Narrative Review Article

Immune Disruption and Disease Development by Microplastic Exposure

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ABSTRACT

Global plastic production will grow from 464 tons in 2020 to 884 tons in 2050, and microplastics (MPs) and nanoplastics (NPs) resulting from the decay of larger pieces have become ubiquitous. Thus, almost all humans are exposed to these particles through ingestion, inhalation, and dermal contact. Research on MPs has grown significantly since their major start in 2018, but because of their novelty, MPs' full effects on human health are not well defined, especially in the immune system. This paper aims to provide a review of this topic. An array of contemporary data has been gathered regarding the effect of MPs on the different types of cells and responses involved in the immune system. This paper also explores the roadblocks in researching this topic. It is concluded that MPs weaken the innate and adaptive immune system, can accumulate in lymphatic tissue, cause inflammation and inflammation-related processes across the body, which result in a variety of negative health effects from autoimmune reactions to cancer susceptibility. This paper provides a comprehensive foundation for the current understanding of the impacts of microplastics on human health and underscores the numerous aspects in which further research is needed.

Keywords: Microplastics; Immune System; Inflammation; Pollution; Lymph; Health; Human Exposure

INTRODUCTION

A plastic is defined as a material that is composed of synthetic or natural polymers. There are numerous types of plastics, including polypropylene (PP), polyethylene (PE), and polyvinyl chloride (PVC), among others. Plastics are highly demanded due to their versatility and unique properties (1). Current research suggests that global plastic production will grow from 464 tons in 2020 to 884 tons in 2050 (2). Different size classes of plastics are formed due to the breakdown of larger plastics: nanoplastics, or NPs (1 nm-1 μm) (3); microplastics, or MPs (0.5-5 mm); mesoplastics (0.5-5 cm); macroplastics (5-50 cm); and megaplastics (>50 cm) (4).

Plastic tends to degrade very slowly naturally (5). These particles can be found in marine areas, such as the open sea (6) and deep-sea sediment (7), likely due to the several million tons of plastic waste that flow into the ocean every year (8). MP particles have also been found in soils. These particles can transport toxins deep into the soil and contaminate groundwater (9).

Particles have also been found in the atmosphere of cities of 6000 people or more across multiple

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continents (10). They have also been found in indoor air environments (generally with low air renovation and high amounts of synthetic materials) at much higher frequencies than outdoor air (11), as well as remote areas with little human exposure (12). Microplastics have been found in commonly consumed substances, such as salt, beer, tap (13) and bottled water (14), honey, sugar (15), and over 220 marine animal species (16). Microplastics have been found in synthetic cloth materials, such as clothing and soft indoor furnishings. Finally, they have been found in substances commonly applied to the skin, like cosmetics, facial cleansers, and shower products (17).

Due to the prevalence of MPs, many humans regularly absorb them through ingestion, inhalation, and dermal contact (18). The immune system is one of the most important systems in the body because it is in charge of fighting infections and cancer. It is also one of the systems that is most exposed to MPs because of its presence throughout the entire body, and thus, it is one of the most affected. Thus, compiling information on the relationship between it and ubiquitous MPs can give new insights into these diseases, and is critical to our understanding of how MPs will continue to impact human health in the future.

This review paper focuses on how MPs can disrupt the immune system and cause pathology. Research in this topic was low until 2018, evidenced by the number of papers published in databases such as PubMed. Most papers in this area are focused on the respiratory, digestive, and cardiovascular systems, leading to a lack of research surrounding the relationship between MPs and the immune system, though it is one of the most affected systems by MPs. The main purpose of this paper is to compile information about how vulnerable the immune system is to MPs and make it more accessible, allowing for more research in this area to continue. This paper will focus on the innate and adaptive immune system, the lymphatic system, and the inflammatory response.

ENTRY OF MICROPLASTICS INTO THE BLOODSTREAM AND IMMUNE SYSTEM

Humans can absorb MPs and NPs into their bodies through ingestion, inhalation, and dermal contact (Figure 1A). Upon ingestion in the gut lumen, very small MP particles smaller than 8 μm can directly cross through the epithelial cell barrier and into the bloodstream (19). Some larger particles in the intestines can also be absorbed by the microvilli of the cells and the microfold (M) cells that cover Peyer's patches (20). Likewise, small inhaled MP particles that are not trapped by the mucosal lining of the respiratory system can also pass across the alveolar epithelial cells barrier to enter the bloodstream (19). Larger MP particles can be trapped more easily by the mucociliary clearance when they are inhaled. However, the constant outward beating of the cilia can cause these particles to be transported back up into the pharynx and swallowed, ultimately ending up in the intestines, where they are absorbed as previously mentioned (21). Humans come into physical contact with MPs through the skin very often; however, dermal contact is the least common way for particle entry. Skin epithelial cells are the first to be exposed to external microplastics. MP particles less than 150 μm have the potential to enter the body through epithelial cells (Figure 1B), where they may then possibly be phagocytosed by certain immune cells and transported throughout the body (22).

MPs in the Human Bloodstream

Because of these three routes of exposure, MPs have been found in the human bloodstream in multiple studies. Leonard *et al*. [2024] analyzed the blood of 20 healthy adult donors in the UK and reported MP concentrations ranging from 1.84–4.65 μg/mL, with polyethylene (PE), ethylene propylene diene, and ethylene-vinyl-acetate/alcohol being the most common (23). Similarly, Leslie *et al*. [2022] studied the blood of 22 healthy adult donors in the Netherlands and reported MP concentrations ranging from 1.6μg/mL, with polyethylene terephthalate (PET), PE, and polymers of styrene being the most frequent (24). (Figure 1C) These studies provide preliminary evidence that MPs circulate in human blood, but the limited sample sizes, differences in methodology, and variation in location show the need for large-scale, standardized studies to fully determine prevalence and health consequences.

Transport of MPs Into Lymph Vessels

Due to their role in filtering interstitial fluid and returning it to the bloodstream, the lymph system also plays an important role in MP absorption. Barboza *et al*. [2018] suggest that MPs that are less than 150 μm can cross from the intestines into the circulatory system, including the lymph, where they can then spread throughout the body (Figure 1C) and reach different tissues (25). The details about accumulation in the lymphatic system will be discussed later.

Uptake of MPs by Immune Cells

After entry into the circulatory system, some MP particles can be phagocytosed or macro-pinocytosed by various innate immune cells (26) (Figure 1D). Other very small particles can pass through the cell membrane of the immune cells directly, by interacting with membrane proteins (26). However, both of these scenarios depend upon the type of plastic: the different charges and structures of the MPs cause different interactions. For example, Abihssira-García *et al*. [2020] exposed different Norway salmon (*Salmo salar*) immune cells to PE MP, PS MP, and both types at once at different particle concentrations, showing that the PE MPs were endocytosed more easily and built up more (27).

