Role of microplastics in the tumor microenvironment (Review)

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Received October 14, 2024; Accepted January 7, 2025

DOI: 10.3892/ol.2025.14939

Abstract. Microplastics (MPs) are pervasive in several ecosystems and have the potential to infiltrate multiple aspects of human life through ingestion, inhalation and dermal exposure, thus eliciting substantial concerns regarding their potential implications for human health. Whilst initial research has documented the effects of MPs on disease development across multiple physiological systems, MPs may also facilitate tumor progression by influencing the tumor microenvironment (TME). This evolving focus underscores the growing interest in the role of MPs in tumorigenesis and their interactions within the TME. In the present review, the relationship between MPs and the TME is comprehensively assessed, providing a detailed analysis of their interactions with tumor cells, stromal cells (including macrophages, fibroblasts and endothelial cells), the extracellular matrix and inflammatory processes. Recommendations for future research directions and strategies to address and reduce microplastic pollution are proposed.

Contents

1. Introduction

The presence of substantial quantities of plastic debris in the environment has been documented since the 1960s (1). However, it was not until 2004 that the term 'microplastic' (MP) was introduced in a report to characterize microscopic plastic debris (2), signifying the commencement of research focused on MPs. The production of plastic has surged markedly in recent decades. As of 2015, ~4.9 billion tons of plastic waste had accumulated in landfills or the natural environment. Projections indicate that this figure could rise to ~12 billion tons by 2050 (3). The nature of global MP pollution is of notable concern.

Compared with other suspended particulate matter, MPs are distinguished by their extensive size distribution, diverse shapes, low densities-often approximating that of water-and high persistence (4). Plastics that accumulate in substantial quantities in the environment undergo degradation due to several environmental factors, including ultraviolet radiation from sunlight, precipitation, water flow, biological oxidation and mechanical weathering. The degradation products exhibit a wide range of forms such as fragments, fibers, spheres, pellets, lines, sheets, flakes and foams, with fragments being the most prevalent (5). These products can be further classified by size into nanoplastics (NPs; ≤0.1 μm), MPs (≤5 mm), medium plastics (0.5-5 cm), megaplastics (5-50 cm) and macroplastics (≥50 cm) (6). The densities of plastics vary markedly, ranging from 50 kg/m^3 for extruded polystyrene foam to 1,400 kg/m^3 for polyvinyl chloride (PVC); however, the densities of numerous plastics are similar to that of water (4).

MPs can also be categorized into primary and secondary types based on their origin. Primary MPs are small plastic particles that are either intentionally manufactured or generated as by-products of industrial processes (7). They are commonly present in products such as exfoliating beads in facial cleansers (8). Secondary MPs originate from the fragmentation or degradation of larger plastic materials (9), with the majority of environmental MPs considered to be secondary in nature (10). Furthermore, the substantial persistence of MPs enables their prolonged presence in waste streams and environmental contexts. Research suggests that these particles can accumulate and persist in natural environments for decades (11). These characteristics notably influence their environmental mobility, distribution patterns, modes of human exposure and potential hazard levels.

A particularly concerning facet of pervasive MP pollution is their potential implications for human health. Research indicates that MPs can enter the human body via ingestion, inhalation or dermal contact, thereby posing diverse health

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Key words: microplastics, tumor microenvironment, tumor cells, stromal cells, extracellular matrix, inflammation

