

論文の内容の要旨

Dissertation Abstract

論文題目

Dissertation Title

Study on the antitumor effect of EGCG and ATRA on gastrointestinal stromal tumor cells and the potential therapeutic effect of PKC412 on leukemia cells harboring ETV6-NTRK3 fusion

(EGCG と ATRA の胃腸管間質性腫瘍に対する抗腫瘍効果と ETV6-NTRK3 融合遺伝子を持つ白血病細胞に対する PKC412 の治療剤としての可能性についての研究)

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Dysregulated protein tyrosine kinase (PTKs) activity is well-known as the most common events which contribute to direct or indirect development of cancers. The abnormally activated PTKs could be the results of chromosomal translocations or frequent occurrence of mutations leading to constitutive activation of PTKs. The mechanism of PTK activation could also be a result of increased expression of a receptor tyrosine kinase, its ligand, or both. Aberrant PTK activation can increase the survival, proliferation, and cytotoxic drug resistance of malignant cells, and in tumors it can increase angiogenesis, invasiveness, and metastatic potential. Blocking of constitutive activation of PTKs by small molecular inhibitors has been shown as an excellent strategy for cancer treatment. The prominent example of such targeted therapy is imatinib-mesylate, an inhibitor of the BCR-ABL fusion gene that is found in more than 95% of patients with Philadelphia positive (Ph+) chronic myeloid leukemia (CML) and in 20-30% of those with Ph+ acute lymphoblastic leukemia (ALL). The excellent clinical results obtained with imatinib in CML have completely changed the therapeutic approach to this disease. However, an unavoidable problem involving using imatinib as for other tyrosine kinase inhibitors is the resistance to inhibitor treatments. Therefore, finding other strategies for improving cancer treatment and/or overcoming inhibitor-resistance is of interest to investigators.

In this study, the first part, I evaluated the antitumor effect of EGCG and ATRA on gastrointestinal stromal tumor (GISTs) cells. EGCG and ATRA have been demonstrated to induce antitumor effects on many types of cancers. However, the effects of EGCG and ATRA on GISTs have not been investigated. The second part, I report that PKC412 could be a potential therapeutic reagent for treatment of leukemia patients expressing a fusion gene, *ETV6-NTRK3*.

Part 1: the antitumor effect of EGCG and ATRA on gastrointestinal stromal tumor cells.

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms occurring throughout the entire region of the gastrointestinal tract and are considered to originate from intestinal cells of Cajal, the pacemaker cells of the gut. The most likely causative oncogenic molecular event in the vast majority of GISTs is an activating mutation of *KIT* or *PDGFRA* which activates these receptor tyrosine kinases (RTKs) by rendering them constitutive phosphorylation. Thereafter, the downstream signaling pathways are activated and promote cell proliferation and/or survival. Imatinib, a selective tyrosine kinase inhibitor, has been used as a standard first-line therapy for

gastrointestinal stromal tumor (GIST) patients. Unfortunately, most patients responding to imatinib will eventually exhibit the resistance mechanisms of which are not fully understood. The serious clinical problems of imatinib-resistance require alternative treatment strategy. (-)-Epigallocatechin-3-gallate (EGCG), a main component of green tea catechin, and all-*trans* retinoic acid (ATRA) have been demonstrated potential anti-tumor effects on many types of cancer cells. Here, I report for the first time that EGCG and ATRA have shown antitumor effects on gastrointestinal stromal tumor (GIST) cells by suppressing cell proliferation and eventually causing cell death. Moreover, GIST cells treated with ATRA and EGCG showed the suppression of KIT activity and its downstream signaling pathways. The suppression of KIT activity by EGCG and ATRA could be one of molecular events for causing cell death. However, the mechanisms of this suppression are unknown. The results suggest that EGCG and ATRA could be used as novel therapeutic or preventive reagents in GISTs.

Part 2: the potential therapeutic effect of PKC412 on leukemia cells harboring ETV6-NTRK3 fusion

The ETV6-NTRK3 (EN) fusion gene which encodes a chimeric tyrosine kinase was first identified by cloning of the t(12;15)(p13;q25) translocation found in congenital fibrosarcoma (CFS). Since then, EN has also been found in congenital mesoblastic nephroma (CMN), secretory breast carcinoma (SBC) and acute myelogenous leukemia (AML). EN is an interesting oncoprotein, being demonstrated to be associated with various types of cancer. However, effective therapy for EN associated tumors has not yet been established. Currently, kinases have become one of the most intensively pursued classes of drug target with approximately 30 distinct kinase targets being developed to the level of a Phase I clinical trial. Of note, the vast majority of these targets are being investigated for the treatment of cancers. The deregulation of kinase functions seems to be a cause or consequence of a disease. And nearly every signal transduction process is wired through a phosphotransfer cascade, suggesting that inhibition of kinase activity elicits a real physiological response. Interestingly, inhibition of kinase activity in normal cells can often be tolerated, presenting a therapeutic window for the selective killing of tumor cells. This has generated considerable interest in the development of small molecule kinase inhibitors for the treatment of diseases. Recently, Tognon CE, et al., reported that targeting the IGF1R signaling pathway could block the EN-mediated breast epithelial cell transformation. However, there are no studies focusing on specific inhibitors of EN. Since EN could transform Ba/F3 and NIH3T3 cells, I hypothesize that specifically blocking EN activity by small molecule kinase inhibitors could induce cell death in cells expressing EN.