EFFECTS OF MPS ON INNATE IMMUNE CELLS

The innate immune system is the first line of active defense against pathogens and foreign materials. The cells that make up this system consist of: phagocytes that ingest antigens, such as macrophages, monocytes, and neutrophils; granulocytes that release enzymes or other proteins upon detecting an infection, such as basophils, eosinophils, and mast cells; natural killer (NK) cells, which attack cancer or infected cells; and dendritic cells, which connect the innate immune system with the adaptive.

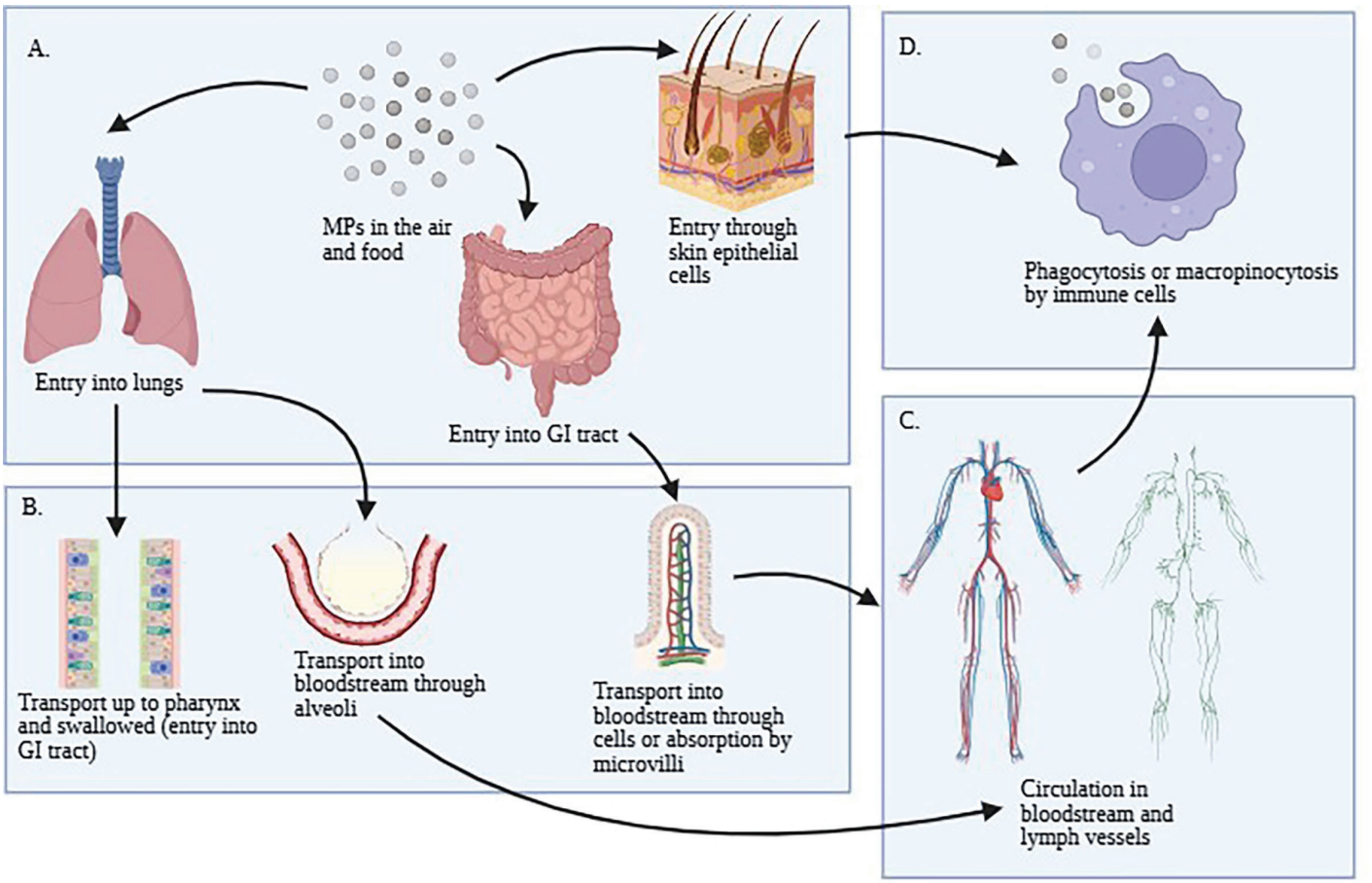

Figure 1. Routes of Exposure to MPs. MPs can enter the body through different routes. A. Representation of ubiquitous MPs entering the body through the lungs, GI tract, or the skin. B. MPs can enter the pharynx and be swallowed to enter the GI tract, be transported from the alveoli into the bloodstream, or be absorbed in the GI tract by microvilli and M cells. C. MPs in the bloodstream and lymph vessels allow them to reach all parts of the body. D. MPs can enter immune cells by active phagocytosis/pinocytosis or interact with membrane proteins to pass through. Created in BioRender.com.

Protein Biocorona

When MP particles enter the blood, numerous blood proteins, such as immunoglobulin chains, lipoproteins, complement proteins, acute phase proteins, and coagulation factors, may attach to the surface of the particles, forming a cover called a protein biocorona. The formation and composition of this corona are dependent on the charge and size of the proteins; this was demonstrated by Lundqvist *et al*. [2008], where 6 types of PS (polystyrene) NP were exposed to the blood proteins of 10 healthy human donors in Europe (28). Since the biocorona will contain different types of proteins, the response to and location of the buildup of the MPs will depend on that (Figure 2A). The small sample size, as well as the limited scope of knowledge on this topic, means observing the response to a few types of MPs is not enough to deduce the effects of every type.

Harmful Effects on Neutrophils and Macrophages

MPs can cause some harmful effects in neutrophils. Park *et al*. [2024] observed that when neutrophils from healthy mice (*Mus Musculus*) and the blood of healthy human donors were exposed to PS MPs, the particles strongly bound to and were engulfed by the neutrophils. They also deduced that by acting as bacterial-antigen mimics, the particles interacted with Toll-Like Receptors (TLRs) on the surface of these cells, causing the cells to enter a proinflammatory state. This eventually leads to apoptosis, caused by upregulation of apoptosis-related genes (29). Similarly, Adler *et al*. [2024] demonstrated that by exposing human macrophages from the THP-1 monocyte cell line to PS microbeads (MBs) and nanobeads (NBs), synthetic sphere-shaped MPs, the particles will often be phagocytosed by the cells and cause cell death (Figure 2B) due to cytotoxicity (30).

