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The impact of micro- and nanoplastics on immune system development and functions: Current knowledge and future directions

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ABSTRACT

The prevalence of microplastics (MPs)/ nanoplastics (NPs) in the environment has raised significant concerns regarding their potential toxicity, particularly their impact on biological systems. These particles, particularly NPs, possess unique properties due to their small size and high surface area, enabling them to more easily cross biological barriers and accumulate in tissues. Among various types of plastic materials, polystyrene (PS) is one of the most studied for its toxicological effects, given its widespread use and environmental persistence. This narrative review examines current research on the effects of MPs/NPs, on the immune system, with a focus on both the development of the immune system and its functional responses. Evidence from *in vitro* and *in vivo* studies suggests that MP/NP exposure can disrupt immune function, including hematopoiesis, immune cell activation, and the production of inflammatory cytokines. Although *in vitro* studies highlight cellular toxicity and altered immune cell behavior, *in vivo* studies reveal more complex outcomes, with some findings suggesting significant effects on organ systems such as the spleen and intestines, while others indicate minimal or no impact under environmentally relevant exposure conditions. Here, we aim to consolidate and summarize the current evidence on the topic, highlight key limitations in the field, and identify areas that warrant further investigation for immunotoxicologists. In addition, we emphasize the importance of using relevant exposure concentrations and complex *in vitro* or *in vivo* models to better understand the potential risks associated with MP/NP exposure and their long-term implications for immune health.

1. Introduction

The growing prevalence of microplastics (MPs)/nanoplastics (NPs) in our environment has become a significant concern for the scientific community. NPs are known to originate from MPs, which themselves are created through processes that can be classified as either primary—where MPs are directly manufactured for industrial applications—or secondary, which involves the degradation of larger plastic debris. The degradation of larger waste into MPs is influenced by natural processes such as ultraviolet rays, abrasion, oxidative stress, and biodegradation [1]. For some time, the size ranges of MPs/NPs were poorly defined. In 2019, Hartmann et al. proposed a convention for the size ranges encompassing both MPs (1–1000 μm) and NPs (1 nm to <1 μm) [2]. In 2023, the International Organization for Standardization (ISO) published an official document defining MPs as plastic particles insoluble in water, ranging from 1 to 1000 μm, and NPs as plastic particles smaller than 1 μm [3].

Various types of polymers contribute to plastic pollution, including nylon, polypropylene (PP), polycarbonate (PC), polyethylene (PE), polyvinyl chloride (PVC), and polystyrene (PS) [1]. Among these, PS is particularly prevalent and has been extensively studied as a model for examining the effects of MPs and NPs due to its widespread use in industry, high stability, and low production costs [4,5]. Leslie et al. also identified the presence of styrene (a product of PS pyrolysis) in 8 out of 22 blood samples analyzed from Dutch individuals in the general population, making PS the most common plastic found in these samples [4]. Altogether, this resulted in PS being one of the most researched plastics concerning toxicity at the nanoscale. The increasing interest in NPs stems from their potentially hazardous effects; due to their small size, NPs can more easily cross biological barriers and possess a higher surface area-to-volume ratio than MPs, potentially leading to increased toxicity [6–12].

It is essential to recognize that plastic contamination encompasses a wide range of sizes, shapes, and materials. Various studies have

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investigated the effects of MP/NP exposure across multiple biological systems, including a vast array of marine species and mammals, and these have been discussed in multiple reviews [13–20]. Importantly, evidence indicates that humans are also directly exposed to these particles. For example, MPs and/or NPs have been detected in various human tissues, including the lungs [21,22], blood [4], placenta [23], testes [24], and fecal matter [25]. Human exposure to MPs and NPs is said to occur primarily through inhalation, ingestion or dermal contact [16,18,26]. Furthermore, exposure studies on rats demonstrated that a single dose of various sizes of PS-MPs and NPs (50, 100, 300, 500 nm, 1 μm, and 3 μm) led to accumulation in several organs, including the stomach, intestines (small and large, including Peyer's patches), colon, liver, spleen, blood, bone marrow, kidneys, lungs, and heart [27]. A more recent study with 50 nm PS-NPs confirmed the presence of these particles in similar organs, adding the testes and brain to the list [28]. Even if these studies focus solely on PS, and therefore their findings may not be applicable to all plastic types, they underscore the systemic reach of these particles following oral exposure, including their presence in immune organs. Further studies by Jani et al. again demonstrated the presence of NPs ranging from 100 nm to 1 μm in similar organs, including the spleen, with the addition of mesenteric lymph nodes, noting very high levels of accumulation [29–31]. This provides additional evidence that immune organs are directly exposed to NPs, at least made of PS, and therefore, the effects of this exposure should be thoroughly investigated.

In recent years, studies investigating the effects of MPs and NPs have emerged across a wide range of fields. As this field's body of literature continues to expand, it has become increasingly important to synthesize the information, for example by organizing it according to research domain. In the field of immunology, recent reviews have begun to compile and analyze these studies, helping to contextualize their findings within broader immune-related mechanisms [17,32–35]. Here, we aim to consolidate and present current evidence regarding the effects of MPs/NPs on the immune system, particularly concerning its development and functional responses. For organizational purposes, the evidence will be divided into two main chapters: the development of the immune system and the immune responses themselves. Furthermore, due to their model differences, studies on immune responses will be separated into two additional sections: *in vitro* and *in vivo* studies. Each section will also include a table summarizing the described information. With this narrative overview of the effects of MPs/NPs on immunity, we aim to support immunologists in their research by summarizing existing findings, highlighting key limitations, and identifying critical questions that remain to be answered.

2. The impact of MPs/NPs on the development of the immune system

As of the time of writing this review, studies focusing on the effects of MPs/NPs exposure on the development of the immune system are scarce. Enyoh et al. investigated the impact of NPs on immunoglobulin A (IgA) present in breast milk, a crucial element for the immune development of newborns. Their *in vitro* findings revealed that various types of NPs, including PS, can bind to and significantly inhibit IgA, potentially posing a risk to infant immune development [36]. Although evidence regarding NP-induced immune responses during immune system development remains limited, Martin et al. demonstrated that exposure to 30 nm and 100 nm NPs in zebrafish embryos resulted in macrophage-NP colocalization, along with increased IL-6 and IL-1β expression and reactive oxygen species (ROS) accumulation [37]. Likewise, zebrafish larvae exposed to PS-NPs (50 and 1000 nm) showed NP accumulation in the gut, which was linked to ROS accumulation and higher mortality rates in immunocompromised individuals [10].

Hematopoiesis, the process of blood cell formation, is essential for the development of the immune system, as it gives rise to immune cells such as lymphocytes and myeloid cells, which are critical for pathogen defense and immune surveillance. Table 1 summarizes studies that have examined the effects of MPs/NPs on immune system development, which are further discussed in this section. Sun et al. investigated MP-induced hematotoxicity in mice using 5 μm PS-MPs at two different daily doses (0.1 and 0.5 mg), over a 28-day period. At the end of the exposure, they observed a significant reduction in peripheral blood white blood cell counts and an increase in platelet numbers, both effects occurring only at the high dose. Following exposure, bone marrow (BM) cells were extracted and cultured for colony-forming unit (CFU) assays. In mice exposed to the high dose (0.5 mg), there was a marked inhibition of colony formation by hematopoietic stem cells and hematopoietic progenitor cells. Transcriptomic analysis of BM cells revealed 41 and 32 differentially expressed genes at the low and high doses, respectively, for example associated with T cell homeostasis. The Jak/Stat and other signaling pathways also appeared to be implicated in these changes [38]. These findings suggested that, to some extent, PS-MPs could induce hematotoxicity and raised interest for research in the field oriented towards NPs.

For instance, Guo et al. exposed mice to PS-NPs for 42 days and observed their accumulation in the BM, reduced blood cell counts, BM damage, and extramedullary hematopoiesis in the spleen. These effects were accompanied by oxidative stress and the activation of cell death pathways, underscoring the hematotoxic potential of PS-NPs [39]. Similarly, Jing et al. exposed mice to PS-MPs (10 μm and 5 μm) and NPs (80 nm) for 42 days, reporting hematopoietic toxicity characterized by disrupted BM cell function and impaired blood cell production. This toxicity was associated with alterations in gut microbiota, metabolic imbalances, and inflammation, suggesting that interactions between the gut microbiota, metabolites, and cytokines play a significant role in NP-induced hematopoietic damage. Notably, the 80 nm NPs induced more severe effects compared to the larger particles [40]. In a follow-up study, the addition of melatonin and probiotics mitigated the hematotoxicity caused by 80 nm NPs, with probiotics showing the strongest protective effects. These findings suggest that modulating the gut microbiota may help alleviate some of the toxic effects of NPs [41]. Indeed, it is already hypothesized that probiotics could specifically offer protection against gut-related toxicity induced by NP exposure [42].

