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### ADIPOCYTE VIABILITY AND FUNCTION BUT NOT INHIBITION OF PREADIPOCYTE DIFFERENTIATION IS COMPROMISED BY INDINAVIR

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**OBJECTIVE:** Atrophy of peripheral subcutaneous adipose tissue is a common side effect observed in many HIVinfected patients treated with combination antiretroviral therapy. Several HIV protease inhibitors were found either to inhibit preadipocyte differentiation or to promote adipocyte cell death. We aimed to investigate the effects of HIV protease inhibitor indinavir (IDV) on adipogenesis and adipocyte survival using the 3T3-L1 preadipocyte cell line.

**METHODS:** Transcription profiles of lipoprotein lipase (LPL), the adipogenic transcription factors CCAAT/ enhancer-binding protein  $\alpha$ , CCAAT/enhancer-binding protein  $\beta$  and peroxisome proliferator-activated receptor  $\gamma$  as well as neuronal apoptosis inhibitor protein and adiponectin were investigated using real-time PCR. Adiponectin production was also determined by ELISA. Cytoplasmic triacylglycerol accumulation was measured using Oil Red O staining. Cell death apoptosis/necrosis was assessed with Hoechst/propidium iodide staining and trypan blue exclusion.

**RESULTS:** When induced to differentiate in the presence of IDV (up to 100  $\mu$ M), 3T3-L1 preadipocytes accumulated normal levels of cytoplasmic triacylglycerol. In addition, they expressed normal levels of LPL, the adipogenic transcription factors CCAAT/enhancer-binding protein  $\alpha$ , CCAAT/enhancer-binding protein  $\beta$  and peroxisome proliferator-activated receptor  $\gamma$ . We were unable to find any inhibitory effect of IDV on critical early events in preadipocyte differentiation and completion of the mitotic clonal expansion phase. Adipocyte function, however, was impaired by IDV as judged by the expression of adiponectin. IDV treatment of fully differentiated 3T3-L1 adipocytes resulted in loss of cell viability and decreased expression of neuronal

apoptosis inhibitor protein (NAIP). In contrast, cell proliferation and viability of preadipocytes were unaffected by IDV treatment.

**CONCLUSIONS:** Molecular or cellular changes that occur during acquisition of the adipocyte phenotype promote susceptibility to IDV-induced cell death. We provide evidence for a direct inhibition of adiponectin production by IDV. These results suggest that IDV may promote adipose tissue atrophy by directly compromising adipocyte function and not by inhibition of preadipocyte differentiation.

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