Redirection of Neutrophils and Macrophages

Although exposure to MPs and NPs can cause apoptosis, exposure to these particles can also cause a redirection of these cells to the area of exposure. For example, Limonta *et al*. [2019] exposed adult zebrafish (*Danio rerio*) to two different concentrations of PE and PS MPs through water over 20 days. It was found that the number of neutrophils in the gill and intestinal epithelial regions was increased, caused by altered immune gene expression. They also predicted that because the neutrophils are being redirected, the ability to fight off infections in other areas may be weakened (31). Similarly, when Chen *et al*. [2024] exposed 6-8 week old male mice to PS NPs through ingestion over 21 days, it was revealed that there was a high number of recruited macrophages and neutrophils in the intestinal area (Figure 2C) due to the particles activating inflammatory pathways and inducing the release of cytokines (32).

Effects on Other Innate Immune Cells

There have been fewer studies done on the other cells of the innate immune system due to their lower frequency and more specific functions. Wei *et al*. [2024] exposed mice to PS and dibutyl phthalate (DBP) – a plastic additive – MPs over 5 weeks. This caused the generation of ROS, which then caused elevated eosinophil levels (eosinophilic inflammation) (33). However, this study was conducted with the intention of finding a link between eosinophillic allergic asthma and MPs in the lungs, which means the effect may not be consistent throughout the whole body. Next, González-Soto *et al*. [2022] showed that when 600 collected wild marine mussels (*Mytilus galloprovincialis*) were exposed to MPs through ingestion over 21 days, the volume density (and the internal pressure) of basophils was increased significantly (34). However, this study not only exposed the mussels to MPs but also to crude oil, meaning the effect is not as definitive. Finally, Zhao *et al*. demonstrated that when adult male C57BL/6J mice were fed MPs over 4 weeks, NK cells increased their infiltration and activation (Figure 2D), causing liver inflammation (35). While this provides a good understanding of NK cell responses, the location is limited to the liver, so the scope may need to be expanded.

EFFECTS ON ADAPTIVE IMMUNE CELLS

The adaptive immune system is the slower but more specific defense against pathogens. This system mainly consists of different T and B lymphoid cells. T cells have three main types: helper (CD4+), which activate other T cells and B cells by releasing cytokines; cytotoxic/killer (CD8), which identify and kill infected or cancerous cells; and suppressor (Tregs), which inhibit the overreaction of other immune cells. After being activated, B cells differentiate into plasma (effector) cells that release antibodies or memory cells that store the information of the antigen for future reencounters. Antibodies, or immunoglobulins, are proteins that tag and neutralize pathogens by attaching to them. Finally,

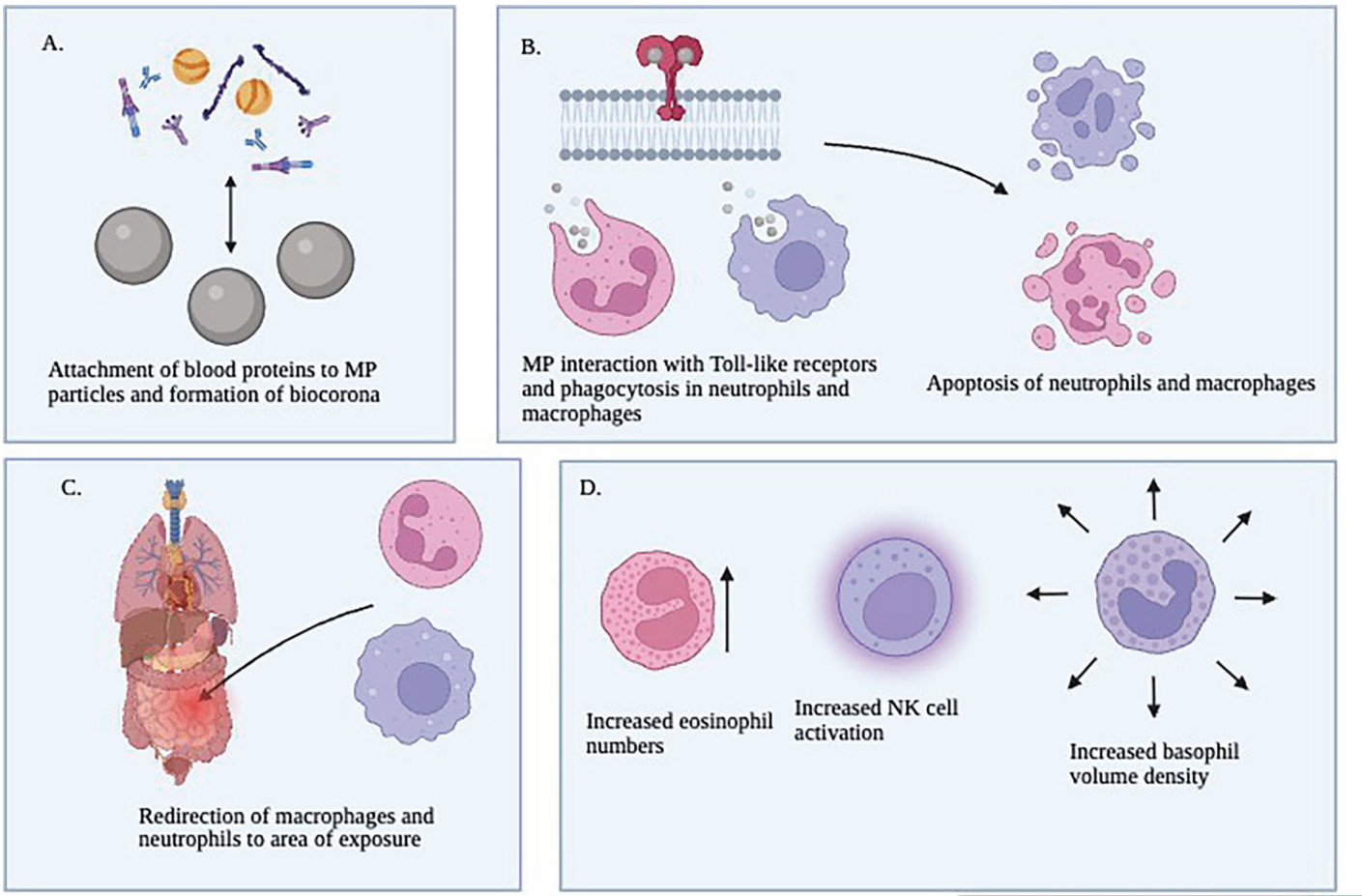

Figure 2. Effects of MPs on Innate Immunity. There are various impacts of MPs on innate immunity. A. An MP particle's fate is determined by the proteins that make up its biocorona. B. MPs can interact with TLRs to induce apoptosis in neutrophils and macrophages. C. MPs can cause a decrease and redirection in macrophages and neutrophils. D. MPs can increase the number of eosinophils, the activation and infiltration of NK cells, and the volume density of basophils. Created in BioRender.com.

dendritic cells mainly function as the bridge between the innate and adaptive immune systems, but also enhance the immune response by releasing cytokines.