Park et al. aimed to investigate the transgenerational effects of PE-MPs (40–48 μm) in mice following 90 days of exposure to doses ranging from 0.125 to 2 mg per day. They observed a significant increase in serum IgA levels at the highest dose, but not in other immunoglobulins (IgG, IgM, and IgE). In the stomach tissues of mice exposed to 2 mg of MPs, the authors noted the migration of granules to mast cell membranes and evidence of degranulation. They also reported abnormal accumulation of organelles within the nuclei and mitochondria in the spleen. Additionally, the splenic $CD8^+/CD4^+$ T cell ratio and the proportion of mature dendritic cells were significantly reduced. Interestingly, offspring from mice mated after MP exposure also appeared affected in terms of body weight, with a decrease observed in the high-dose group. In these offspring, a reduced proportion of splenic T cells was noted in females, while impaired dendritic cell maturation was observed in males but not in females. These alterations were primarily seen in the offspring of parents exposed to the highest PE-MP dose (2 mg). Overall, most of the observed effects occurred at the highest dose, which is not environmentally realistic. In contrast, the lowest dose (0.125 mg), which more closely reflects real-life exposure, resulted in significantly fewer changes. Together, these findings suggest a dose- and context-dependent effect of MPs on the immune system and the health of offspring in mice [43].

3. The impact of MPs/NPs on the immune responses

3.1. *In vitro* studies

In recent years, numerous *in vitro* studies have emerged, focusing on the effects of MPs/NPs primarily on cell lines. While these studies are not

Table 1
Studies investigating the impact of MPs/NPs on the development of the immune system.

Type	Size & modification	Exposure			Subject	Main observations	Ref.
		Dosage	Time	Route & diluent			
PS	30, 100 nm	0.1, 1, 10 ppm	96 h	Tank water	Zebrafish embryos[A]	Mϕ-NP colocalization, IL−6/IL−1βb expression, ROS Acc	[37]
PS	50 nm, 1μm (ζ)	10 mg/mL	24 h	Tank water	Zebrafish larvae[A]	Acc in the gut, ROS Acc, ↑ mortality in immunocompromised subjects	[10]
PS	5 μm	0.1, 0.5 mg/d	28d	Oral, water	C57BL/6 mice (M)[A]	Peripheral blood: ↓ white blood cells, ↑ platelets (high dose only). BM: inhibition of colony formation by hematopoietic stem cells and hematopoietic progenitor cells (high dose only). Transcriptomic changes, e.g. T cell homeostasis	[38]
PS	80 nm (ζ)	0, 30, 60, 120 μg/d	42d	Oral, PBS	C57BL/6 mice (M)[A]	Acc in bone tissue, ↓ blood cell count, BM damage, ↑ oxidative stress & cell death pathways, spleen extramedullary hematopoiesis	[39]
PS	80 nm, 5, 10 μm (ζ)	60 μg/d	42d	Oral, water	C57BL/6 mice (M)[A]	Hematopoietic toxicity, BM cells disruption, impaired blood cell production, inflammation/metabolic imbalance/gut microbiota alteration	[40]
PS	80 nm (ζ)	60 μg/d	42d	Oral, water	Strain not specified, mice (M)[A]	Melatonin & probiotics treatment = ↓ NP-induced hematotoxicity, associated with gut microbiota modulation	[41]
PE	40–48 μm (COOH, OH)	0.125, 0.5, 5 mg/d	90d to 110 d (dams only)	Oral, water	ICR mice (M/F)[A]	↑ serum IgA. Stomach: mast cell granule migration & degranulation. Spleen: organelle buildup in nuclei/mitochondria, ↓ $CD8^+/CD4^+$ ratio, ↓ mature DCs. Offspring: ↓ body weight, ↓ splenic T cells (F), ↓ DC maturation (M)	[43]

[A] : *in vivo* study, ζ: zeta potential is provided, ↑: increased, ↓: decreased, PS: polystyrene, PE: polyethylene, Acc: accumulation, BM: bone marrow, Mϕ: macrophage, DC: dendritic cell, ROS: reactive oxygen species, PBS: phosphate buffered saline, d: day

performed on complex organisms, they are valuable as they offer initial insights into the toxic effects of MPs/NPs and reveal direct interactions between these particles and various isolated cell types. Such studies serve as a critical foundation for guiding subsequent *in vivo* research. Table 2 summarizes the studies described in this section.

3.1.1. Mouse cells

Li et al. conducted an *ex vivo* study on murine splenocytes exposed to 20 nm and 50 nm PS-NPs. The findings revealed that all NPs were internalized by the cells, affecting both cell viability and apoptosis. Among the tested particles, neutral and positively charged 20 nm NPs had the most pronounced effects, increasing ROS levels and impairing mitochondrial function, except for the positively charged 20 nm particles. Additionally, these NPs reduced the activation of T lymphocytes upon stimulation and decreased their secretion of IFN-γ and IL-2. It was unclear whether these effects were dose-dependent, as only concentrations of 40 μg/mL and 200 μg/mL for 20 nm and 50 nm NPs, respectively, were used in all experiments, except for the apoptosis and viability assays [44]. Similarly, Schwarzfischer et al. reported that exposure to 50 nm PS-NPs and 25 nm PMMA-NPs triggered a pro-inflammatory response in mouse bone marrow-derived macrophages (BMDM), characterized by increased expression of TNF-α and IL-6. These effects were dose-dependent: the lower dose (100 μg/mL) did not induce significant effects, whereas the highest dose (400 μg/mL) did for both materials [45].

The J774A.1 mouse macrophage cell line was exposed to a range of PS-MPs/NPs of varying sizes (40–90 nm, 0.7–0.9, 1.7–2.2, 2.5–4.5, and 6–8 μm). Although no toxic effects were observed, the exposure resulted in alterations in oxidative stress, lysosomal and mitochondrial functions, and changes in the expression of immune-related surface markers, including CD11a/b, CD18, CD86, PD-L1, and CD204. Interestingly, these changes were more pronounced in cells that internalized higher amounts of NPs/MPs[46].

A series of studies on RAW264.7 cells, a murine macrophage cell line, demonstrated multiple adverse effects upon NP exposure. Jiang et al. reported that these cells rapidly internalized PS-NPs of 50 and 500 nm, leading to polarization toward an M1 (pro-inflammatory) phenotype. This was characterized by a dose-dependant increase in the expression of CD86, iNOS, and TNF-α, along with a decrease in CD206, IL-10, and Arg-1 expression. Some of these effects were more pronounced when using 50 μg/mL compared to 10 μg/mL of NPs [47]. Additionally, Florance et al. showed that 200 nm PS-NPs affected lipid metabolism in these cells, inducing lipid droplet accumulation, foam cell formation, and acute mitochondrial oxidative stress. Notably, these effects were significant only when the NPs were modified with a sulfate group and were specific to macrophage cell lines, including RAW264.7 and THP-1 [48]. Tang et al. found that 100 nm PS-NPs exacerbated inflammation and lipopolysaccharide (LPS)-induced necroptosis in the same cells. The *in vivo* component of this study is discussed in the next sections [49]. Similarly, 80 nm PS-NPs induced apoptosis and specifically increased IL-6 secretion, while both 80 nm PS-NPs and 3 μm PS-MPs triggered apoptosis and elevated the inflammatory cytokines TNF-α and IL-10, likely due to ROS accumulation. These effects were both size- and dose-dependent, as lower concentrations of PS-NPs (as little as 0.01 μg/mL) were sufficient to induce them [50]. Finally, 100 nm PS-NPs were shown to trigger apoptosis through activation of the innate immune cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway, leading to nuclear factor-κB (NF-κB) signaling and increased expression of pro-inflammatory mediators TNF-α and IL-6. Interestingly, despite this pro-inflammatory profile, IL-1β expression was decreased, which appears contradictory and suggests a selective or regulated inflammatory response. These changes appeared to be dose-dependent, with 220 μg/mL inducing more pronounced effects than 60 μg/mL [51]. Other studies reported comparable dose-dependant effects, including oxidative stress, cell death, NF-κB signaling activation, and cGAS-STING pathway involvement in RAW264.7 cells exposed to 75–90 nm PS-NPs [52,53].

3.1.2. Human cells

Wolff et al. investigated the effects of PS-NPs of various sizes (50, 200, and 1000 nm) on human blood-derived T lymphocytes, macrophages, and dendritic cells (DCs). At higher concentrations (100 μg/mL), 50 nm NPs increased CD62L expression in T lymphocytes and altered inflammatory markers, including downregulation of IL-1β and IFN-γ, and upregulation of CCL2, IL-17A, and IL-10. DCs and macrophages exhibited greater sensitivity to NPs, with DCs showing reduced co-stimulatory markers and macrophages shifting toward an anti-inflammatory M2 phenotype [54]. Weber et al. compared PVC and PS-NPs and found that only PVC NPs (<50 μm) significantly increased pro-inflammatory (IL-6, TNF) and anti-inflammatory (IL-10) markers in

Table 2
In vitro studies investigating the impact of NPs on immune responses.