risks (12). Among these, ingestion is identified as the predominant exposure pathway, with frequent vectors including marine crustaceans, fish (13), sea salt, lake salt (14), tap water, spring water and bottled water (15). Schwabl *et al* (16) reported the presence of MPs in human feces, indicating that following ingestion, MPs can traverse the esophagus, stomach, small intestine and large intestine. This pathway may lead to their accumulation in specific target organs, thus posing potential health risks. Research performed on mice and zebrafish has reported that ingested MPs can accumulate in the intestines, potentially causing intestinal damage or dysbiosis of the gut microbiota (17,18). Furthermore, prolonged accumulation of MPs may contribute to carcinogenesis (19). MPs are also present in atmospheric deposition as well as in both indoor and outdoor environments (20). These particles may originate from urban dust, synthetic textiles, material abrasion (such car tires or buildings) and the resuspension of surface MPs (21). Plastic particles measuring <5 μm in length and <3 μm in diameter are readily inhalable (22), with certain particles accumulating in lung tissue due to their inherent durability. This accumulation has the potential to contribute to pulmonary inflammation, fibrosis or cancer (23,24). Moreover, occupational exposure, particularly amongst workers in the textile or mining industries, has been associated with higher incidences of respiratory irritation (25). Previous studies have also highlighted dermal contact as a potential route for MPs to enter the body, with personal care products such as cosmetics, toothpaste and soaps being major sources (26,27). Wu *et al* (27) reported that the dermal barrier could be crossed by NPs (<100 nm), synthetic fibers (<25 μm), the monomers, as well as the additives due to the skin pores ranging from 40 to 8 μm. Furthermore, plastic particles may also gain entry through wounds, sweat glands or hair follicles (28).

In previous years, the relationship between MPs and tumorigenesis has emerged as a key focus in MP and human health research. Owing to their extensive surface area and high adsorption capacity, MPs serve as vectors for several environmental toxicants, including polycyclic aromatic hydrocarbons (29,30), heavy metals (31) and organochlorine pesticides (32), all of which are recognized as potent carcinogens. These substances can enter the human body alongside MPs and, under certain conditions, may be either released or retained, thus increasing the risk of carcinogenesis. Moreover, research indicates that MPs with diameters ranging from 0.25-10 μm can penetrate cell membranes and accumulate within cells, indicating their potential for prolonged persistence within the body (33,34). MPs may interact with cellular components through mechanisms (35-37) such as: i) Elevating intracellular reactive oxygen species (ROS) levels, which can lead to oxidative stress, lipid peroxidation, protein oxidation and DNA damage; ii) promoting cytokine release upon cellular contact, activating specific pathways and triggering inflammatory responses; and iii) disrupting immune surveillance by interacting with immune cells, activating innate immune receptors [such as toll-like receptors (TLR)] and perpetuating chronic inflammation. These mechanisms collectively create a conducive environment for tumor growth and influence the tumor microenvironment (TME).

The TME is a complex network consisting of tumor cells, several stromal cells (such as fibroblasts, lymphocytes, macrophages and endothelial cells) and extracellular components [such as cytokines, inflammatory cells, signaling molecules and extracellular matrix (ECM)] (38). It serves a crucial role in cancer development and progression. Recent *in vitro* experiments have demonstrated that exposure to polystyrene (PS)-NPs can promote the progression of ovarian cancer in murine models by modifying the TME (39), thereby providing further evidence of the connection between MPs and the TME.

Given that direct research on the TME in the context of MPs remains in its nascent stages, the present review aimed to analyze the interactions between MPs and the TME. By evaluating previous studies on the interactions of MPs with tumor cells, macrophages, fibroblasts, endothelial cells and inflammatory processes, the present study aimed to consolidate the latest evidence from research on both cancerous and normal tissue cells. Furthermore, the present study aimed to elucidate the potential links between MPs, the TME and tumorigenesis.

2. MPs and the TME

MPs can influence the TME by affecting several cell types. Fig. 1 illustrates a brief overview of the role of MPs in the TME.