Effects on T Cells

MPs have varying effects on T cells. In a 2024 study by Swenger *et al.* aimed at metabolic dysfunction-associated steatotic liver disease (MASLD), it was found that the number of killer T cells from a bariatric sample population increased along with the number of MP fibers detected in the stool (36). However, due to the limited scope of the study to the liver, stool samples, and GI tract, as well as the limited sampling from those undergoing bariatric surgery (36), the results are not conclusive. In contrast, Zhang *et al.* [2023] found that when adult female BALB/c mice were exposed to different types of MPs and NPs for 28 days, it was found that there was a large decrease in T cell differentiation and thus a much lower number of mature T cells in the mesenteric lymph nodes (37). Due to differences in experiment design, such as using mice, as well as analyzing the lymph nodes instead of the liver, the results are directly contradictory to the previous ones. Yet, when Wolff *et al.* [2023] exposed human T cells to different sizes of pristine (not degraded by the environment) PS, pristine polymethyl methacrylate (PMMA), and amine-modified (addition of NH_2) PS MP, it was found that the proportion of

living cells remained relatively constant, except in the case of the amine-modified PS, when it induced cytotoxicity (38). Here, the results likely differed from the previous studies because of the different MPs being tested. Finally, a data set analysis by Zeng *et al*. [2025] about diabetic nephropathy (a condition where diabetes weakens the kidneys) found that PET MPs can induce DN by reducing the number of killer T cells and increasing the number of suppressor T cells in humans (39). This study was different from others due to the different types of T cells having different responses to MP exposure. Though this has a large sample size, the study is limited in scope to this kidney-specific disease and does not provide a full view of the effects.

Effects on B Cells

Similarly, MPs can also affect B cells in different ways. In the previous study by Swenger *et al*. [2024], B cells also had a similar positive correlation to total MPs detected in the stool (36), but the scope and sampling are limited in the same ways. Similarly, when Li *et al*. [2023] exposed 5-week-old female C57BL/6 J mice to PS NPs for 32 weeks to find the effects of chronic MP exposure on the intestinal barrier, it was found that the proportion of B cells, compared to T cells, in the mesenteric lymph nodes increased (40). The scope of this study is limited to the mesentery and does not cover the effect on the periphery of the body; thus, it is not comprehensive for the whole body. On the other hand, when Zwollo *et al*. [2021] exposed rainbow trout (*Oncorhynchus mykiss*) primary culture cells to PS MPs and microbeads, it was found that the biggest impact of the exposure was the significant reduction of the population of developing B cells (41). In this case, the entirely different species being studied means it may not correlate with humans, meaning it can only be taken lightly as preliminary evidence.

Effects on Antibody Production

The effects of MPs on antibodies may also harm the human body. A computer-simulated study by Enoyh *et al*. [2023] was conducted to investigate the potential toxicity and immunosuppression caused by microplastics in infants through breast milk. It was found that all the NPs used in the simulation bound to IgA antibodies more so than the control substances, and had the potential to inhibit the antibodies from functioning once ingested by the infant (42). Though the highly regulated computer modeling methodology can give plausible results, this study is not concrete until the same scenario is tested in an actual experiment. Xu *et al*. [2025] investigated the impacts of MPs on asthma by exposing 6-8 week old male pathogen-free C57BL/6 mice to MPs and measuring the levels of IgG and IgE antibodies in their plasma. The normal group exposed to MPs had significantly higher IgG antibodies, while the asthma group exposed to MPs had higher levels of both IgG and IgE antibodies (43). Overproduction of these antibodies may cause inflammation and excess immune response throughout the body: IgG antibodies bind to mast cells and basophils, which can cause excess allergic response, and IgE antibodies bind to phagocytes, which can cause inflammation and overactive immunity. Due to the targeted scope of this study for the link between asthma and microplastics, it is unclear whether the increased IgE antibodies in asthmatic mice are a result of their condition, MP exposure, or both.

Effects on Dendritic Cells

Microplastics can cause detrimental effects in dendritic cells. Weber *et al*. [2022] exposed primary human monocyte-derived dendritic cells from buffy coats to PS, PMMA, and PVC NPs. It was found that the dendritic cells internalized the PS and PMMA NPs, causing a decrease in pro-inflammatory cytokines, with the strongest effect being from irregular PVC (44). This study has a wide scope, focusing on general dendritic cells, and uses different variations of MPs, meaning the results are more certain. In Wolff *et al*.'s [2023] study from 3.2, monocyte-derived human buffy coat dendritic cells were exposed to unweathered PS, unweathered PMMA, and amino-modified PS MPs. They were affected by all of the types of MPs that they were exposed to, showing a large decrease in the proportion of living cells, especially after exposure to high concentrations. The expression of most CD surface receptors was decreased after exposure to the aminated PS MPs, and the expression of CD40 and CD80, two surface molecules responsible for activating the adaptive immune response, was also significantly decreased after exposure to the unweathered MPs. The expression of CD25, an activation marker, was increased after exposure to all types; there may be a correlation between certain dendritic cell subtypes with this surface molecule and T cell proliferation suppression (38). In this case, very similar experimental conditions as the previous study, such as the use of PS and PMMA MPs and buffy coat dendritic cells, led to similarly observed negative effects.

EFFECT ON THE INFLAMMATORY RESPONSE

The inflammatory response is a sequence of nonspecific, innate reactions the body has to infections and tissue damage that causes various effects. After an injury, cytokines, chemokines, and acute-phase proteins are released to attract and mobilize innate immune cells. Firstly, increased blood flow and vessel permeability result in redness, heat, and swelling in the area. Next, pain arises as the level of stimulating chemicals rises to combat infections. Finally, a reduction in the ability of tissues to perform their normal tasks occurs due to a combination of these effects. All inflammatory pathways involve the same sequence: inducers that come from signs of infection and injury are detected by cell receptors that pick up the signal and trigger a response by activating immune cells within the affected tissue. The inflammatory response has 3 different levels based on the duration of the response: acute inflammation, the immediate response that lasts for the first few days; subacute inflammation, when the acute response is not resolved after 2 weeks; and chronic inflammation, when tissue remains inflamed for months or years, and is marked by the migration of lymphocytes to the site of infection. Although the goal of inflammation is to restore homeostasis, uncontrolled inflammation can result in tissue damage and scar tissue buildup (fibrosis) (45).