Type	Size & modification	Exposure			Subject	Main observations	Ref.
		Dosage	Time	Route & diluent			
PS	20 (+/-/0), 50 nm (ζ)	5–800 μg/mL	3 h	Culture medium (S^+)	Mouse (BALB/c) splenocytes[A]	NP uptake, ↓ viability & mitochondrial function, ↑ apotposis & ROS, ↓ T cell activation & IFN-γ/IL−2 production	[44]
PS PMMA	50 nm 25 nm	100, 200, 400 μg/mL	2, 4, 8, 24 h	Culture medium ($S^?$)	Mouse (C57BL/6) BM-derived Mϕ[A]	Pro-inflammatory response, ↑ TNF-α and IL−6	[45]
PS	40–90 nm, 0.7–0.9, 1.7–2.2, 2.5–4.5, 6–8μm (ζ)	20 μg/mL	24 h	Culture medium (S^+)	J774A.1 cell line[A]	NP uptake, oxidative stress, lysosomal & mitochondrial functions alteration, CD11a/b, CD18, CD86, PD-L1, and CD204 expression changes	[46]
PS	50, 500 nm (ζ)	10, 50 μg/mL	48 h	PBS ($S^?$)	RAW264.7 cell line[A]	NP uptake, M1 polarization, ↑ CD86, iNOS, & TNF-α, ↓ CD206, IL−10, & Arg−1	[47]
PS	200 nm (sulfate)	100 μg/mL	24–48 h	Culture medium ($S^?$)	RAW264.7 cell line[A]	Lipid droplets Acc, foam cells formation, acute mitochondrial oxydative stress	[48]
PS	100 nm	100 μg/mL	24 h	Not specified ($S^?$)	RAW264.7 cell line[A]	↑ inflammation and LPS-induced necroptosis	[49]
PS	80 nm, 3 μm	0.01, 0.1, 0.5, 1, 5, 10 μg/mL	24 h	Culture medium ($S^?$)	RAW264.7 cell line[A]	Apoptosis, TNF-α, IL−6, and IL−10 secretion. May be caused by ROS production	[50]
PS	100 nm (ζ)	0, 60, 140, 220 μg/mL	12, 24, 48 h	Culture medium ($S^?$)	RAW264.7 cell line[A]	Apotposis through cGAS-STING and NF-κB pathways signaling, ↑ TNF-α, IL−6, ↓ IL−1β	[51]
PS	80 nm (Ø, COOH, NH_2), 5 μm (ζ)	10–1000 μg/mL	24 h	Culture medium (S^+)	RAW264.7 cell line[A]	MAPK and NF-κB pathways activation, ROS accumulation, IL−6 and TNF-α production	[52]
PS	75, 90 nm (ζ)	50, 100, 200 μg/mL	6, 24 h	Culture medium (S^+)	RAW264.7 cell line[A]	Oxidative stress, cell death, IL−1β, IL−6, TNF-α, NLRP3 genes expression, cGAS-STING pathway activation	[53]
PS	50, 55 (NH_2), 200 nm, 1 μm	1–100 μg/mL	24–72 h	PBS ($S^?$)	Human PBMC-derived T cells, Mϕ and DC[A]	T cells: ↓ IL−1β/IFN-γ, ↑ CD62L/CCL2/IL−17/IL−10; DC: ↓ co-stimulatory markers; Mϕ: M2 phenotype	[54]
PS PVC PMMA	50, 100, 310 nm < 50 μm < 600 nm	100, 300 particles/cell	18 h	Saline ($S^?$)	Human PMBC-derived monocytes & DCs[A]	↑ IL−6, TNF, IL−10 (only with PVC)	[55]
PS	75 nm (ζ)	200 μg/mL	2 h	Culture medium (S^-)	Mouse (C57BL/6) BM-derived neutrophils[A]	Neutrophil extracellular traps (NETs) formation and ROS induction	[56]
PS PC	41 nm (ζ) 158.7 nm (ζ)	0.025, 0.05, 0.1, 0.2 μg/μL	2 h	HBSS (S^-)	Fathead minnow neutrophils[A]	↑ degranulation of primary granules and NET release	[57]
PS	460 nm, 1, 3, 10, 40, 100 μm (ζ)	10, 100, 500, 1000 μg/mL	4d	PBS or culture medium ($S^?$)	HDF, HMC−1 cell lines & human PBMCs[A]	Only the highest concentration induced viability decrease. PBMCs: ↑ TNF-α, IL−6 (only 460 nm), no changes in IL−10 and IL−2. HMC−1 cells: no changes in histamine release	[58]
PP	~20 and 25–200 μm	10, 100, 1000 μg/mL	4d	PBS or culture medium ($S^?$)	HDF, HMC−1 cell lines & human PBMCs[A]	PBMCs: Minimal changes in ROS levels, ↑ TNF-α, IL−6 (20 μm). HMC−1: ↑ histamine release	[58]
PVC, ABS	27–75, 75–200 μm (irregular)	10, 100, 1000 μg/mL	4d	Culture medium ($S^?$)	HDF, HMC−1 cell lines & human PBMCs[A]	PBMCs: ↑ TNF-α (PVC, all sizes and concentrations), ↑ IL−6 (ABS, 25–75 μm, high concentration) HMC−1: ↓ histamine release HDF: No viability decrease	[60]
PE	1–10, 50, 100 μm (spherical), 27–75, 75–200 μm (irregular)	10, 100, 1000 μg/mL	4d	Culture medium (S^+)	HDF, HMC−1 cell lines & human PBMCs[A]	PBMCs: ↑ IL−6 (1–10 μm spherical), ↑ TNF-α (100 μm spherical & 27–75 μm irregular) HMC−1: no histamine change HDF: no significant ROS accumulation	[61]
PS	50 nm (ζ)	5, 10, 25, 50 μg/mL	3, 24, 48 h	Culture medium ($S^?$)	Raji-B, TK6, THP−1 cell lines[A]	THP−1: high uptake, low toxicity. Raji-B/TK6: low uptake, mild toxicity, ROS production, genotoxicity	[62]
PS	50, 200, 500 nm (ζ)	5, 10, 25, 50, 100 μg/mL	3, 24, 48 h	Culture medium ($S^?$)	Raji-B, TK6, THP−1 cell lines[A]	Internalization (↑50 nm) by all cell lines (less with TK6), loss of mitochondrial membrane potential (excpet for TK6)	[11]
PS PVC PE PET	50 nm (Ø, NH_2) 235 nm 611 nm 16 nm	50 μg/cm^2	24 h	Culture medium (S^+)	THP−1 cell line[A]	NLRP3 activation and IL−1β/IL−8 release caused only by PS-NH_2	[63]
PS PVC	50 nm (Ø, NH_2) (ζ) 200–350 nm (ζ)	5, 10, 50 μg/cm^2	24 h	Culture medium (S^+)	Caco−2[a], HT29-MTX-E12[b], THP−1[c] cell lines[A]	PS-NH_2 (positive control): ↑ DNA damage[a,b], IL−1β[c] in healthy model. PVC: ↑ IL−1β, ↓ epithelial cells (in inflammed model)	[64]
PS	100 nm (Ø, COOH, NH_2) (ζ)	10, 50, 100 μg/mL	0–72 h	Not specified ($S^?$)	Human PMBC-derived Mϕ[A]	PS-NH_2: ROS accumulation, NLRP3 inflammasome activation, IL−1β release	[65]
PS	500, 1000, 3000 nm	1.04, 1.6, 10–1500 μg/mL	24, 48, 72 h	Culture medium ($S^?$)	THP−1 and human PBMC-derived Mϕ[A]	Internalization of all sizes. 500 nm NPs caused cytotoxicity in THP−1 Mϕ, and increased necrosis in PBMC Mϕ	[67]
PE	30.5 ± 10.5 and 6.2 ± 2.0 μm	10, 100, 500, 1000 μg/mL	24–48 h	Cultume medium ($S^?$)	Caco−2, HaCaT, A549, U937, THP−1, Jurkat cell lines[A]	↑ ROS production (U937, THP−1, Jurkat, Caco−2), IL−6: ↑ in HaCaT, TNF-α: ↓ U937 & THP−1	[68]
PS	85 nm (ζ)	20, 50, 100 μg/mL	12, 24, 48 h	Culture medium (S^-)	A549 cell line[A]	During influenza A infection: NP-virus binding increased viral infection by endocytosis and viral titers and reduced IL−1β production	[77]

