

3D HUMAN CARDIAC TISSUE MODELS AS PLATFORMS TO INVESTIGATE MICRO- AND NANOPLASTIC-INDUCED CARDIAC STRESS

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Human exposure to micro- and nanoplastics (MNPs) is increasing and has raised growing concerns for cardiovascular health, while their effects on the heart remain largely unexplored. Moreover, age-related changes in myocardial structure and function may influence the cardiac response to environmental toxicants. In this context, advanced and physiologically relevant *in vitro* cardiac models are required to investigate environmentally induced cardiotoxicity.

In this work, three-dimensional (3D) cardiac tissue models mimicking different stages of myocardial aging (young and mature tissue) were developed and characterized. The models consisted of fibronectin-functionalized, anisotropic polyurethane (PUR) scaffolds fabricated by melt extrusion additive manufacturing, combined with a photocurable gelatin methacryloyl (GelMA) hydrogel at 5% and 10% w/v to replicate the mechanical properties of young and mature myocardium, respectively. GelMA acted as a carrier for a co-culture of human induced pluripotent stem cell-derived cardiomyocytes and human coronary artery endothelial cells in an 80:20 ratio.

The cellularized GelMA was integrated into the PUR scaffolds and photo-cured at 365 nm and 10 mW/cm² for 30s to obtain stable biphasic constructs. Cell-based models were cultured for up to 11 days, and cell viability and oxidative stress were monitored over time to assess tissue functionality and age-dependent behavior. Multi-omics analyses, including transcriptomics, proteomics, and metabolomics, were performed to identify molecular signatures associated with myocardial maturation, revealing that the mature models displayed specific biomarkers related to cardiac damage, mitochondrial dysfunction, protein breakdown and lipidic impairment, thus leading to membrane disorganization and alteration of processes related to muscle contraction and inflammatory pathways.

Overall, this study demonstrates that the developed 3D cardiac models effectively recapitulate key features of young and mature human myocardium *in vitro*. These models represent a promising and versatile platform for future investigations on age-dependent cardiac responses to environmental contaminants, including MNPs.

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