Abstracts

Basic and clinical interface in targeted cancer therapy

Screening of bioactive metabolites that inhibit cancer growth and natural immune reactions
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Microbial and plant-derived bioactive metabolites are a treasury of organic compounds having various structures and biological activities. We have previously isolated signal transduction inhibitors such as protein-tyrosine kinase inhibitors, protein-tyrosine phosphatase inhibitors, anti-Ras compounds, phospholipase C inhibitors, and pancreatic beta-cell inducers from microorganisms and plants. Recently we are more interested in inhibitors of transcription factors that are involved in the etiology of diseases. Especially, NF-kB appears strongly involved in natural immune reactions by macrophages. Excess macrophage activation may enhance cancer growth. Therefore, we looked for NF-kB inhibitors from nature, and examined their anti-inflammatory and anticancer activities. We have designed dehydroxyethylpropynoquinomicin (DHMEQ) based on the structure of epoxyquinomicins. DHMEQ inhibited the constitutively activated NF-kB in various neoplastic cells. DHMEQ inhibited the secretion of inflammatory cytokines from cancer cells and macrophages. DHMEQ inhibited the growth of carcinoma and leukemia cells in vivo in which NF-kB is constitutively activated. It effectively suppressed prostate carcinoma, thyroid carcinoma, breast carcinoma, pancreatic carcinoma, multiple myeloma, and adult T-cell leukemia in nude or SCID mice without any side effect. It is likely that the anticancer activities are due to the suppression of inflammatory reactions in tumor tissues, since its cytotoxicity is comparatively weak. Recently, we found that DHMEQ directly binds to p65 to inhibit the NF-kB functions by SPR and MALDI-TOF-MS analyses. DHMEQ is a very specific inhibitor of NF-kB, and its toxicity is low. It is now being developed as an anticancer and anti-inflammatory agent. We have also isolated 9-methylstreptimidone from microorganisms as NF-kB inhibitors. 9-Methylstreptimidone was shown to induce apoptosis selectively in adult T-cell leukemia cells. Lipopolysaccharide (LPS) is located on the surface of Gram negative bacteria, and involved in the pathogenesis of various inflammatory syndromes. LPS activates NF-kB through the cell surface receptor, TLR-4. We then looked for the compounds that inactivate LPS functions, and we isolated a novel cyclic depsipeptide, which we named heptadepsin, from the culture filtrate of Paenibacillus. Heptadepsin was shown to directly bind to lipid A, a component of LPS. Thus, these immune modulators of low molecular weight may be useful as the chemical ligands to study the mechanism of diseases and also as the seeds for chemotherapeutic agents.

Application of Biological Imaging for Radiotherapy
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Background: 11C-PD153035, a specific and potent inhibitor of EGFR tyrosine kinase, has been developed for positron emission tomography (PET) imaging of EGFR. Preclinical studies suggest that it was promising in NSCLC. We report a pilot study evaluating the feasibility and utility of 11C-PD153035 PET/CT imaging in NSCLC.

Methods: Eleven patients with pathologically proved NSCLC were enrolled. Ten of these cases underwent 11C-PD153035 PET/CT one week before surgery. The other one who had post-operative recurrence at the T9 vertebra had received EGFR-targeted therapy (gefitinib) 10 days prior to PET/CT scan. After intravenous injection 384.5±105.7MBq of 11C-PD153035, whole body CT and PET scan from skull to pelvic cavity were executed. Image fusion and calculation of tumor subvolumes was performed on Xeleris workstation. Radioactivity concentrations, derived from regions of interest, were analyzed mathematically to tumor/normal ratio and standardized uptake value (SUV). Immunohistochemistry (IHC) of surgical specimen was utilized to confirm EGFR expression and the intensity was scored using a three-tier system.

Results: The tracer showed rapid blood clearance, both hepatobiliary and renal excretion. Image fusion of PET with CT was feasible in all cases. Tumor uptake of 11C-PD153035 was observed in 7 patients and SUVs ranged from 2.7 to 5.9(3.9±1.1). There was significant difference in 11C-PD153035 uptake and SUVs (p<0.01) between tumor and normal tissue. Tumor/blood and tumor/lung ratio at 20 min were 2.45±1.08 and 4.21±1.90, respectively. The SUV didn’t correlate with tumor size or histological type in our limited data. Tumors with 11C-PD153035 uptake were confirmed EGFR expression by IHC and the SUVs also correlated with IHC scores(r=0.87, p=0.011). The other 3 patients without 11C-PD153035 uptake had negative or tiny EGFR expression. The patient with gefitinib administration presented a negative PET image although the section demonstrated high expression of EGFR.

Conclusion: Our data indicate that 11C-PD153035 is a novel PET radiotracer and 11C-PD153035 PET/CT is a promising method for in vivo imaging of EGFR in NSCLC. This technique may play a vital role for non-invasive assessment of EGFR expression and determine the efficacy of EGFR-targeted therapy.