(*continued on next page*)

Table 2 (*continued*)

Type	Size & modification	Exposure			Subject	Main observations	Ref.
		Dosage	Time	Route & diluent			
PS	500–1000 nm (ζ)	12.5, 25, 50 or 100 μg/mL	2 h	Not specified ($S^?$)	HEK-293T, Caco−2, VERO-E6 cell lines[A]	NP-SARS-CoV−2 pseudoviruses binding. ACE2-dependant cell internalization. Confirmed with real virus (↑ entry and TNF-α)	[78]
PS	80, 150 nm	25, 50, 100, 200 μg/mL	1, 2, 12, 24 h	Not specified ($S^?$)	Huh7.5.1 cell line[A]	NPs = ↑ cholesterol levels = larger lipid droplets = ↑ number of migrasomes = ↑ migrasome-mediated viral entry of VACV	[79]

[A] : *in vitro* study, ζ: zeta potential is provided, S^+: media supplemented with serum, $S^?$: unclear whether the media was supplemented with serum, S^-: media without serum was used, ↑: increased, ↓: decreased, PS: polystyrene, PMMA: polymethacrylate, PVC: polivinyl chloride, PC: polycarbonate, PE: polyethylene, ABS: acrylonitrile butadiene styrene, PET: polyethylene terephthalate, Acc: accumulation, BM: bone marrow, Mϕ: macrophage, ROS: reactive oxygen species, PBS: phosphate buffered saline, HBSS: Hank's balanced salt solution.

human DCs and monocytes. While PS-NPs did not show significant effects, the authors noted a trend suggesting that irregular NPs had a more pronounced effect compared to spherical ones [55]. Zhu et al. focused on mouse neutrophils exposed to 75 nm PS-NPs, showing that these particles could trigger NETosis, an immune mechanism that traps pathogenic microorganisms by releasing DNA fibers and proteins [56]. While not being derived from human cells, fathead minnow neutrophils incubated with 40 nm PS-NPs or 150 nm PC-NPs showed similar tendencies [57].

Hwang et al. investigated the effects of PS-MPs/NPs (460 nm, 1, 3, 10, 40, and 100 μm) on human dermal fibroblasts (HDFs), human peripheral blood mononuclear cells (PBMCs), and the human mast cell line HMC-1. Concentrations up to 500 μg/mL did not induce toxicity in any of the cell types, whereas 1000 μg/mL led to a significant loss of viability in HDFs. In PBMCs, the 460 nm NPs were internalized by neutrophils and macrophages but not by lymphocyte-like cells, a pattern also observed in HDFs. At concentrations of 10, 100, and 500 μg/mL, only the highest dose of 460 nm NPs caused a significant increase in TNF-α and IL-6 levels, with no significant changes in IL-10 or IL-2. Finally, no significant histamine release was detected in HMC-1 cells [58]. In another study by the same group using PP-MPs (~20 μm and 25–200 μm), a significant increase in histamine release from HMC-1 cells was observed at similar concentrations (500 μg/mL). Comparable trends in cytokine production were observed in human PBMCs exposed to 20 μm PP-MPs, while only minimal changes in ROS levels were detected [59]. Their later work also focused on PVC and acrylonitrile butadiene styrene (ABS) MPs, in size ranges of 25–75 μm and 75–200 μm, to investigate their effects on cytokine and histamine release by human PBMCs and HMC-1 cells, respectively. TNF-α levels were increased in human PBMCs following exposure to PVC-MPs of both sizes at nearly all tested concentrations (10, 100, 1000 μg/mL). In contrast, IL-6 levels showed only a slight increase, and only at the highest concentration (1000 μg/mL) of 25–75 μm ABS-MPs. Interestingly, most size and concentration combinations of both MP types led to a decrease in histamine release by HMC-1 cells [60]. In a related study, pro-inflammatory cytokine release was assessed in human PBMCs using both spherical (1–10, 50, and 100 μm) and irregular (25–75 and 75–200 μm) PE-MPs. IL-6 levels increased only in response to spherical PE-MPs of 1–10 μm at the highest tested concentration (1000 μg/mL). TNF-α levels were elevated by 100 μm spherical PE-MPs, also at the highest concentration, and by irregular PE-MPs of 25–75 μm at their highest tested concentration (500 μg/mL) [61].

As described, the toxic *in vitro* effects of MPs/NPs have been observed and characterized in multiple immune mammalian cell lines. However, it is important not to assume that these effects apply to all cell types or organisms. For instance, Rubio et al. emphasized the importance of selecting appropriate cell lines when evaluating the effects of PS-NPs, highlighting the variability in adverse effects depending on the model. In their study, Raji-B (B lymphocytes), TK6 (lymphoblasts), and THP-1 (monocytes) cell lines were exposed to 50 nm PS-NPs, and internalization, cytotoxicity, ROS production, and genotoxicity were assessed. Interestingly, while THP-1 cells exhibited the highest cellular uptake of NPs, they did not show notable adverse effects. In contrast, the other cell types exhibited less particle uptake and displayed evidence of mild toxicity, ROS production, and genotoxicity [62]. In another study, PS-NPs of sizes 50, 200, and 500 nm did not induce toxicity in these three cell lines, despite evidence of internalization across all sizes, with TK6 cells showing the least uptake. As hypothesized, toxicity was negatively associated with NP size. While a loss of mitochondrial membrane potential was observed in all cell lines and particle sizes, with the exception of TK6cells, no accumulation of ROS was noted in any case [11]. Similar findings were reported by Busch et al., using THP-1 cells, where 50 nm PS-NPs did not activate the NLRP3 inflammasome or cause the release of IL-1β and IL-8 unless the particles were amide-conjugated (PS-NH_2) [63], a type of NP commonly used as a positive control for toxicity [64]. Previous studies have shown that PS-NH_2 particles (at 100 nm) can activate the NLRP3 inflammasome in human macrophages [65], a well-studied marker of NP-induced inflammation *in vitro* [66]. In line with these findings, Adler et al. investigated the effects of 500 nm PS-NPs on human monocyte-derived macrophages, observing internalization, cytotoxicity, and necrosis [67]. Additionally, Busch et al. used an *in vitro* triple culture model (Caco-2/HT29-MTX-E12/THP-1) to mimic healthy and inflamed human intestines and study the effects of PS- and PVC-NPs on inflammatory processes. Interestingly, only PVC-NPs, but not PS-NPs, induced negative effects in the inflamed triple culture model, including an increase in IL-1β release and loss of epithelial cells [64].

It is interesting to note that most of the mouse cell-based studies described so far observed pro-inflammatory signs (e.g., increased levels of pro-inflammatory cytokines, M1 polarization) following MP/NP exposure. However, some human cell-based studies have also reported the presence of anti-inflammatory markers, such as IL-10, or even no effects at all. Although MPs/NPs are often viewed as strictly pro-inflammatory, their effects can vary depending on various factors, including the organism (mouse vs. human) and the specific cell lines used [62,68]. This could highlight species-specific differences between mice and humans. While inflammation is central to most MP/NP effect readouts, it would be equally important to investigate other immune-related outcomes that may contribute to host defense impairment, such as tolerogenic, exhaustive, and immunosuppressive effects.

Furthermore, it is important to consider that *in vitro* models, especially immortalized cell lines, may not fully represent *in vivo* conditions or primary cells. Cancer cell lines, such as THP-1 cells, which are used in some of the studies discussed here, have been shown to be less sensitive than primary cells to activating stimuli [69,70]. This makes these cell lines useful for investigating basic mechanisms, but more subtle effects may be overlooked when using these models. As studies increasingly aim to detect dose-response relationships in the context of MP/NP effects, the use of primary cells, organoids, and organ-on-chip (OOC) technologies (reviewed in [71,72]) could greatly enhance the relevance and sensitivity of *in vitro* studies.