Effects of MPs on pyroptosis

Research by Berkel *et al*. [2023] shows that microplastics may induce pyroptosis, an inflammation-related cell death. PS MPs have been shown to cause oxidative stress by the generation of ROS in mice, rats (*Rattus norvegicus domestica* strain), and chickens (*Gallus gallus domesticus*), leading to the activation of inflammasome complexes. This then activates gasdermin proteins, causing the release of inflammatory cytokines and the formation of disruptive transmembrane pores, damaging the membrane. Inflammatory caspases are also activated, which promote the release of cytokines such as IL-1β (Figure 3A). Eventually, these events start the cascade for a full inflammatory effect in the area of exposure (46). Despite this compelling evidence, this review is limited in its sample size, as there have not been studies of the same reaction to MPs occurring in humans.

Effects of MPs on inflammatory cytokine release

Prietl *et al*. [2014] exposed isolated human and mouse macrophages and monocytes (primary culture and immortalized monocyte cell lines) to carboxyl PS MPs of different sizes, and found that the exposure increased the secretion of IL-6 and IL-8 cytokines, especially in the THP-1 cell line (47). Both are involved in the inflammatory response. IL-6 is a general mediator with many excitatory immune effects, while IL-8 attracts and activates neutrophils (48). Smaller particles did not affect IL-8 secretion as much in differentiated cells, while bigger particles did not affect the secretion of IL-6 in both undifferentiated and differentiated cells as much (47), showing that MPs can potentially trigger inflammation by excess cytokine secretion. Though this provides strong evidence for a possible effect, the scope of the study is limited to two of the types of cells out of the several that produce inflammatory cytokines. Similarly, when Sun *et al*. [2021] exposed groups of mice to two different PE MP concentrations by ingestion over 30 days, it was found that the expression of IL-6, IL-8, and IL-10 cytokines in the intestinal lumen increased significantly, while the expression of IL-1β decreased significantly (49). The decrease of IL-1β was unexpected, as it stimulates the production of proinflammatory proteins such as acute-phase proteins. Similarly, IL-10, an inhibitory cytokine that targets the antigen presentation ability of dendritic cells and macrophages (48), also increased (49). Though it does provide compelling evidence, this study is also limited in its scope, as it focuses only on ingestion and the relative effect in the GI tract.

Effects of MPs on Intestinal Inflammation

When Qiao *et al*. [2019] exposed healthy adult zebrafish to two different concentrations of PS MBs by ingestion over 21 days, there were high levels of oxidative stress in the intestines, causing inflammation (50). Though over 200 fish were used to confirm testing results, the fundamental differences between zebrafish and humans mean that the MPs may have different effects in the human gut. Li *et al*. [2019] found that when 5-week-old male C57BL/6 mice were exposed to three different concentrations of PE MPs through ingestion, the highest concentration group showed signs of severe chronic intestinal inflammation, with high amounts of lymphocytes and plasma cells migrating to the site of exposure (51). Finally, Shi *et al*. [2024] exposed carp (*sp. unspecified*) to MPs by ingestion over 30 days, and their midguts experienced inflammation, shown by increased release of ROS, high levels of macrophage activation, increased IL-1β production, and

mobilization of lymphocytes (52) (Figure 3B). Again, while this provides some evidence, the anatomy of the carp is very different from humans, meaning the results are not necessarily conclusive.

Effect on Extracellular Traps

Finally, another way MPs can cause and perpetuate inflammation is by inducing the formation of extracellular traps (ET). An extracellular trap is a net-like structure consisting of dsDNA, histones, and other proteins, which aids in trapping and killing pathogens. These structures have been found in various innate immune cells such as neutrophils, eosinophils, basophils, monocytes, and macrophages (53). In Yin *et al*. [2023]'s study that exposed 1-week-old chickens to PS MPs for 42 days, it was shown that phagocytosis of the MPs by macrophages caused autophagy and lysosome rupture, releasing calcium ions that led to the formation of unnecessary ETs and thus inflammation (54). However, since only the liver of the chicken was examined, the results around the peripheral macrophages are not as concrete. A narrative review by Huang and Sullivan around new roles of ETs suggests that this effect could happen with any immune cell that utilizes it, and explains how it can continue inflammation. Proteases and other enzymes are released along with ETs; this injures surrounding cells and starts the inflammatory cascade again. However, inflammation itself can also cause the release of ETs. In NETosis, the immune cell releases its ET and undergoes cell death. Caspases, one of the proteins involved in pyroptosis, can induce NETosis (55). Thus, inflammation can cause nearby immune cells to release their ETs, which can further cause inflammation (Figure 3C).