MPs and tumor cells. Tumor cells, which represent a substantial component of the TME, engage in a reciprocal relationship with their environment, mutually influencing their behaviors and progression. As articulated by Paget (40) in their 'seed and soil' hypothesis over a century ago, the TME serves a critical role in tumor development. Modifications in the TME can notably affect the growth and proliferation of tumor cells. For example, research by Chen *et al* (39) demonstrated that the administration of water containing PS-NPs to mice resulted in an increased growth rate of epithelial ovarian cancer tumors. The analysis indicated that exposure to PS-NPs markedly disrupted immune responses and pathways within the TME (39). Similarly, research utilizing human colonic organoids and the Caco-2 colonic cell line demonstrated that MPs could compromise intestinal barrier function, thereby altering the cellular microenvironment and affecting the proliferation and wound healing of Caco-2 cancer cells (41). Upon colonization of host tissues, tumor cells induce substantial molecular, cellular and physical alterations that, to varying extents, promote the development of the TME (42). Several researchers contend that MPs have the potential to augment tumor cell proliferation, modify metabolic processes and facilitate metastasis, thereby impacting the dynamics of the TME (29,39,43). For instance, in breast cancer cells, Park *et al* (44) demonstrated that exposure to 16.4 μm fragment-type polypropylene (PP)-MPs in breast cancer cells, specifically MDA-MB-231 and MCF-7 lines, resulted in increased expression of genes associated with the cell cycle and elevated secretion of interleukin (IL)-6, without inducing cytotoxic effects. This exposure consequently enhanced the metastatic potential of these cancer cells (44). A separate study examined the effects of MPs on human breast epithelial and breast cancer cells, reporting that 1.0 μm PS particles increased the proliferation rate of MDA-MB-231 cells and facilitated tumor cell migration (45). Moreover, experiments performed by Wang *et al* (43) demonstrated that

