PhD Proposal

Environmental Nanoplastics as Emerging Drivers of Immune Aging and Tumor-Promoting Tissue Dysfunction

Rationale

Micro- and nanoplastics (MNPs), particularly polystyrene nanoparticles, represent a growing class of environmental contaminants with bioactive properties. Originating from industrial activity, packaging waste, and degradation of macroplastics, these particles are now widely detected in terrestrial and aquatic environments (8). Due to their nanoscale size and physicochemical persistence, MNPs readily translocate into biological systems via ingestion and inhalation, accumulating in barrier and immune-associated organs such as the gastrointestinal tract, lungs, placenta, and lymphoid tissues (2, 3, 4).

Cumulative evidence from toxicological and immunological studies indicates that chronic exposure to MNPs compromises epithelial barrier function, elicits reactive oxygen species (ROS) generation, and triggers persistent low-grade inflammation (6, 7). These processes are implicated in the pathogenesis of metabolic disorders, immune senescence, and neoplastic transformation (6). Polystyrene MNPs, in particular, have been demonstrated to perturb gut microbiota homeostasis, skew macrophage activation, and foster a tumor-promoting immune landscape (1, 5, 9).

This doctoral project aims to elucidate the mechanistic interplay between environmental MNP exposure and immune dysfunction, focusing on the emergence of lipid-laden, senescent macrophages characterized by impaired phagocytosis and altered secretory phenotypes. These dysfunctional macrophages are hypothesized to create an immunosuppressive milieu that facilitates tumor progression and immune evasion.

Hypotheses and aims:

- Hypothesis 1: MNPs induce a lipid-rich senescent macrophage phenotype.
    - Aim 1: Characterize the induction of lipid accumulation and senescence markers (SA-β-gal, p16, p21) in macrophages upon MNP exposure.
- Hypothesis 2: Senescent macrophages drive T cell exhaustion and functional decline.
    - Aim 2: Assess the impact of senescent macrophages on T lymphocyte exhaustion (PD-1, TIM-3, LAG-3 expression) and effector function.
- Hypothesis 3: MNP-bound peptides modulate antigen processing and immune recognition.
    - Aim 3: Identify immunogenic peptides adsorbed onto MNP surfaces and evaluate their impact on antigen presentation.

- Hypothesis 4: In vivo models recapitulate immunosenescence and tumor-supportive immune changes.
    - Aim 4: Validate observations in organoids and mice exposed chronically to MNPs.

Methodological Plan and Work Plan Timeline

- Year 1: Establish in vitro exposure platforms using primary and immortalized macrophages; quantify lipid deposition, senescence, and phagocytic capacity.
- Year 2: Conduct macrophage-T cell co-culture assays; apply spectral flow cytometry and transcriptomics (RNA-seq) to decipher exhaustion signatures; perform proteomic profiling of MNP-adsorbed peptides.
- Year 3: Develop gut/tumor organoids and chronic exposure models in mice; assess immune competence and tumor growth dynamics.

Phase	Year 1	Year 2	Year 3
In vitro macrophage modeling	•••	•	
Senescence/lipid analysis	•••	•	
Macrophage-T cell co-culture and exhaustion		••	•
MNP peptide proteomics		••	•
Organoids and mice studies			•
Thesis and thesis dissertation			•••

With • as 2 months.

Expected Impact

This research will elucidate how environmental nanoplastics impair immune surveillance via cellular senescence, identifying potential checkpoints for therapeutic modulation. Furthermore, it will advance our understanding of the immunotoxicological implications of plastic pollution and inform environmental health policies.

Feasibility and Technical Resources

The project is supported by the host institution's infrastructure and technical capabilities, ensuring feasibility across all planned experimental stages. A collaboration with Dr. Stoyan Ivanov's group for possible analyses might be considered at a more advanced stage of the PhD to gain access to advanced spectral flow cytometry to enable high-dimensional profiling of senescent immune subsets (e.g., PD-1, p16, p21, ROS markers).

Collectively, this proposal leverages cutting-edge methodologies to bridge environmental toxicology and immunology, addressing a timely and critical question on the health effects of microplastic pollution.

References:

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