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## INDINAVIR-INDUCED NUCLEAR LAMINA ALTERATIONS ARE CORRELATED WITH ADIPOCYTE DYSFUNCTIONS IN CULTURED ADIPOCYTES

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**OBJECTIVES:** Adipose cells have been identified as a major target of protease inhibitors (PIs) both *in vivo* and *in vitro*. We have previously observed that the adverse effects of indinavir on 3T3-F442A adipocyte differentiation and response to insulin could be related to the altered expression and nuclear localization of the transcription factor sterol regulatory element-binding protein-1 (SREBP-1). To gain further insights into the mechanism by which indinavir altered adipose cell functions, we tested the implication of lamin A/C, a protein of the lamina network mutated in a severe monogenic form of insulin-resistant lipodystrophy (the Dunnigan-type familial partial lipodystrophy, FPLD) that shows similarities with antiretroviral treatment-related lipodystrophy. We investigated whether indinavir could alter the nuclear lamina structure and maturation in 3T3-F442A adipocytes.

**METHODS:** Nuclear organization was assessed by conventional and confocal microscopy after dapi staining and lamin A/C and B immuno-labelling. Lamin A/C maturation was investigated by western blot using antibodies against the premature and mature forms of lamin A/C. Lamina fragilization was assessed by western blot after sequential extractions of nuclear fractions with detergent and salt. SREBP-1 cellular distribution was studied by confocal microscopy and western blot.

**RESULTS:** Chronic exposure of 3T3-F442A adipocytes to a clinically relevant concentration of indinavir (15  $\mu$ M) partly impaired SREBP-1 nuclear penetration as shown by immunofluorescence and sequential cell fractionation. Ten percent of PI-treated adipocytes had dysmorphic nuclei that could not accumulate SREBP-1 and presented an altered distribution of lamin A/C and lamin B. Indinavir inhibited prelamin

A maturation. Most of the nuclei of indinavir-treated adipocytes were abnormally fragilized, as shown by the extractibility of lamin A/C and B by low salt solutions. Nuclear alterations correlated with the ability of indinavir to decrease adipose cell conversion, as shown by lipid staining and protein expression of the transcription factors SREBP-1, PPAR $\gamma$  and C/EBP $\alpha$ , and to promote insulin resistance and apoptosis.

**CONCLUSIONS:** These results indicated that indinavir impaired lamin A/C maturation, induced nuclear lamina disorganization and fragilization, together with adipocyte dysfunctions. This strongly suggests the existence of a causal relationship between indinavir-induced defective lamin A/C processing, disruption of nuclear architecture and altered adipose cell functions.

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