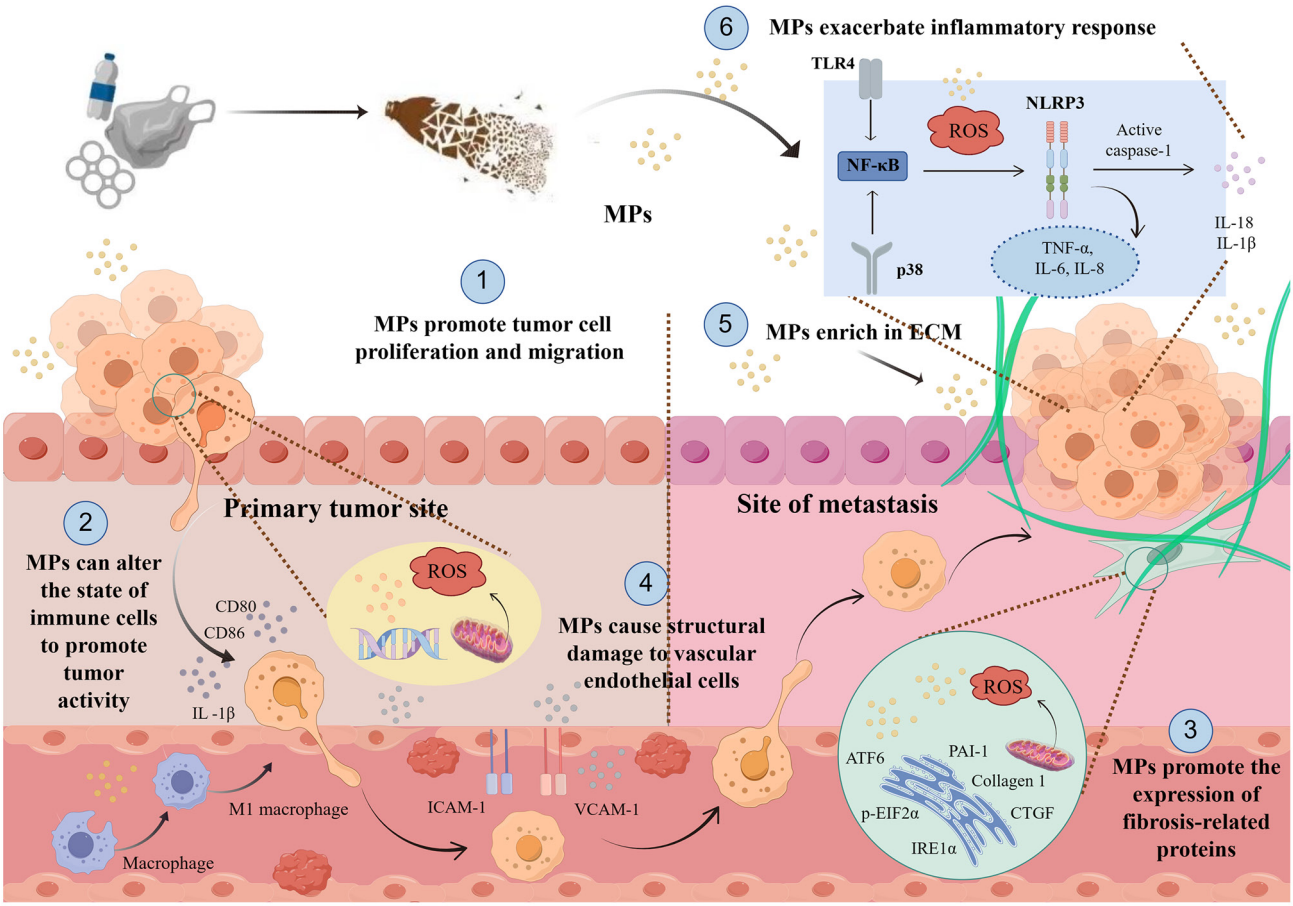

Figure 1. Schematic representation of the proposed mechanism illustrating the regulation of MPs on cells in the TME, created using Figdraw2.0 (www.figdraw.com). As plastic products degrade, they generate numerous MP particles, which can influence several components of the TME upon contact with the tumor. MPs affect tumor cell proliferation and migration within tissues and blood vessels and alter immune cell states to enhance tumor activity, causing structural damage to endothelial cells, promoting fibroblast activation and the expression of related proteins and directly impacting the ECM and inflammatory factors. MP, microplastic; TME, tumor microenvironment; ECM, extracellular matrix; TLR4, toll-like receptor 4; ROS, reactive oxygen species; ICAM-1, intercellular adhesion molecule 1; VCAM-1, vascular cell adhesion protein 1; NLRP3, NLR family pyrin domain containing 3; ATF6, activating transcription factor 6; PAI-1, plasminogen activator inhibitor-1; p-EIF2α, phosphorylated eukaryotic translation initiation factor 2α; IRE1α, inositol requiring enzyme 1; CTGF, connective tissue growth factor.

MPs could be internalized by skin squamous cell carcinoma lines in a time- and dose-dependent manner. This internalization resulted in elevated mitochondrial ROS, activation of the NLR family pyrin domain containing 3 (NLRP3) inflammasome and ultimately promoted the proliferation of skin cancer cells (43).

Contrary to these findings, Goodman *et al* (46) observed that the viability of cultured human alveolar A549 cells remained relatively stable when exposed to 1 and 10 μm PS-MPs across different concentrations. However, both metabolic activity and proliferation rates exhibited marked reductions (46). Similarly, Da Silva Brito *et al* (47) performed experiments on A549 cells under controlled conditions, simulating environmental scenarios to generate secondary PP-MPs via laser ablation. After exposing human alveolar A549 cells and HaCaT cells to PP-MPs and a positive control group, amine-modified PS-MPs (PS-NH_2-MPs), it was observed that PP-MPs only enhanced the metabolic activity of A549 cells at elevated concentrations, whereas HaCaT cells remained unaffected. Conversely, the PS-NH_2-MPs control group exhibited reduced metabolic activity and notably increased cell death (47). The study concluded that laser-ablated PP-MPs did not exhibit cytotoxic effects nor did they influence metabolic proliferation during acute *in vitro* exposure.

