HYPOTHESIS: AN ECTOPIC SYNTHESIS OF THE MELANIN IN ADIPOSE MAY HELP TO COUNTERACT METABOLIC SYNDROME

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Melanin is a common cutaneous pigment in animals. In our previous high-throughput microarray study of visceral adipose tissue of morbidly obese patients we detected a statistically significant over-expression of melanogenic genes encoding tyrosinase related protein 1 (TYRP1), dopachrome tautomerase (DCT/TYRP2), melanosome transport protein RAB27a and Melan-A (MLANA). Those findings prompted us to hypothesize that the melanin biosynthesis pathway is functional in adipose tissue and is excessively stimulated in morbidly obese patients.

Recently, we demonstrated the presence of the melanin in human adipose tissue both by Fontana-Masson staining and by permanganate degradation of melanin coupled with LC/UV/MS determination of its PTCA derivative. A measurement of the total melanogenic activity using the L-[U-14 C] tyrosine assay showed its marked heterogeneity in individual adipose tissue extracts. According to our observations, melanogenesis is excessively stimulated in morbidly obese patients. We hypothesize that the ectopic synthesis of melanin in obese adipose may serve as a compensatory mechanism that utilizes its anti-inflammatory and its oxidative damage absorbing properties. With the progression of obesity and an increase of the cellular fat deposition, adipocytes become more exposed to endogenous apoptotic signals, especially ROS. To counteract pro-apoptotic ROS effects, the adipocytes in turn may ectopically activate the genetic program of melanogenesis, thus neutralizing excessive ROS. Adipocytic melanin

would also suppress the secretion of pro-inflammatory molecules, thereby decreasing the pro-inflammatory background in obese subjects and alleviating the metabolic syndrome. High levels of polymorphisms in human genes regulating melanin biosynthesis may account for the highly individual melanogenic responses of adipocytes and for the differences in an individual's propensity to develop secondary complications of obesity. Interestingly, limited clinical information available for 5 out of the 9 patients sampled for visceral adipose tissue allowed to reveal positive correlation between fasting glucose levels and total outputs of the melanogenic pathway in adipose tissues ($R=0.9685$, $p<=0.007$). This observation might indicate a connection between adipocytic melanogenesis and insulin resistance.

If the hypothesis linking the production of the melanin to the suppression of the pro-inflammatory effects of the accumulation of the visceral fat is confirmed, its potential impacts on the global health could be quite significant. The molecular compounds stimulating melanin biosynthesis, a number of the synthetic agonists of α-MSH receptors, have already been proven safe in human trials for therapeutic tanning and are scheduled for the pivotal stage III clinical trials for other, non-obesity related diseases. These compounds need to be tested as the preventive medications aimed at curtailing the development of devastating metabolic complications in obese and overweight populations.