

# Progress toward Implementing Multiomic Approaches in Atherosclerotic Cardiovascular Disease: Update from the 4<sup>th</sup> AtheroNET Meeting in Sarajevo (Bosnia and Herzegovina)

## Functional and metabolomic characterization of human cell models to address obesity and metabolic dysfunction-associated steatotic liver disease pathogenetic mechanisms

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<https://doi.org/10.56095/eaj.v4i2.110>

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**Introduction and Aim:** Obesity and metabolic dysfunction-associated steatotic liver disease (MASLD) are global health concerns linked to an increased risk of atherosclerotic cardiovascular disease (ASCVD). Despite progresses in elucidating relevant pathophysiological mechanisms involved in obesity and MASLD, a comprehensive understanding toward ASCVD risk is missing due to the lack of reliable *in vitro* models reproducing obesity-related dysfunctional adipose tissue and MASLD.

This study focuses on developing and characterizing innovative *in vitro* models recapitulating key features of these conditions assessing novel molecular signatures for potential drug targeting.

**Methods:** Human-derived SW872 adipocytes, dysfunctional SW872 (SW872-OA) obtained by 7-days 100  $\mu$ M oleic acid (OA), 17-days spontaneously differentiated SW872 (SW872-AUTO), human hepatoma HepG2 cells, and a HepG2-based steatotic-like model induced with 7-days 100  $\mu$ M OA (HepG2-OA), were selected. All *in vitro* models were characterized using <sup>1</sup>H NMR spectroscopy, light-microscopy, spectrophotometry, flow cytometry, and RT-qPCR.

**Results and Discussion:** Metabolomic and lipidomic analysis allowed to identify specific metabolite signatures associated with dysfunctional

patterns in both SW872 and HepG2 cell models. SW872-OA, SW872-AUTO, and HepG2-OA models showed increased lipid/triglycerides accumulation, confirmed by light-microscopy observations, and spectrophotometry quantification. HepG2-OA cells exhibited elevated triglyceride synthesis genes expression. Functional assays revealed reduced glucose uptake and elevated ROS production across all dysfunctional models. Trolox antioxidant treatment mitigated ROS levels in SW872 and HepG2 cells with minor effects on SW872-OA, SW872-AUTO, and HepG2-OA. Gene expression analysis (GEA) showed significant upregulation of oxidative stress-related genes in HepG2-OA cells. GEA in SW872-OA and SW872-AUTO cells revealed upregulation of genes involved in adipocyte differentiation, inflammation, and glycemic homeostasis.

**Conclusion:** These results showed that OA-treatment and SW872-spontaneous differentiation generate *in vitro* models recapitulating dysfunctional adipose tissue and MASLD.

**Relevance for AtheroNET:** Dysfunctional SW872 and HepG2 cell models show specific molecular, metabolomic and lipidomic signatures which may translate to innovative pharmacological targets for obesity, MASLD, and ASCVD.