The physicochemical properties of MPs/NPs are important to consider when interpreting data, as they influence cellular interactions

such as uptake, transport, and cytotoxicity. One of the most influential phenomena affecting their biological behavior is the formation of a protein corona around these particles [73]. Proteins present in *in vitro* culture serum (e.g., fetal bovine serum) or in biological matrices *in vivo* contribute to the development of this corona [74]. This formation can increase particle diameter, promotes aggregation, may induce conformational changes in the associated proteins, and can even enhance MP/NP genotoxicity [75]. Its composition and properties are, in turn, influenced by the intrinsic characteristics of MPs/NPs, such as material type, size, and surface modifications [76]. Unfortunately, some crucial parameters (e.g., the use of serum in tissue culture) are sometimes underreported. For instance, more than half of the *in vitro* studies listed in Table 2 did not specify whether serum was included in the MP/NP diluent. While investigating the direct effects of MPs/NPs on cellular cultures is crucial, their impact on ongoing cellular processes, such as antiviral responses, should also be considered. Wang's team examined the interaction between NPs and virus-infected cells, showing that exposure of A549 cells, a human lung cell line, to 85 nm PS-NPs increased the expression of specific viral proteins necessary for influenza A infection. Furthermore, viral titers nearly doubled, leading the authors to conclude that the presence of NPs could potentially enhance viral infectivity. This effect was attributed to the virus binding to the NPs and entering cells via endocytosis, also reducing cell IFN-β production and weakened the antiviral immune response of the infected cells [77]. It was, however, unclear whether the increased viral titers were attributable solely to facilitated viral entry or if viral replication itself was also affected. Future studies should therefore investigate the latter. Similar findings were observed by Zhang et al., who demonstrated that PS-NPs and MPs (500–1000 nm) could bind to SARS-CoV-2 pseudoviruses. The resulting complex was internalized by HEK-293T cells expressing the ACE2 receptor, which the virus uses for entry. This interaction was also observed in Caco-2 and VERO-E6 cells, facilitating viral entry in an ACE2-dependent manner. This result was confirmed with real SARS-CoV-2 virions, which promoted viral entry but not replication. Additionally, an increase in TNF-α levels was noted, suggesting a stronger inflammatory response in the cells [78]. To further investigate viral transmission, the Huh7.5.1 cell line was used to study the impact of 80 and 150 nm PS-NPs on vaccinia virus (VACV) infection. NPs facilitated viral entry through migrasomes (organelles recently identified as playing a role in cell communication and viral transmission) by 15 hours post-infection, compared to the typical onset at 36 hours. NPs also influenced cholesterol levels, leading to larger lipid droplets and an increased number of migrasomes [79]. Together, these findings suggest that interactions between NPs and viruses can influence host cell infection, potentially impacting antiviral immunity. These findings highlight more indirect effects of MPs/NPs, as they appear to impact viral infectivity itself rather than directly affecting the immune system. Since viral entry, infectivity, and loads directly influence immune responses either positively or negatively, these effects remain important to consider, although this nuance must be acknowledged.

3.2. *In vivo* studies

Recent *in vivo* studies have examined the impact of MPs/NPs on

Table 3
In vivo studies investigating the impact of NPs on immune responses.

Type	Size & modification	Exposure			Subject	Main observations	Ref
		Dosage	Time	Route & diluent			
PS	20, 500, 5000 nm (ζ)	5, 50, 5000 μg/d	14, 28 d	Oral, PBS	BALB/c mice (F)[A]	↓ intestinal IgA levels (20 & 500 nm), ↓ proportions CD4 + & CD8 + T cells in mesenteric lymph nodes (all sizes)	[80]
PS	100 nm, 5, 200 μm	500 μg/L	21 d	Tank water	Zebrafish[A]	scRNAseq showed dysfunctions in intestinal cell: immune responses of enterocytes, phagocytes, and lymphocytes	[81]
PS PE	500 nm (ζ)	10 mg/kg/d	7 d	Oral, CMC	BALB/c mice (sex not specified)[A]	↑ colon Mϕ activation (Il−1β production), lysosomal damage, ↑ proportions of CD4 + (T_H2, T_H17, and Treg) T & NKT cells	[83]
PE	500, 2000 nm (ζ)	10 mg/kg/d	1, 8 w	Oral, CMC	BALB/c mice (M/F)[A]	Gut Mϕ activation, lysosomal damage and IL−1β production, effect on brain immunity	[84]
PS	50 nm (ζ)	0.1, 1, 10 mg/mL/d	28, 32 w	Drinking water	C57BL/6 mice (F)[A]	Histological abnormalities in intestines, ↑ proportion of B lymphocytes in mesenteric lymph nodes, ↓ CD8 + T lymphocytes in lamina propria. ↑ IL−6, TNF-α, IL−1β	[85]
PS PMMA	50 nm 25 nm	0.05 mg/mL	4, 5, 6 m	Drinking water	C57BL/6 mice (F)[A]	No effect on acute DSS-induced colitis	[45]
PS	500 nm (ζ)	0.5, 5, 50 mg/kg/d	6w	Oral, water	C57BL/6 mice (M)[A]	Small intestine Acc, pathological damage, ↑ lymphocyte infiltration. ↑ immune genes: B cell-mediated immunity, Ig production, Ig receptor binding. ↑ serum IgG/IgA	[86]
PS	100 nm	5 μg/g every other day	2w	IP, saline	C57BL/6 mice (M)[A]	Accumulation in the spleen, ↑ LPS-induced disruption of the organ's architecture, necroptosis and oxidative stress	[49]
PS	100 nm	30, 300, or 3000 μg/L	1w	Tank water	Juvenile orange-spotted grouper[A]	↑ replication rate of two viruses targeting the spleen and brain of the fish. ↓ genes related to interferon and TLRs (antiviral responses)	[6]
PS	50 nm (COOH, NH_2)	1 μg	96 h	IP, PBS	European sea bass[A]	Upon viral challenge: ↑ viral replication & clinical signs. ↓ inflammatory & antiviral responses	[90]
PS	40, 200 nm (ζ)	0.01 or 0.1 mg/day	35d	Oral, water	C57BL/6 mice (M/F)[A]	↑ splenocytes IL−12p35 & IL−25 secretion, spleen DNA damage. ↓ splenocytes viability	[91]
PP	5.2, 23.9 μm	500, 1000 or 2000mg/kg/d	28 d	Oral, corn oil	ICR mice (M/F)[A]	No changes in thymocytes and splenocytes numbers. IFN-α/IL−4 ratio: ↓ in females & ↑ in males. ↑ TNF-α production & ↓ IgG2a/IgG1 ratio in females	[92]
PE	40–48 μm (COOH, OH)	0.125, 0.5, 5 mg/d	90d to 110 d (dams)	Oral, water	ICR mice (M/F)[A]	↑ serum IgA. Stomach: mast cell granule migration & degranulation. Spleen: organelle buildup in nuclei/mitochondria, ↓ $CD8^+/CD4^+$ ratio, ↓ mature DCs. Offspring: ↓ body weight, ↓ splenic T cells (F), ↓ DC maturation (M)	[43]
PS	100 nm	1, 50 mg/mL	49d	Drinking water	BALB/c mice (F)[A]	Spleen transcriptomic & metabolomic analysis: regulatory pathways changes, no differences on histopathological or humoral/cellular immunity pathways	[93]
PS	100, 500 nm (ζ)	0.15, 1.5 mg/d	28d	Oral, water	C57BL/6 mice (M/F)[A]	No impact on humoral and cellular antiviral immune responses against VSV and LCMV	[94]

[A] : *in vivo* study, ζ: zeta potential is provided, ↑: increased, ↓: decreased, PS: polystyrene, PE: polyethylene, PMMA: polymethacrylate, PP: polypropylene, Acc: accumulation, BM: bone marrow, Mϕ: macrophage, ROS: reactive oxygen species, PBS: phosphate buffered saline, d: day, w: week.

immune responses. These studies highlight the complex interactions between these particles and immune cells, emphasizing the importance of realistic exposure concentrations in toxicity assessments. This section describes these findings, with a particular focus on gut immunity and the spleen. Table 3 summarizes all the studies described in this section.

3.2.1. MPs/NPs and gut immunity

The intestines, potentially the most exposed organ to MPs and NPs during oral administration, are the focus of numerous studies evaluating the histopathological effects of such exposure. Intestinal mucosal immunity plays a crucial role in the immune system, and its disruption by the presence of these particles has raised significant concern. Recent studies have revealed alterations in intestinal immunity caused by MP and NP exposure.

For example, Zhang et al. exposed mice to PS-MPs/NPs of 20, 500 nm, and 5 μm and found that the two smaller particle sizes led to a significant decrease in IgA levels in the intestines. Additionally, all three sizes resulted in a notable reduction in the proportions of CD4 + and CD8 + T lymphocytes in mesenteric lymph nodes, even at doses as low as 5 μg per day over a period of 28 days. Only female mice were used in this study, and it would therefore be valuable to determine whether the same results can be replicated in males [80]. This reduction in IgA and T lymphocytes highlights the potential impact of NPs on intestinal immunity. A similar pattern was observed in zebrafish, where single-cell RNA sequencing (scRNA-seq) was used to study the effects of PS-MPs/NPs on the intestine (100 nm, 5 μm, and 200 μm for 21 days). Dysfunctions were noted across various intestinal cell populations, including enterocytes, phagocytes, and lymphocytes, as well as a reduction in the detoxification/antioxidant capacity of enterocytes and the chemotaxis of secretory cells. The effects appeared to be size-dependent, with the 100 nm NPs causing the most pronounced impacts [81]. As a highly versatile and traceable model, zebrafish can provide valuable insights into MP/NP interactions with the immune system. That said, it is important to acknowledge its differences from mammalian systems, both in terms of immune function and exposure routes. These immunological differences, which are discussed and reviewed in [82], include a delayed onset of adaptive immunity and later development of its components (4–6 weeks post-fertilization) compared to mammals. Considering these differences, comparisons with mammals should be made with caution when using this animal model.

