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New role of oxysterols as regulators of adipogenic differentation in adipose-derived mesenchymal stem cells

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Growing evidence indicates that adipose tissue (AT) represents a potential source of pluripotent mesenchymal stem cells. However, the mechanisms underlying the lineage-specific commitment of human adipose-derived stem cells (ASC) remain still not fully elucidated. Oxysterols are cholesterol oxide products resulting from non-enzymatic (ie, 7-Ketocolesterol) or enzymatic (ie, 5,6-Secosterol) oxidation of cholesterol, which are now emerging as reliable markers of adipose "oxidative stress" in vivo. Recent data suggest that, by regulating the adipogenic differentiation of ASC, lipid peroxidation products may play an important role in linking the adipose dysfunction with impairment of glucose homeostasis. In this study we combined a lipidomic approach with the subcutaneous (sc) microdialysis technique to characterize the adipose-derived profile of fatty acids (FA) and oxysterols in vivo. ASC were isolated from abdominal sc, mesemteric (MES) and omental (OM) fat specimens obtained from obese nondiabetic (OB) and type 2 diabetic (OBT2D) patients. Flow cytometry (FC) was used for the evaluation of cell viability, mitochondrial status and cell immunophenotyping. In AT interstitial fluid, abundant concentrations of oxysterols (7κC and 5,6-S) and fatty acids (lipokines) were found. Experimental challenging with 7κC and 5,6-S showed a different time-dose-response effect. Indeed, the MTT assay, we found that in ASC isolated from the sc depot 5,6-S (50 and 10μM) reduced cell viability after 24, 48 and 72 h, respectively. In contrast, in the same cell-type population, the effect of 7κC at 10μM was observed only after 72 h. FC analysis indicated a similar effect of both oxysterols even after short-time exposure either in ASC from the MES or the OM fat depot. Notably, cell challenge with 7κC and 5,6-S at 10, 5 and 1 μM, respectively, was accompanied by an impairment of mitochondrial status only in OM, but not in MES. Furthermore, both the oxysterols (10μM) downregulated the expression of stemness surface markers suggesting a different "susceptibility" of the ASC to lipid peroxidation cell damage. Accordingly, 7κC at 10 and 1μM impaired the adipogenic differentiation of sc and OM ASC isolated from either OB or T2DOB, and demodulated the mitochondrial activity of the differentiated adipocytes. Altogether, our results suggest human AT as a critical compartment for storage and secretion of lipokines and oxysterols, which, when in excess, appear to detrimentally modulate the mitochondrial activity and the adipogenic differentiation of adipose precursor cells.

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