Novel Micro-Physiological Model of Human Adipose Tissue Mimicking Fibrotic and Pro-Inflammatory Microenvironments

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OBJECTIVE: Through its lipid storage and destocking activities, adipose tissue (AT) constituting the hypodermis represents the main energy reservoir of the human body. AT is also recognized as an endocrine organ able to produce adipokines that act positively on the capacity of dermal fibroblasts to synthesize matrix proteins, thus participating in the maintenance of skin integrity. For these reasons, AT is now considered as an innovative and unmissable biological target for cosmetic products. The development of physiological models integrating the complexity of adipose tissue is thus necessary to improve the understanding of skin biological processes such as skin aging, cellulite, and physio-pathological alterations.

METHODS: Starting from liposuction surgery waste subcutaneous fat, we developed a breakthrough patented technological process [1] called "ExAdEx" (*Ex vivo Adipocyte Expansion*) to establish an *ex vivo* study model retaining the viability, structure and functions of the native human adipose tissue. The innovativeness of the process lies in the isolation and enrichment of endogenous proliferative adipose progenitor cells (APCs), combined with the use of nonenzymatically emulsified tissue units as a natural bioactive matrix.

RESULTS: We have shown in a recent paper [2] that ExAdEx process is able to preserve the 3D micro-structure of the donor's native subcutaneous adipose tissue and to allow APC expansion in a microenvironment including the extracellular matrix and endothelial cell network. The generated *ex vivo* models can be maintained at least 8 weeks in culture conditions and display lipid droplet size comparable to the native tissue, in contrast with other 3D spheroid models. ExAdEx models are able to respond to physio-pathological stimuli including beiging differentiation, lipolysis and lipogenesis and mimicking typical pro-inflammatory and pro-fibrotic conditions of human adipose tissue. Use of anti-inflammatory and anti-fibrotic compounds is able to revert the altered phenotype, demonstrating the relevance of ExAdEx models for ingredient testing and cosmetic claims.

CONCLUSION: Our micro-physiological clinically relevant explant models of human adipose tissue provide an original and unique approach for multiparametric screening and long-term studies to assess the chronic effect of cosmetic products, characterize their biological effects on hypodermis and evaluate their efficacy for weight management, skin ageing and skin health.

Keywords: hypodermis; adipose tissue; ex vivo models; inflammation; fibrosis; skin health.

[1] WO/2020/144381, Method for the in vitro or ex vivo amplification of human adipose tissue stem cells.
[2] Dani, V.; Bruni-Favier, S.; Chignon-Sicard, B.; Loubat, A.; Doglio, A.; Dani, C. Regulation of Adipose Progenitor Cell Expansion in a Novel Micro-Physiological Model of Human Adipose Tissue Mimicking Fibrotic and Pro-Inflammatory Microenvironments. Cells 2022, 11, 2798