S13-4 Discovery and development of isozyme-selective inhibitors

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Pyripyropene A (PPA) was isolated from a fungal culture broth as a potent inhibitor of acyl-CoA: cholesterol acyltransferase (ACAT). ACAT is responsible for cholesterol absorption from the intestine, lipoprotein production in the liver and macrophage-derived foam cell formation in the artery. Therefore, it has been regarded as an ideal target of atherosclerosis. A number of synthetic inhibitors, in fact, have been reported, but none has been clinically used so far. In 1990s, two genes for ACAT were cloned. ACAT1 isozyme is ubiquitously expressed, while ACAT2 isozyme is expressed exclusively in the small intestine and liver. Accordingly, it became important to understand the selectivity of inhibitors toward the isozymes. For this, we introduced a cell-based assay using ACAT1- or ACAT2-expressing mammalian cells, and evaluated the selectivity of ACAT inhibitors we have discovered. As a result, pyripyropenes were the only ACAT2-selestive inhibitors, and in particular PPA showed the highest selectivity. Therefore, efficacy of PPA in an atherogenic mouse model was investigated. During the oral administration (10-50 mg/kg/day) of PPA, plasma cholesterol levels decreased in a dose-dependent manner. After 12 weeks, the atherosclerotic lesions in the aortas and hearts decreased significantly (40-50% inhibition). Thus, we first demonstrated the *in vivo* efficacy of the ACAT2 inhibitor in an atherogenic mouse model. We expect further developmental study of PPA as a lead for antiatherosclerotic agents.