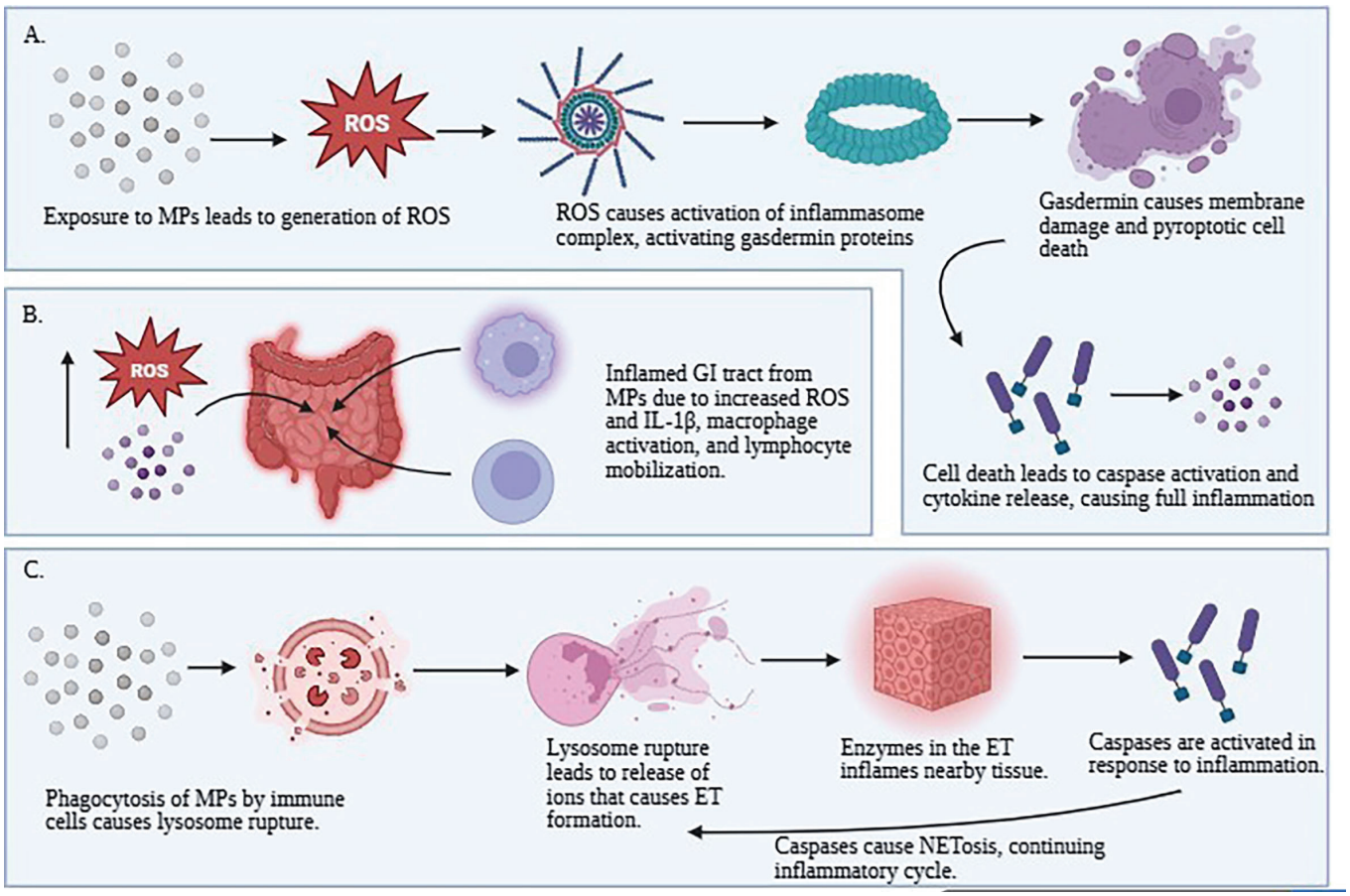

Figure 3. Effects of MPs on Inflammation. A. MPs can cause pyroptotic cell death by generating ROS, activation of inflammasome complexes, and gasdermin proteins that disrupt cell membranes. Pyroptosis can cause caspase activation and the release of cytokines, causing inflammation. B. Increased ROS and inflammatory cytokines due to MPs can cause GI tract inflammation. C. Lysosomal rupture in immune cells that phagocytosed MPs can cause the release of ETs, inflammation, and activation of more ET release. Created in BioRender.com.

EFFECTS AND ACCUMULATION OF MPS IN THE LYMPH SYSTEM

The lymph system is an important part of the circulatory and immune system. It absorbs and filters excess extracellular fluid, called lymph, from blood vessels. After lymph is picked up by lymphatic capillaries, it travels through larger lymphatic vessels. Located along the vessels are lymph nodes, tissue that monitors and filters lymph, drains excess fluid and proteins, attacks pathogens, and controls immune responses. Lymphocytes and monocytes enter the fluid at these sites as well. There are also various organs with lymphatic functions. The primary lymphatic organs, the bone marrow and thymus, are responsible for the maturation and production of immune cells (56). The bone marrow is responsible for the primary production of all immune cells using hematopoietic stem cells (HSCs). The thymus is responsible for the maturation of T lymphocytes, and it uses two types of selection to ensure T cells are active but do not cause autoimmunity (57). The thymus has a direct lymphatic connection to easily supply T cells that are ready to be activated. The secondary lymphatic organs, the spleen, tonsils, and mucosal membranes, are places where immune cells can mount attacks against pathogens. The spleen (composed of white and red pulp) filters blood and stores lymphocytes; the tonsils trap and destroy pathogens; finally, the various mucosal membranes prevent the entry of pathogens (56).

Accumulation of MPs in Lymphatic Vasculature and Lymph Nodes

Because the lymph system is constantly filtering blood, it is not surprising to find that MPs can build up in the vasculature (Figure 4B). When Muhammad *et al*. exposed male BALB/c mice to PS MP and NP through pharyngeal aspiration, the particles built up most rapidly in the lymph nodes, with 35-60% of absorbed particles being deposited there, when compared to other organs and tissues. The largest factor controlling the speed of the MP buildup was the size of the particles (58). In contrast, Triantafyllaki *et al*. [2024] conducted computer simulations of human respiratory tracts that were exposed to airborne MPs, and found that only a very small amount of the particles will be absorbed by the lymph nodes (59). Despite a precise computer modeling methodology, this study is still only based on the theoretical scenario and does not give a result on the actual effect. Also, the massive disparity between this study and the previous study shows that more trials must be conducted. When Browne *et al*. [2008] exposed mussels (Mytilus edulis L.) to seawater-MP treatments and then transferred them to clean conditions, it was found that the particles moved from the gut to the circulatory system in 3 days, and continued to persist in the hemolymph for over 48 days (60). The hemolymph is very different from the mammal circulatory system, so results do not translate concretely to humans; however, continuous exposure to MPs may lead to the same persistent buildup of MPs in the lymph vasculature, as supported by other studies on different mammalian guts have yielded results that support this. A collection of studies from a book by the Food and Agriculture Organization of the United Nations suggests that MPs of many different sizes can enter the lymphatic system through M cells in the Peyer's patches; the translocation of these particles into the lymph has been observed in humans, dogs (*Canis lupus familiaris*), rabbits *(Oryctolagus cuniculus), and* rodents (61).

