Noninvasive Diagnosis and Quantitation of Multi-drug Resistance by PET

Development of [11]C-Colchicine for the Noninvasive Diagnosis and Quantitation of Multi-drug Resistance by Positron Emission Tomography

Tumor multiple drug resistance (MDR) is defined as the property of cancer cells to resist the action of a large variety of chemically and functionally unrelated substances, including but not limited to chemotherapeutic drugs. MDR has been explained by a variety of mechanisms, the most studied of which is overexpression of P-glycoprotein (P-gp). P-gp is the 170-kDa, 1280-amino acid product of the mdr1 gene normally found on the long arm of chromosome 7 (near 7q21.1) and is classified as a member of the ATP-binding cassette (ABC) superfamily of transmembrane transporters. Early diagnosis of MDR in the clinic would improve the efficacy of chemotherapeutic intervention and quality of life for patients.

In this project, we are developing a new positron-emitting MDR tracer [11C]-colchicine ([11C]-CHC). Unlike the existing MDR tracers, such as [99mTc]-Sestamibi, this compound is electroneutral, and its biodistribution, therefore, is not affected by perturbations of membrane potential. Dynamic PET imaging of [11C]-CHC has been performed with nude rats xenografted with CHC-sensitive and CHC-resistant strains of human neuroblastoma. [11C]-CHC scans were accompanied by a transmission scan and a static [18F]-FDG scan for improved image localization of the tumors.

A new mathematical model was developed to analyze the *in vitro* biodistribution of [11C]-CHC in a series of increasingly CHC-resistant clones of the human neuroblastoma BE(2)-C cell line. A 2-fold difference between [11C]-CHC accumulation in sensitive and resistant tumors was observed. A model-derived parameter, r, shown to be proportional to the level of CHC resistance of the tumors, was evaluated. The sensitive-to-resistant tumor ratio of the parameter r determined by PET *in vivo* was identical to the ratio of CHC accumulation in the corresponding sensitive and resistant cell lines *in vitro* usec for xenografts.

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