high expression level of survivin gene-*BIRC5* may be a potential biomarker for poor prognosis in endometrial carcinoma. It has also demonstrated novel antitumor mechanisms of kaempferol and celecoxib through suppression of survivin in endometrial and ovarian carcinomas respectively. Unlike other apoptosis-based therapies, survivin-targeting therapies may offer additional advantages by antagonizing multiple cellular signaling networks and providing more favorable toxicity profile since it does not affect normal cells or tissues.