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Cytochrome P450 3A4 enzyme is responsible for the metabolic activation and inactivation of the majority of clinically used drugs in human liver and intestines. Recently it was reported that inflammatory stimuli cause changes in the activities and expression levels of various forms of P450. Here, we have shown the effects of ceramide on cytochrome P450 3A4 expression in human colon carcinoma HT-29 cells. Tumor necrosis factor (TNF)- $\alpha$ , which is known to produce ceramide in cells, blocked the synthesis of P450 3A4. Treatment with synthetic C6-ceramide or bacterial sphingomyelinase (SMase) also strongly suppressed expression of human P450 3A4 in concentration and time-dependent manner. To test the possibilities of cross-talk between inducible nitric oxide synthase (iNOS) and P450 3A4, the effect of nitric oxide on P450 3A4 expression was determined. Interestingly, we found that N<sup>G</sup>-monomethyl-L-arginine (L-NMMA), a competitive inhibitor of NOS, was able to protect ceramide-dependent suppression of P450 3A4. In contrast, the addition of S-nitroso-N-acetylpenicillamine (SNAP), a NO donor, to HT-29 cells reduced P450 3A4 expression. The addition of iNOS antisense oligonucleotide prevented ceramide-induced iNOS expression, and restored P450 3A4 expression. Our results demonstrate that ceramide is a mediator of P450 3A4 suppression by TNF- $\alpha$ , and increased NO from iNOS induction by ceramide signaling may modulate P450 3A4 expression in cells.

[OC-2] [ 04/20/2001 (Fri) 14:15 - 14:30 / Room 2 ]

### Silibinin enhances C/EBP $\alpha$ and PPAR $\gamma$ expression and induces differentiation of 3T3-L1 preadipocytes

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The effects of silibinin, an active flavonoid of milk thistle, on the adipocyte differentiation were studied in a 3T3-L1 adipocyte model in vitro. Silibinin was found to stimulate differentiation of 3T3-L1 cells in a dose-dependent manner. Silibinin also induced the intracellular levels of CCAAT enhancer binding protein(C/EBP) $\alpha$  and peroxisome proliferator activated receptor(PPAR) $\gamma$  in a dose-dependent manner, as demonstrated by RT-PCR and immunoblots analysis. In the transfection experiments, silibinin induced PPAR $\gamma$ 2 promoter activation in 3T3-L1 preadipocytic cells transiently cotransfected with a C/EBP $\alpha$  expression vector. During adipogenesis in culture, silibinin also induced the expression of several genes that are known to turn on during adipocytic differentiation, such as ap2, Adn, IRS-1 and GLUT4. Furthermore, gel shift assays revealed that silibinin decreased NF- $\kappa$ B-DNA binding and enhanced PPRE-DNA binding. Taken together, these results suggest that silibinin enhances adipocyte differentiation through the specific induction of C/EBP $\alpha$  and PPAR $\gamma$ .

[OC-3] [ 04/20/2001 (Fri) 14:30 - 14:45 / Room 2 ]

### Compound A6792-2 inhibits preferentially the mycelial phase of *Candida albicans*

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*Candida albicans* is an opportunistic pathogen of humans which shows either yeast-like form or pseudomycelium form in response to different environmental conditions, and the switch from a yeast-like form to a filamentous form often correlates with pathogenicity. Fungal pathogens such as *C.*