Yang et al. conducted a study on mice exposed to PE-NPs (500 nm for 7 days). RNA-seq analysis of the cells revealed activation of colon macrophages, with increased IL-1β production. This response was attributed to lysosomal damage caused by the NPs, which also led to an increase in the proportions of CD4 + T lymphocytes and NKT cells in the same region. Specifically, the proportions of T_H2, T_H17, and Treg cells increased, alongside some immunosuppressive markers, suggesting that the NPs induced both an inflammatory and immunosuppressive environment [83]. In the same study, similar results were observed with 500 nm PS-NPs, underscoring a similarity of mechanisms. In another study, the authors confirmed that 500 nm PE-NPs caused IL-1 secretion by intestinal macrophages due to lysosomal damage [84]. However, these exposure periods are in the subacute range, and it would be interesting to investigate whether longer exposures would produce more pronounced effects. Additionally, Li and colleagues examined the effects of prolonged exposure (32 weeks) to 50 nm PS-NPs administered to mice via drinking water. This exposure led to histological abnormalities in the intestines, an increase in the proportion of B lymphocytes in the mesenteric lymph nodes, and a decrease in CD8 + T lymphocytes in the lamina propria. Furthermore, elevated levels of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β were observed. It would be important to determine whether these results can be replicated in male mice [85]. These findings suggest intestinal toxicity linked to prolonged NP exposure, along with a potential impact on the immune system in that region.

Interestingly, Schwarzfischer et al. exposed mice to 50 nm PS-NPs through drinking water and did not observe negative impacts on gastrointestinal health or on the severity of experimentally induced colitis. However, they did find toxicity and inflammation in BMDMs (as described previously). This led authors to emphasize the importance of using more complex *in vivo* models when assessing the toxic effects of NPs [45]. This contrast in findings, compared to the previously mentioned studies, was attributed to the exposure concentrations. The concentrations used in this study were environmentally relevant (estimated at 0.2 mg per day), while other studies typically employed higher concentrations, which could explain the more pronounced toxic effects observed in those cases.

Zhao et al. exposed mice to 500 nm PS-NPs for 6 weeks to investigate the effects of NP exposure on gut immunity. The NPs accumulated in the small intestine and their presence was linked to pathological damage and increased lymphocyte infiltration. Interestingly, serum IgG and IgA levels were slightly and significantly elevated, respectively, following exposure. At the transcriptomic level, genes related to immune responses and homeostasis, such as those involved in B cell-mediated immunity, immunoglobulin production, and immunoglobulin receptor binding, were enriched in the small intestine[86]. However, it remains unclear whether the observed pathologies are directly caused by NPs or rather by additives and/or contaminants present on the particles.

Gut immunity is closely related to and influenced by the gut microbiota [87] and disruptions in host–microbiome interactions have been shown to impair immune function and elevate the risk of inflammatory and metabolic disorders [88]. Potential effects of MPs/NPs on the latter could therefore have a significant indirect impact on gut immunity. As previously mentioned, some studies within the scope of our review have investigated this axis: Jing et al. reported that 80 nm PS-NPs disrupted microbial communities and metabolite profiles, driving inflammation and hematopoietic toxicity in mice [40]. Probiotic treatment ameliorated these effects, highlighting a microbiota-dependent mechanism [41]. Furthermore, the effects of MPs/NPs on gut microbiota and the gut itself have been recently reviewed by Pan et al. [89]. Briefly, MPs/NPs appear to impair gut microbiota homeostasis and cause toxicity through the gut axis, impacting various organs, including the brain, liver, and lungs. This means that the effects of MPs/NPs on the gut microbiota should be further investigated to understand the underlying mechanisms.

3.2.2. MPs/NPs and the spleen

The spleen, a critical organ in adaptive immune responses, is another potential target for MP and NP effects. As noted earlier, bioaccumulation studies have demonstrated that a wide range of plastic sizes can reach this organ following oral administration. Given this, it is crucial to investigate whether this accumulation leads to significant consequences for the spleen and the immune responses it supports.

Tang and colleagues have conducted research on the effects of NPs on the spleen. They evaluated the impact of 100 nm PS-NPs on splenic inflammation induced by LPS injection in mice. Their findings showed that the intraperitoneal (IP) injection of NPs led to their accumulation in the spleen, exacerbating the disruption of the organ's architecture caused by LPS. In addition to the inflammation induced by LPS, the NPs further promoted necroptosis and oxidative stress [49]. As an administration route, IP injection is not representative of typical exposure route for MPs/NPs [16], which should be acknowledged as a limitation when interpreting these conclusions. Still,while this study is somewhat distant from the context of oral administration, it highlights the sensitivity of the spleen to NP exposure. Interestingly, Wang et al. conducted another study on the orange-spotted grouper, a fish species, demonstrating that PS-NPs reduced protection against certain viral pathogens. Both *ex vivo* and *in vivo* observations indicated that NPs increased the replication rate of two viruses targeting the spleen and brain of the fish. Moreover, the expression of genes related to interferon and Toll-like receptors (TLRs) was reduced, suggesting an impact on the antiviral response [6]. Similar

evidence, including increased viral titers, elevated inflammation markers, and decreased antiviral markers, was found in European sea bass exposed to 50 nm NPs [90]. Although these studies do not focus on mammals, they are crucial for illustrating how NPs can affect antiviral responses, particularly those related to the spleen.

In male mice, Nikolic et al. showed that prolonged exposure to 40 or 200 nm NPs for 35 days resulted in increased secretion of IL-12p35 and IL-25, as well as a decrease in splenocyte viability and an increase in DNA damage in the spleen of the mouse. These effects suggest significant immune and cellular disruption [91]. Kusma et al. also studied the effect of polypropylene (PP) MPs (5.2 and 23.9 μm) on thymic and splenic immune populations in both male and female mice. While the doses used in this study were relatively high, with the lowest being 500 mg/kg/day, corresponding to approximately 15 mg/day for a 30 g mouse, no significant differences were found in the numbers of thymic CD4 + , CD8 + , and CD4 +CD8 + T cells, as well as splenic cytotoxic T cells, helper T cells, and B cells after four weeks of exposure. Furthermore, *ex vivo* activation of splenocytes showed a lower interferon-γ to IL-4 ratio in females, while the opposite was observed in males, independent of particle size and dose. Female splenocytes also exhibited increased TNF-α production. Finally, the serum IgG2a to IgG1 ratio was reduced only in female mice that received the larger MPs [92].

A more recent study conducted transcriptomic and metabolomic analyses of mouse spleens after 49 days of exposure to 100 nm NPs via drinking water (1 and 50 mg/mL). Despite some changes in regulatory pathways, no significant histopathological differences or direct impacts on humoral or cellular immunity pathways were observed, even at such high concentrations [93].

Finally, our group recently showed that 28 days of oral exposure to 100 nm and 500 nm PS-NPs did not have significant effects on antiviral responses in both male and female mice. More specifically, using vesicular stomatitis virus (VSV) and lymphocytic choriomeningitis virus (LCMV) as viral infection models, humoral and cellular antiviral responses were assessed in the context of NP oral exposure. NPs did not alter the total or specific antibody responses against VSV, nor did they affect the cellular responses (T cell phenotypes, activation, exhaustion, and functionality toward viral epitopes) against LCMV. Additionally, splenic immune populations and serum pro-inflammatory cytokines remained unaffected in both experimental models [94].

Several studies mentioned in this review demonstrate (1) the importance of more complex in vivo models, as well as (2) the use of environmentally relevant exposure concentrations when assessing the toxicity of NP exposure. Exposure studies conducted in complex organisms (e.g. mice) with relevant concentrations tend to reveal fewer alarming results.

4. Discussion

4.1. Key findings

Based on the evidence discussed, it appears that MPs/NPs affect immunity at multiple levels. *In vitro* studies using mouse immune cells (e.g. the RAW 264.7 macrophage cell line or BMDMs) show that MP/NP internalization is associated with cytotoxicity, ROS accumulation, and apoptosis. These effects seem to depend on several factors, including dose, particle size, and surface functionalization of the particles used.