Effect of MPs in Primary Lymphatic Organs

Since the primary lymphatic organs are very important for the development of immune cells, the accumulation of MPs in them is particularly concerning. Bone marrow can be negatively affected by MPs (Figure 4C). Guo *et al*. [2024] analyzed 16 bone marrow samples from individuals with blood cell disorders and found that all samples contained five different plastic types, including PE and PS particles. Of these, PS was found in all samples collected. The average MP concentration in the samples was lower than that in artery tissues, but higher than in the blood, meaning that these MPs most likely accumulated by flowing in through the blood (62). However, due to the samples being from diseased individuals, their concentration of MPs may be particularly high and not representative of the whole population. When Sun *et al*. [2021] exposed five-week-old male C57BL/6 mice to two different doses of PS MPs through ingestion, it was found that the particles built up in the limb bone marrow of the mice, causing significantly lowered white blood cell levels in the higher concentration dose (63). Jiang *et al*. [2024] exposed C57BL/6 and C57BL6. SJL mice to PS and PMMA MPs through ingestion and intravenous injection. This exposure decreased the self-renewal abilities for the HSCs (Haematopoietic stem cells) (64). However, it was not the result of the direct damage from MPs, but instead a cascade through gut permeability and the microbiome, meaning these

exact conditions may not be replicated in humans. The thymus can also be negatively affected by MPs (Figure 4D). Xia *et al*. [2024] exposed mice to PS MPs through intratracheal instillations and found that the particles induced inflammation in the thymus, shown by infiltration of phagocytes, increased immune receptor expression (such as TLRs and Myd88), and increased proinflammatory cytokines such as TNF-α and IL-1β (65). Though the evidence provided is strong, intratracheal instillation is an intrusive method of exposure that does not fully replicate how a human may be exposed to MPs. When Li *et al*. [2023] studied young broiler chickens that had been exposed to PS MPs through ingestion, it was found that the particles reached the thymus and triggered the downstream production of proinflammatory and apoptotic proteins, such as IL-1β, caspase-3, and Beclin1, causing inflammation, apoptosis, and autophagy of thymus tissue (66).

Effect on Secondary Lymphatic Organs

Microplastics have been found in secondary lymphatic organs as well. In the previously mentioned experiment where mice were exposed to PS MPs through intratracheal instillations, similar signs of inflammation, such as immune cell infiltration, increased immune proteins, and increased inflammatory cytokines, were also found in the spleen (65). Again, the strong evidence does not account for the differences in exposure method when the mice are subjected to intratracheal instillation. Zhang *et al*. [2023] exposed 1-week-old female Japanese quail (*Coturnix japonica*) to different concentrations of PS MPs through ingestion, it was found that the spleen experienced inflammation (Figure 4D), shown by cell dissarrangement, membrane lysis, cell vacuolation, increased levels of proinflammatory cytokines (such as TNF-α and IL-1β), and decreased levels of anti-inflammatory cytokines (IL-10) (67). When Zhang *et al*. [2024] exposed adult male C57BL/6 mice to two different sizes of PS MPs through ingestion for 8 weeks, it was found that the smaller-sized particles could spread to and accumulate in the spleen, causing inflammation, a blurred interface between red and white pulp, sparse cell arrangement, and hyperplasia of red pulp (68). Finally, when Zhu *et al*. [2024] analyzed tissue samples for MPs, it was found that the tonsils had accumulated a significant amount of particles (Figure 4E), with 7 different types of plastics being identified (69). Though MPs were identified, it is unclear how much damage they are actually causing to the tissue, meaning exposure in that area may not be important at all.

DISEASES ASSOCIATED WITH EFFECTS OF MPS

Autoimmune and Chronic Allergic Disorders due to MPs

The epithelial barrier is necessary for keeping the homeostasis of the body by protecting it from outside objects, and its disruption (such as a defective skin barrier or leaky gut epithelium) by different factors, like MPs, can lead to immune stress and the development of autoimmune diseases and allergies (70). In a previous narrative review by Huang and Sullivan [2022], it was found that immune cell ETs, which can be released upon the cell interacting with MPs, are known to contain over 70 autoantigens. Exposure to MPs can cause the release of ETs, and thus the release of autoantigens that can start autoimmunity (55). This may be especially damaging to the body's tissues under chronic MP exposure.

Chronic Inflammation and MPs

Although previous studies observed inflammation in a few specific areas, a review by Mahmud *et al*. [2024] suggests that interactions between MPs and immune cells can cause proinflammatory cytokines almost anywhere in the body, causing the inflammation cascade (71). As previously mentioned, chronic exposure to MPs can trap immune cells in a cycle of inflammation, where damage due to the response continually triggers the immune system to attack. When the immune system is repeatedly exposed to low levels of pollutants, like MPs, that it struggles to eliminate, the chronic inflammation can cause a variety of diseases, such as arthritis, allergic asthma, chronic obstructive pulmonary disease (COPD), and inflammatory bowel disease (IBD). Chronic inflammation is also associated with chronic fatigue, mood disorders, diabetes, cardiovascular diseases, and chronic kidney disease (72).

Cancer and MPs

Chronic exposure to MPs has been linked to cancer development. For instance, a narrative review by Goswami *et al*. [2024] compiled that MPs can impact epistatic gene expression, cell cycle proteins, and mimic hormones like estrogen and androgen, which can all promote the formation of tumor cells (73). Apart from this direct effect of MPs, it is known that multiple

