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Advanced Human 3D *in vitro* Models to Explore the Toxic Effects of Environmental Contaminants and Probiotic-Driven Mitigation

Christian Giommi
Department of Life and Environmental Sciences (DiSVA), Developmental and Reproductive Biology Laboratory - Polytechnic University of Marche (UNIVPM)

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Within a One Health vision, endocrine-disrupting chemicals (EDCs) emerge as invisible pollutants that disturb the delicate balance linking human metabolism, bone homeostasis, and microbial ecosystems, raising growing concern over how these widespread contaminants silently shape health across interconnected biological and environmental spheres. Human exposure to EDCs, such as bisphenol A (BPA) and perfluorooctanoic acid (PFOA), can impact intestinal and skeletal health. Despite regulatory restrictions, replacement compounds often retain similar toxic effects, highlighting a critical gap in strategies to limit their impact. To address the need for innovative mitigation strategies, this research employs advanced human 3D organoid and spheroid models to investigate how microbiome-derived interventions can counteract contaminant-induced alterations. A central and novel aspect of this approach is the use of live probiotic organisms directly within human intestinal organoids, a human-relevant model capable of recapitulating epithelial architecture, barrier function, and metabolism. This enables to evaluate the mitigating potential of a multispecies probiotic formulation against EDC-triggered damage in a controlled and physiologically meaningful micro-environment. Complementing this, we introduce a second innovative strategy by applying probiotic-derived metabolites to human osteoblast spheroids, providing a perspective on how gut microbiota modulates bone susceptibility to environmental toxicants. These metabolites, derived from a nine-strain probiotic formulation, represent a promising bioactive alternative capable of influencing extracellular matrix organization, cellular viability and resilience under chemical stress. Together, these models establish an integrated translational framework to dissect contaminant-specific mechanisms of toxicity while advancing microbiome-based strategies for mitigation. In ongoing research, we are expanding this approach to investigate the mitigation potential of probiotics and postbiotics on intestinal alterations induced by a broader spectrum of EDCs as well as by pro-inflammatory factors derived from pathogenic bacteria.

Info: rosita.gabbianelli@unicam.it

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