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Preserved cytochrome c oxidase activity despite mitochondrial DNA depletion in adipose tissue of HIV-infected patients with lipodystrophy

MJ Kim^{1,2}, C Jardel¹, C Barthélémy¹, V Jan^{2,3}, J-P Bastard^{2,3}, S Chapin¹, S Houry⁴, P Levan⁵, J Capeau^{2,3} and A Lombès¹

¹INSERM 582, Institut de Myologie, Biochimie B, Hôpital de La Salpêtrière, AP-HP, Université Paris VI, Paris, France; ²INSERM 680, Faculté de Médecine Saint-Antoine, Université Paris VI, Paris, France; ³Service de Biochimie et Hormonologie, Hôpital Tenon, AP-HP, Paris; ⁴Service de Chirurgie Viscérale, Hôpital Tenon, AP-HP, Paris, France; ⁵Service de Chirurgie Plastique, Hôpital Rothschild, AP-HP, Paris, France

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OBJECTIVES: To evaluate the mechanisms of mitochondrial toxicity in subcutaneous adipose tissue from patients with lipodystrophy.

METHODS: Samples of abdominal subcutaneous adipose tissue from 15 HIV-infected patients with severe facial lipodystrophy were compared with 15 age- and body mass index-matched controls in a cross-sectional analysis. DNA and RNA analyses used PCR-based techniques. Mitochondrial proteins and activities were evaluated with ELISA and spectrophotometric assays respectively.

RESULTS: Mitochondrial DNA (mtDNA) was depleted but did not harbour qualitative alterations such as multiple deletions and point mutation. Severe decrease of the mtDNA-encoded COX2 respiratory chain subunit mRNA contrasted with significant increase of the nuclear DNA-encoded COX4 subunit mRNA, the latter suggesting upregulation of mitochondrial biogenesis. However transcription factors involved in mitochondrial biogenesis were not increased (mtTFA, NRF1 and NRF2) or even significantly decreased (PGC1a). At the protein level, mitochondrial proliferation was demonstrated by increase of the COX4 protein and of two mitochondrial activities (citrate synthase and malate dehydrogenase). It was associated with normal amount of the mtDNA-encoded COX2 protein and normal mtDNA-dependent cytochrome c oxidase activity.

CONCLUSIONS: Despite severe mtDNA depletion, mitochondrial function and proteins depending on the mtDNA are preserved in the patients' adipose tissue. This is associated with mitochondrial proliferation, the mechanism of which remains to be clarified as it was not explained by upregulation of transcription factors usually involved in mitochondrial biogenesis. Alteration of transcriptional regulation of mitochondrial biogenesis was related to that of adipogenesis and to metabolic parameters supporting a complex role for mitochondria dysfunction in lipodystrophy.



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