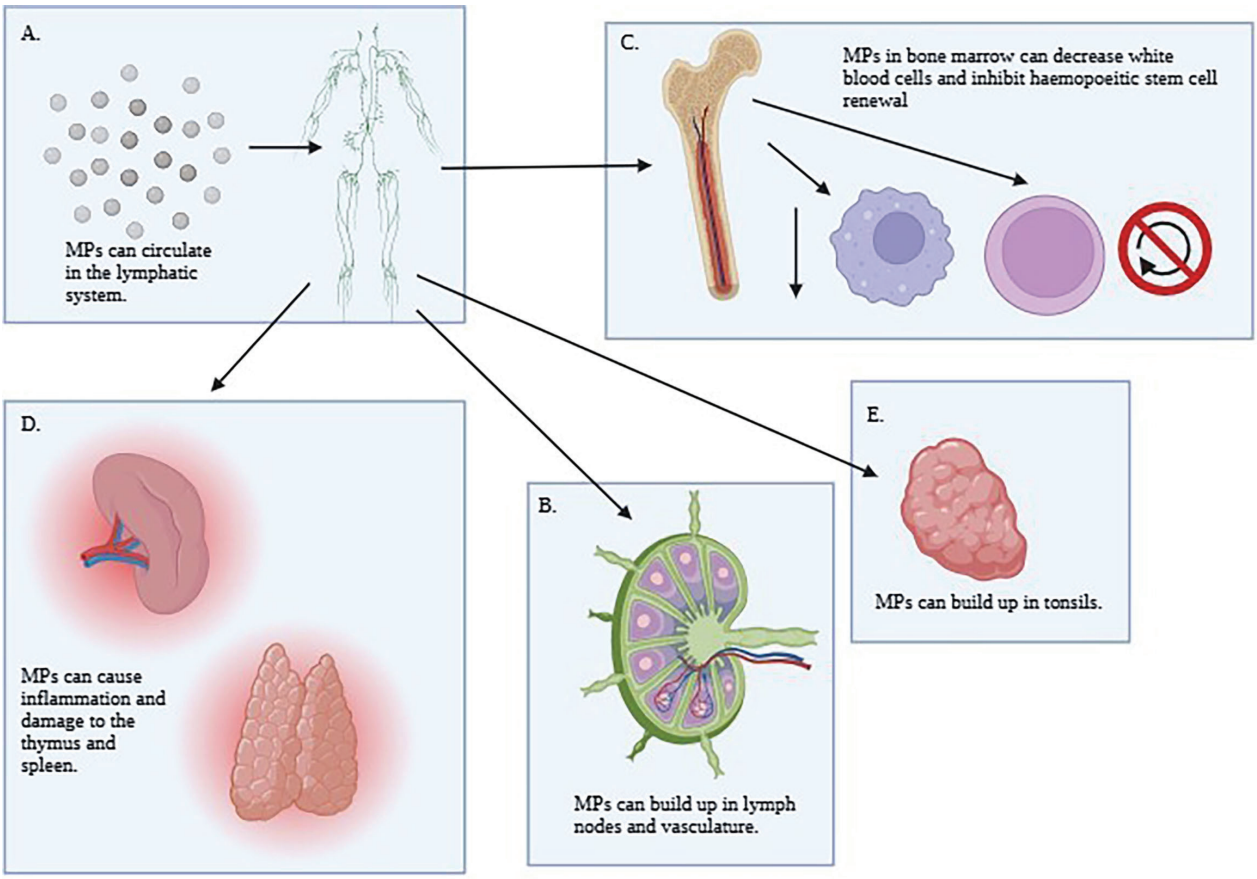

Figure 4. Effects of MPs on Lymphatic Organs. A. MPs can circulate throughout the lymph system and reach many parts of the body. B. MPs can be deposited and build up in lymph vessels and nodes in varying quantities. C. MPs can damage the bone marrow's stem cell renewal ability and decrease the white blood cell count. D. MPs can cause inflammation and tissue damage by building up in the thymus or spleen. E. MPs can be deposited in tonsils, but the damaging effects on them are unclear. Created in BioRender.com.

immune cells are involved in the process of cancer cell detection and clearance, such as macrophages, neutrophils, T cells, and dendritic cells, which can be affected by MPs. As previously mentioned, exposure to MPs can affect the activity and availability of these immune cells to fight cancer cells (29, 30, 32, 37, 38). This means that upon exposure to MPs, the immune system may have a decreased capacity for combating the cancer.

Immunodeficiency and Infections in relation to MPs

Exposure to MPs may also lead to a directly weakened immune system against any infection. This is all due to the decreased numbers and redirection of immune cells, and the increase of other cell types, such as suppressor T cells, causing a reduced immune response against pathogens. Evidence suggests that airborne microplastics can carry viruses, specifically the SARS-CoV-2 virus that caused the COVID-19 pandemic, over long distances and prolong their survival in the open environment. A study by Amato-Lourenço *et al.* [2021] measured air around the Sao Paulo megacity and found that the majority were housing the virus (74). Though this study is limited to one city and is largely focused on the SARS-CoV-2 virus, it provides preliminary evidence that future research in similar matters can be based on. A narrative review by Cholewińska *et al.* [2022] suggests that by contacting MP particles, various pathogenic and opportunistic bacteria species can create a colony known as a biofilm. The species that make up the biofilm are dependent on the type of MP. MP particles

can easily disperse throughout the water and enter many aquacultural animals, allowing bacteria to infect people when they otherwise could not have. This can cause numerous diseases, such as cholera and diarrhea (75). However, scenarios discussed in this review are only based on water and are focused on aquaculture, meaning the effect may not be the same on land.

CONCLUSION

Due to the high and increasing prevalence of MPs in the environment, we should be concerned about their effects on human health. Current evidence suggests that MPs enter the body through ingestion, inhalation, and dermal contact. After entry, MPs can circulate through the blood and lymph to interact with various tissues and immune cells. Neutrophils and macrophages were shown to be directed to the area of microplastic exposure. Neutrophils and macrophages were both observed to undergo cell death after internalizing MPs. It has been suggested that the function of IgA antibodies could be limited by MPs, while IgE and IgG could increase in response to MPs. Studies also find that dendritic cells exposed to MPs can undergo cell death or have a lowered capability for proper immune response. MPs may induce inflammation, especially in the intestinal tract, as well as a variety of inflammation-related effects, such as pyroptosis, increased inflammatory cytokine release, and release of immune cell extracellular traps (ET). MPs have been found to reduce the function of hemopoietic stem cells in bone marrow and cause inflammation in the thymus and the spleen. Finally, all this can lead to the development of many diseases. For one, damage to the epithelium and constant release of autoantigens from ETs may lead to chronic allergic diseases and autoimmunity. Constant MP exposure can also cause an inflammatory cycle, leading to chronic inflammation and a variety of complications. MPs have also been found to weaken some cells responsible for attacking cancer and increase suppressor T cells, leading to the possibility that the body is more susceptible to developing cancer. MPs can increase infections by weakening immune cells and carrying bacteria and viruses on their surface.

In conclusion, ubiquitous MPs can cause a variety of issues in the human immune system, negatively affecting innate and adaptive immune cells, aggravating the inflammatory effect, causing issues in the lymph system, and directly or indirectly causing diseases such as autoimmunity or cancer. However, although the general understanding is established, there are still numerous gaps in the research and limitations in the data available. Some claims discussed in this paper are contradictory, such as whether MPs lead to the decline or increase of T cells and B cells, and the amount and speed of MP accumulation in lymph tissue. Many studies are also limited in their materials. Since PE and PS MPs are the most widely available and present types of plastic, most research done in this area is based around these two. While this does give an opportunity for studies to find conclusions that are widely applicable across the population, it can leave gaps in the knowledge on the effects of less prevalent microplastics that may be more harmful than others, even in lower doses. As mentioned in the introduction, since MPs are ubiquitous, it is difficult to analyze samples from humans and come to a definitive conclusion. Since all samples will be contaminated by MPs, there is effectively no control group as a starting point. Solutions may be to analyze data from the past or to get more isolated groups to participate. Neither is a perfect solution: the former may not be accurate, and the latter has many ethical issues. Experiments could be done with non-human subjects to get a control group, but the model organism must be under highly controlled conditions and have similar biological traits to humans to yield valid results. Finally, the effects of lifelong exposure to MPs will be difficult to account for, since MPs have only emerged relatively recently, and the full effects may not be felt until decades later. This poses a problem in that there is an uncertainty about how much awareness should be paid to MPs. More research is urgently needed for this field to establish a consensus on the range of responses the immune system can have to MPs. By understanding the damage they could do, the proper process for the prevention of MPs can be taken, allowing us to lessen or mitigate the health effects.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to this work.

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