These studies also link ROS accumulation to the activation of inflammatory pathways, such as the cGAS–STING, NF-κB, and MAPK pathways. While the precise mechanisms of ROS-mediated activation, such as through mitochondrial DNA release and detection, are beyond the scope of this review, they are well characterized in the following references for the three mentioned pathways, respectively: [86–88]. Activation of these pathways can, in turn, lead to downstream outcomes such as increased apoptosis and the secretion of pro-inflammatory cytokines like IL-1β, IL-6, and TNF-α. Notably, some of these responses may also involve the inflammasome, as suggested by increased NLRP3 gene expression. Some studies involving T cells also report reduced functionality, although further investigation is needed to clarify the underlying mechanisms. In parallel, many studies using mouse primary cells or macrophage cell lines report a polarization toward the pro-inflammatory M1 phenotype, which aligns with the above observations.

Interestingly, *in vitro* studies using human-derived cell lines show both similar and divergent outcomes. ROS accumulation and pro-inflammatory cytokine release are also observed; however, some studies report anti-inflammatory effects as well, including IL-10 secretion and macrophage differentiation toward the M2 phenotype. Histamine release by mast cell lines also appears to be affected by MPs, either positively or negatively, depending on their size, dose, and material type. However, there are still not enough studies on this topic, and this cell type needs to be further investigated. These findings are important, as they suggest that results from mouse-based studies may not be directly translatable to humans, a limitation that will be discussed in the next subsection. Lastly, human cell-based *in vitro* studies indicate that MPs/NPs may also influence viral infections: increased viral titers have been observed in the presence of these particles. However, it remains unclear whether this effect is due to enhanced viral entry, increased replication, or both. Fig. 1 provides a schematic of the key *in vitro* findings discussed in this section.

There are fewer *in vivo* than *in vitro* studies assessing the impact of MPs/NPs on immunity. Nevertheless, some conclusions can already be drawn. Many of these studies focus on gut immunity, as it is considered the most exposed area, and report inflammation-related phenotypes, including the presence of inflammatory cytokines, such as IL-6, TNF-α, and IL-1β, alterations in immune cell proportions (macrophages, T cells, B cells), lysosomal damage, histological abnormalities in the intestines, and changes in immunoglobulin levels, particularly IgA.

The spleen has also been assessed, but the observed effects vary between studies. Some report DNA damage and reduced splenocyte viability, while others find no significant effects in these areas or in immune-related metabolic and transcriptomic profiles. These discrepancies may be due to differences in experimental models. As previously noted, MPs/NPs also appear to have limited or no significant impact in pathological models, such as DSS-induced colitis or viral infections, although data from such models, particularly in mammals, remain limited. It remains an open question whether these effects would remain the same in different, potentially more environmentally relevant models (see next subsection). Other secondary lymphoid organs, such as lymph nodes and mucosa-associated lymphoid tissues, are currently underrepresented in this area of research and should therefore be investigated more thoroughly.

4.2. Limitations of current models

Our understanding of the effects of MPs/NPs on the immune system is becoming more precise, but there is still much work to be done on the subject. While *in vitro* studies involving various cell lines, both mouse- and human-derived, are increasingly common, *in vivo* exposure studies on immune responses remain limited. Even when using such complex models, it is important to remain cautious when translating conclusions to humans. As observed in *in vitro* studies comparing mouse and human cells, overall trends differed between the two, with mouse cells exhibiting more pronounced pro-inflammatory effects, while some anti-inflammatory responses were observed in human cells. Although the mouse is the most used animal model, it differs fundamentally from humans in some aspects. This means findings in mice should not be directly generalized to humans [95]. For instance, at least 169 immune-related genes exhibit species-specific differences between the two [96]. One notable example is the ratio of lymphocytes to neutrophils in peripheral blood: humans typically have a higher percentage of neutrophils and fewer lymphocytes compared to mice [97]. While this topic is beyond the scope of the present review, it is essential to consider

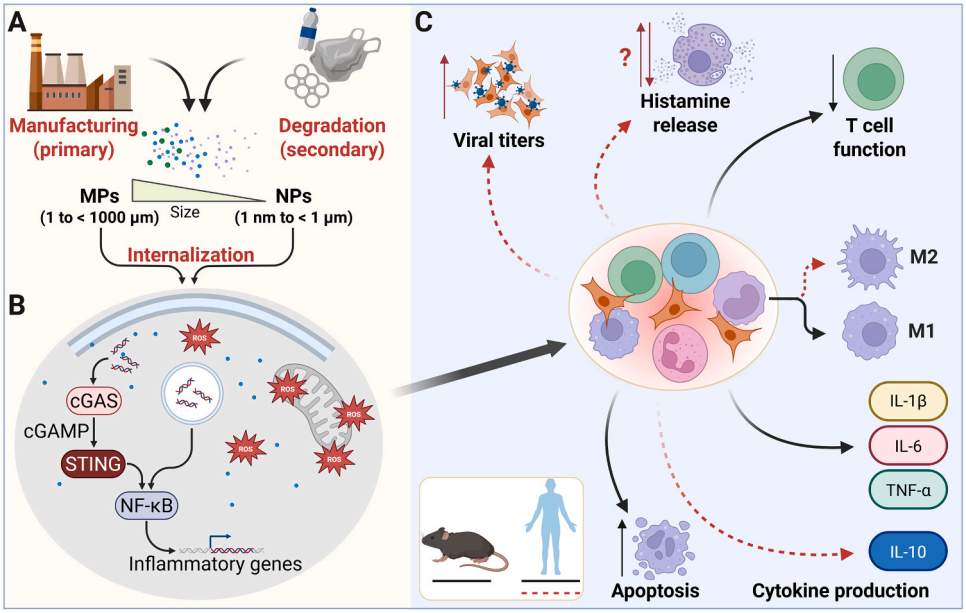

Fig. 1. ***In vitro*** **effects of MPs/NPs on immune cells. (A)** Engineered or degradation-derived microplastics (MPs) and nanoplastics (NPs) can be internalized by murine and human cells. **(B)** Intracellular accumulation of MPs/NPs induces reactive oxygen species (ROS) generation, DNA damage and lysosomal dysfunction, activating inflammatory pathways, such as the cGAS–STING and NF-κB pathways and causing the expression of inflammatory genes. **(C)** MPs/NPs exposure alters key immune functions, including cytokine production, macrophage polarization, apoptosis, T cell function, mast cell histamine release and viral infection. Solid black arrows indicate effects observed in both murine and human cells. Dashed red arrows indicate findings specific to human cells. Question mark indicates that both increases and decreases have been observed, depending on experimental context. Created in https://BioRender.com.

such interspecies differences, as reviewed by Bin et al. [95]. Mechanistically, a number of studies have linked the observed inflammatory markers to ROS accumulation, but also inflammasome activation, and induction of the cGAS–STING and NF-κB pathways. Understanding how MPs/NPs interact with key mediators of these pathways would provide valuable insight.

As an alternative to animal models, we mentioned OOCs to study the effects of MPs/NPs in a more physiologically relevant environment. Nanoparticle toxicity, such as that of gold and titanium dioxide, has already been assessed using various OOC models, such as endothelium-on-a-chip, lung-on-a-chip, heart-on-a-chip, gut-on-a-chip, and liver-on-a-chip (reviewed in [72]). These technologies enable the study of their effects under physiological conditions that more closely mimic *in vivo* environments. For example, incorporating flow in endothelium-on-a-chip models prevents nanoparticle sedimentation typically observed in standard flask cultures and simulates real blood circulation. As OOC technology is still a relatively new field, there are very few studies investigating the effects of MPs/NPs using these systems. Abdessalam et al. recently reviewed studies utilizing OOCs to assess the impact of various toxicants. More importantly, they also compiled the limited number of publications exploring MP/NP effects using OOC models [98]. With advancements in the field and the emerging development of immunocompetent OOC models [99], these systems could soon serve as alternatives to animal models for investigating the effects of MPs/NPs on the immune system.

4.3. Physiochemical considerations

Most of the studies cited in this review, which is well representative of the current state of the MP/NP literature, at least regarding immunity, use spherical MPs/NPs. This tendency stems from an effort to ensure control and reproducibility but ultimately distances the experimental samples from environmental MPs/NPs. Considering that some studies have found different effects depending on the shape of MPs used, for example, beads show less gut accumulation and toxicity than fragments and fibers in zebrafish [100], shape should be considered as important a variable as size, as further discussed in [101]. Relying solely on perfectly spherical MPs/NPs may lead researchers to underestimate the actual toxicity of these materials. Much of the evidence presented here comes from studies using PS as the primary material. Yet, as shown in studies comparing different polymers, the effects can vary depending on the type of plastic used. Therefore, some of the conclusions drawn should not be generalized to all plastic types, as this may misrepresent real-world scenarios.

