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Role of FAP48 in HIV-associated lipodystrophy

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The introduction of highly active antiretroviral therapies (HAART) has significantly changed the clinical course of HIV disease, with prolonged survival and better quality of life for HIV infected patients. However, this successful therapeutic advance has been partially marked by the development of serious long-term side effects including metabolic alterations, cardiovascular disease, kidney impairment, bone alterations and adipose tissue redistribution. This last phenomenon is currently indicated as HIV related lipodystrophy (Barbaro, 2006). Even if some studies suggested an independent role for HIV in the development of lipodystrophic phenotype, there is a widely accepted consensus that the risk to develop fat redistribution in HIV patients has to be mostly related to antiretroviral therapy.

In order to investigate new pathways involved in the development of lipodystrophy, our group performed an array screening using two identical filter arrays with cDNA-labeled probes, generated from the adipose tissue of either HIV patients affected or not affected by lipodystrophy. Among the genes selected, we focused our attention on a recently described 48 kDa protein of 417 amino acids named FAP48. Our results suggest, using 3T3-L1-FAP48 stable clone, that FAP48 over-expression results in rapid NFAT dephosphorilatyon by activating CaN and in the increase of aP2 gene transcription, a gene expressed at the last phase of the adipocyte differentiation. These data support the role of Fap48 in the activation of adipocyte differentiation through a pathway involving NFAT.

Moreover we evaluated the expression of PPARγ and aP2 in 3T3-L1 FAP48pcDNA stably transfected cells treated with five antiretroviral drugs (Indinavir, Amprenavir, Efavirenz, Stavudine and Saquinavir), belonging to the three main classes of anti-HIV drugs, that were able, in our experimental model, to affect adipocyte differentiation (Esposito et al., 2009). We observed that cells treated with Saquinavir and Efavirenz, using 3T3-L1-FAP48 stable clone, are characterized by an increased expression of PPARγ and aP2, during the 6 day time course, compared with the control cells. This evidence supports the hypothesis of a protective mechanism, that in 3T3L1 cells could counteract the toxicity of Efavirenz and Saquinavir or could be activated in presence of these drugs. Drawing from our experimental results it can be then postulated that this mechanism could work trough FAP48/ FBP52/Hsp90 pathway, suggesting this complex as a potential target for novel therapeutic approaches to the HAART related lipodystrophy in patients treated with regimen including Efavirenz and Saquinavir.

References

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