NANOPLASTICS IN THE EXPOSOME: FROM BREACHING BIOLOGICAL BARRIERS TO THEIR IMPACT ON CELLULAR FUNCTION

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Abstract: Nano- and microplastics (NMPs) are emerging as ubiquitous "xeno-nanoparticles" that naturally sit at the interface between nanomedicine and exposomics. Their size, shape and surface chemistry, together with the formation of a biomolecular corona, enable them to cross key biological barriers, including intestinal, pulmonary, cutaneous, placental and blood–brain barriers, through endocytic and transcytotic pathways that closely resemble those exploited by engineered nanocarriers. We therefore conceptualise NMPs as part of the nano-exposome, a pool of unintentionally engineered nanoparticles whose internal burden and molecular signatures can be interrogated with nanomedicine and exposomic tools.

Once internalized, NMPs trigger oxidative stress, characterised by increased reactive oxygen species, lipid peroxidation and DNA damage, which in turn activate pro-inflammatory signalling and cytokine release in immune and barrier cells. These processes contribute to a state of chronic, low-grade inflammation increasingly recognised as a common denominator of cardiometabolic, neurodegenerative and other chronic diseases. In parallel, several studies indicate that NMPs directly target mitochondria, inducing membrane depolarization, impaired electron transport chain activity and leakage of mitochondrial DNA. The resulting feed-forward loop between mitochondrial dysfunction, oxidative stress and inflammatory pathways such as cGAS–STING promotes cellular senescence and tissue remodelling, linking NMP exposure to hallmarks of aging rather than just acute toxicity.

Our preliminary work in murine BV2 microglia exposed to polystyrene NPs (PS-NPs; 25 nm and 100 nm) at humanrelevant concentrations (1.6–10 µg/mL) shows a reduction in cell viability for both sizes, followed by partial recovery at 48 h, suggesting activation of recovery pathways. However, voltametric biosensors and Western blot analyses demonstrate that 25 nm PS-NPs induce a more pronounced redox imbalance, and differences in the cytosolic SOD1 and the mitochondrial SOD2 expression compared to controls and 100nm treated cells, consistent with persistent oxidative and inflammatory stress. Confocal microscopy confirms internalisation of both particle sizes but highlights prolonged intracellular retention and mitochondrial co-localisation of 25 nm particles compared with 100 nm, which are more efficiently cleared at 48 h. Together, these data identify mitochondria as a critical organelle target and show that the effects of NMPs can be investigated using the same paradigms employed for therapeutic nanoparticles.

Within an exposomic and longevity framework, we hypothesise that size-dependent persistence of NMPs in barrier and immune cells, drives chronic mitochondrial oxidative stress and downstream epigenetic and angiogenic reprogramming, ultimately modulating brain aging pathways and healthspan. In this contribution, we will integrate mechanistic literature with our preliminary BV2 data to propose a nano-exposome model linking chronic NMP exposure, neuroinflammation and aging-related mechanisms, and discuss how the nanomedicine toolbox can be leveraged to quantify internal NMP burden, identify vulnerable phenotypes and design targeted mitigation strategies, as well as to inform the future design of safer nano-therapeutics.

Key words: nano- and microplastics; nanomedicine; nano-exposome; mitochondrial dysfunction; hallmarks of aging

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