In line with the two previous points discussed above, the vast majority of studies described here use MPs/NPs prepared in laboratories rather than real-world samples. This represents a limitation in the field, as environmental samples may differ significantly not only in terms of material and shape but also because they can carry adsorbed pollutants or contaminants that could influence immune responses. MNPs may serve as vectors for a variety of pollutants, including heavy metals, pharmaceuticals, bacteria (which may be antibiotic-resistant), and even viruses (reviewed in [102]). The ability of MNPs to serve as vectors for bacteria and viruses has been confirmed for multiple pathogens [103], and some of the studies discussed here have shown that they can influence viral infections *in vitro*. This area of research warrants further investigation, not only into the effects of plastic-bound pathogens but also other associated pollutants.

The formation of a protein corona, as previously described, is an important factor to consider. However, other physicochemical characteristics of MPs/NPs also play critical roles. Surface functionalization is one such characteristic. As demonstrated in several studies, particularly *in vitro*, it can significantly influence interactions with cells. The most commonly studied surface modifications involve the addition of positively charged amino (-NH_2) groups and negatively charged carboxyl (-COOH) groups, especially on PS particles. Both modifications are known to enhance interactions between MPs/NPs and cells, with amino groups generally associated with higher toxicity than carboxyl groups (as reviewed in [104,105]). This increased toxicity was also observed in some of the studies discussed here [63–65]. Surface functionalization is also known to directly influence protein corona formation, which tends to occur more readily on negatively charged MPs/NPs [106]. In

addition to surface charge, the zeta (ζ) potential (which is influenced by the formation of a protein corona) is another important factor that affects interactions with cells and MP/NP toxicity [105]. A positive correlation has been reported between zeta-potential and cellular internalization [107]. For this reason, MP/NP studies commonly assess and report the zeta-potential of their particles, as shown in our tables.

Different methods are used to produce MPs/NPs each of which can influence their physicochemical properties. Techniques such as cryomilling and laser ablation tend to generate more environmentally relevant particles, as they involve the breakdown of larger fragments into smaller ones, resulting in irregular shapes and heterogeneous sizes [108], [109]. In contrast, methods like solvent evaporation or emulsion polymerization produce particles with uniform sizes and shapes (reviewed in [110]) and are sometimes used by commercial MPs/NPs suppliers. Although a detailed description of these methods is beyond the scope of this review, it is important to consider the material variability introduced by different production techniques during analysis. For instance, laser ablation has been shown to introduce weak acid groups on PET-NPs [111], whereas cryomilling did not alter the surface chemistry of PS-MPs/NPs [108]. This highlights that the production method can influence the shape, size distribution, and surface chemistry of MPs/NPs, thereby affecting key physicochemical parameters such as protein corona formation and ζ potential and ultimately impacting cell interactions and cytotoxicity. Most of the studies described here use pristine, non-functionalized MPs/NPs, which may differ from those obtained using some of these methods and biologically relevant samples. Consequently, as stated by Gouin et al., a comprehensive evaluation of the potential health risks associated with environmental MP/NP exposure requires improved particle characterization and the development of standardized methods for producing relevant model particles [112]. Exposure duration, dose, and pathway

Additionally, future studies should focus on using more environmentally relevant exposure doses, as well as longer exposure periods. Most of the *in vivo* findings discussed were conducted using high doses over subacute timelines (28 days or less). The physiological relevance of this kind of model could be questioned, as real-life exposure more closely resembles a low-dose, chronic scenario. Employing subchronic (around 90 days) and chronic (around 180 days) [113] exposure durations in longitudinal studies could be particularly valuable, as they better reflect real-life exposure conditions. This approach could reveal delayed or persistent immune effects that are not detectable under current study designs.

The route of exposure should also be considered an important variable, as oral administration is commonly performed either via gavage or by dilution in drinking water. While gavage ensures consistency and reproducibility, it is highly invasive and can induce significant stress. This stress may influence certain experimental readouts, especially regarding immunity, and its effects may be hard to dissociate from MP/NP-related effects. In that context, having the right controls becomes even more important. In contrast, dilution in drinking water is non-invasive and does not require handling but presents challenges in accurately quantifying exposure. Consequently, exposure via drinking water should be privileged for longitudinal studies as it is less invasive and more representative of real-world exposure.

Furthermore, there is still a lack of studies investigating the intergenerational effects of NPs on immunity. Such longitudinal studies could also examine whether NP-induced toxicity affects the development of the offspring's immune system. While some evidence discussed here suggests adverse immune effects in offspring following maternal exposure to MPs (40–48 μm), it remains essential to assess whether similar effects occur with smaller MPs or NPs [43]. Moreover, the observed effects occurred at relatively high doses and further investigations using more environmentally relevant exposures are needed to better understand their impact on immune responses. MP/NP transgenerational effect has also been investigated and reviewed in other biological contexts, such as (non-exhaustively) survival, energy metabolism, and development [114], but evidence specifically concerning immune function remains limited. Combined with environmentally relevant doses (mimicking human low-dose exposure setting), such experiments could produce highly meaningful results with greater relevance to human health. Ultimately, conventional doses should be established to ensure that data gathered across different systems and models can be compared.

4.4. Future directions

Many studies focus on the immune responses elicited by MP/NP exposure, but research exploring their impact on the onset of immune responses against foreign antigens (e.g. viruses) is scarce, especially in mammals. To date, there is only one *in vivo* study of this type [94], which investigates antiviral immune responses with a focus on the spleen. Given the evidence that PS-NPs (75–90 nm) can induce lung damage (e.g. fibrosis, inflammation, necrosis) in mice through cGAS-STING signaling activation [53], it can be hypothesized that viral pulmonary infections, such as those caused by influenza A, could be influenced by NP exposure, thereby supporting the already established *in vitro* evidence [77]. Infection coupled with MP/NP exposure should therefore be a subject for future *in vivo* investigations. Such studies could provide insight into possible reasons for poor establishment of immune responses, immune memory, and anti-vaccinal responses in certain contexts. While the presented studies appear to show limited effects of MPs/NPs on spleen-mediated immune responses, this does not rule out the possibility of effects on antiviral responses elicited by other secondary lymphoid organs or on vaccination responses. NP accumulation is variable between organs, with the digestive system being the most exposed in oral exposure settings [27], [28]. Study models should account for this and explore immune responses against pathogens with different tropisms. Norovirus, which targets the gut in mice, could serve as a suitable model to study immune responses in this context [115]. We acknowledge that other secondary lymphoid organs, such as lymph nodes and mucosa-associated lymphoid tissues, are scarcely covered in this review. This is due to the current lack of studies investigating the effects of MPs/NPs on these organs, which represents a significant limitation in the field. Consequently, future research should also account for that gap.

Finally, while foreign antigen responses warrant exploration in the context of MP/NP exposure, autoimmune, immunocompromised, and inflammatory disease models should also be investigated in similar contexts, like already demonstrated in an induced colitis model [45]. Autoimmune diseases, such as systemic lupus erythematosus, could also be studied using commonly used mouse models like the MLR/lpr strain, known to spontaneously develop the disease [116]. The establishment and maintenance of immune memory (whether through humoral or cellular responses) should also be investigated in similar contexts, as it is a key component of the adaptive immune system. While the direct effects on immune responses may not be immediately evident, immune memory could also be affected over time, which may not be apparent at first glance.

5. Conclusions

The growing prevalence of MPs/NPs in the environment raises significant concerns regarding their potential toxicity, particularly in relation to immune system health. Studies have highlighted the widespread distribution of MPs/NPs across various biological systems, with evidence suggesting that these particles can accumulate in critical immune organs. Although *in vitro* and *ex vivo* studies provide valuable insights into the direct toxic effects of MPs/NPs on immune cells, results from *in vivo* studies are more nuanced, emphasizing the need for more realistic exposure models. First, *in vitro* studies show tendencies toward cellular toxicity and altered immune cell behavior. Mouse cell-based studies tend to show predominantly pro-inflammatory responses,

whereas studies using human cell lines report more variable results, with both pro- and anti-inflammatory effects observed. In contrast, *in vivo* studies reveal more complex outcomes, with some suggesting significant effects on organ systems such as the spleen and intestines, while others conducted under environmentally relevant exposure conditions indicate minimal or no impact.This means that, despite some evidence of MNP-induced immune disruption, including inflammation and changes in immune cell function, the effects appear to be dose, model and material-dependent and may vary across different species and exposure conditions. Importantly, the fact that environmentally relevant concentrations of MPs/NPs often lead to less severe outcomes, underscores the necessity of considering exposure levels in toxicity assessments. This has important implications for human health, as the immunopathological effects of NPs remain unclear, while the available evidence suggests potentially alarming, context-dependent effects. To establish clear policies on plastic production and use, robust evidence of their effects on various biological systems, including the immune system, is essential, highlighting the need for further research in this area.

Moving forward, more comprehensive studies are needed to fully understand the long-term implications of NP exposure on immune system development and function, with more focus on the interactions between NPs and pathogen responses.

CRediT authorship contribution statement

Alain Lamarre: Writing – review & editing. **Guillaume L. Lopez:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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