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THE HIV-PROTEASE INHIBITOR INDINAVIR IMPAIRS ADIPOCYTE DIFFERENTIATION AND INDUCES INSULIN RESISTANCE BY PROBABLY ALTERING ADD1/SREBP-1 MATURATION

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BACKGROUND: HIV-protease inhibitors (PIs), causally associated with lipodystrophy and insulin resistance, were shown to alter adipocyte differentiation of cultured cells.

OBJECTIVES: To delineate the mechanism whereby indinavir altered adipocyte function, we studied its effect on cell differentiation and responsiveness to insulin in 3T3-F442A pre-adipocytes.

DESIGN: 3T3-F442A pre-adipocytes were cultured and differentiated by fetal calf serum and insulin in the absence or presence of indinavir. The differentiation markers ADD1/SREBP-1, PPAR- γ and insulin receptors were evaluated by Western blotting. Cellular localization of immunoreactive ADD1/SREBP-1 and PPAR- γ was checked by confocal microscopy. Cell sensitivity to insulin was tested by IRS1 tyrosine phosphorylation and MAP kinase activation.

RESULTS: In pre-adipocytes indinavir did not alter cell growth and insulin responsiveness. In addition, the drug did not impair the initial step of cell differentiation, in other words clonal proliferation. However, indinavir inhibited adipose conversion by 50-60%, as shown by: (1) the decreased number of newly formed adipocytes; (2) the lower level of the adipogenic markers, ADD1/SREBP-1, PPAR- γ and insulin receptors; and (3) the absence of the transcription factors ADD1/SREBP-1 and PPAR- γ inside the nucleus of most treated cells. Partial loss of adipose conversion correlated with a defective SREBP-1 maturation, as evidenced by the increased expression of a partially-

processed SREBP-1 fragment and SREBP-1 accumulation at the nuclear periphery. Moreover, indinavir rendered the adipocytes which succeeded or not into differentiation, resistant to insulin for MAP kinase activation at a step distal to IRS-1 tyrosine phosphorylation.

CONCLUSIONS: Indinavir impaired adipocyte differentiation at an early step of adipose conversion probably involving the proteolytic maturation of SREBP-1, a major transcription factor controlling adipocyte differentiation and cell response to insulin. Our findings provide a possible explanation for the mechanism of subcutaneous cellular fat loss in PI-associated lipodystrophy.

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