In addition to the direct effects of MPs, certain compounds adsorbed onto transported by MPs may also impact tumor cells and the broader TME. Böckers *et al* (48,49) investigated two typical plasticizers-bisphenol compounds and tri-o-cresyl phosphate, commonly used in plastic products, and reported that both compounds could interact with estrogen receptor α in MCF-7 breast cancer cells. This interaction resulted in 14 upregulated genes (*ADORA1*, *DDIT4*, *CELSR2*, etc.) and three downregulated genes (*BCAS3*, *PHF19*, *PRKCD*), which are associated with cell growth, invasion, migration, apoptosis and cancer development. Consequently, the impact of MPs on tumor cells is multifaceted and cannot be universally characterized. Variables such as the type of tumor cells, the surrounding microenvironment, the type, shape and size of MPs, the duration of exposure and the presence of adsorbed substances all potentially influence these interactions (Table I).

MPs and stromal cells

Immune cells. Tumor-associated macrophages, which are the predominant infiltrating immune cells within the TME and

Table I. Summary of information on the studies of microplastics and cancer cells.

First author/s, year	Particle type	Size	Cell/animal model	Aim	Conclusion	(Refs.)
Chen *et al*, 2024	PS-NPs	100 nm	Human EOC HEY cells and mouse EOC cells	To investigate the potential effects and molecular mechanisms of PS-NPs on EOC.	PS-NPs exposure markedly accelerates EOC tumor growth in mice and reduces EOC cell viability in a dose-dependent manner by altering the TME.	(39)
Ling *et al*, 2020	MPs	N/A	Human colorectal adenocarcinoma Caco-2 cells	To investigate the effect of MPs on Caco-2 cells.	MPs impact the growth of Caco-2 cancer cells, impair wound healing and disrupt cellular metabolism.	(41)
Park *et al*, 2023	PP-MPs	16.4 μm	Breast cancer MDA-MB-231 and MCF-7 cells	To investigate the effect of 16.4 μm fragmentary PP-MPs on breast cancer.	PP-MPs upregulate the expression of genes associated with metastasis and increase cytokine production in breast cancer cells.	(44)
Schnee *et al*, 2024	PS-microbeads	0.5, 1.0 and 4.5 μm	Breast cancer HS-578-T-DSP1-7 and MDA-MB-231-DSP1-7 cells	To investigate the influence of MPs on human mammary epithelial cells and breast cancer cells.	MPs are taken up in a dose- and particle size-dependent manner by human breast cancer cells and have an impact on cell proliferation and migration.	(45)
Wang *et al*, 2023	PE-MPs	1 μm	Skin squamous cell carcinoma SCL-1 and A431 cells	To investigate the effect of MPs on skin cancer.	MPs promote tumor cell proliferation while causing damage to normal skin cells through NLRP3-mediated inflammation and scorch death.	(43)
Goodman *et al*, 2021	PS-MPs	1 and 10 μm	Human alveolar A549 cells	To examine the potential toxicological effects of MPs on human cells	A549 cells exposed to PS-MPs shows a population-level decrease in metabolic activity paralleled by a marked decrease in proliferation rate.	(46)
Da Silva Brito *et al*, 2022	PP-MPs and PS-NH_2-MPs	PP-MPs (200 nm) and PS-NH_2-MPs (50 nm)	Human alveolar A549 cells	To investigate the biological response of laser-ablated MPs in human cell lines	Laser-ablated PP-MPs do not show cytotoxic effects or affect metabolic proliferation after effects acute exposure *in vitro*.	(47)
Böckers *et al*, 2020	TOCP	N/A	Breast cancer MCF-7 cells	To define the overall endocrine potential of TOCP and its underlying molecular mechanisms.	TOCP interacts with estrogen receptor-α in MCF-7 breast cancer cells, alters gene expression and promotes tumor cell growth and proliferation.	(49)
Böckers *et al*, 2020	Bisphenolic compounds	N/A	Breast cancer MCF-7 cells	To define the overall endocrine potential of bisphenolic compounds and their underlying molecular mechanisms.	Bisphenolic compounds bind to estrogen receptor-α in MCF-7 breast cancer cells, changing gene expression and enhancing tumor growth.	(48)

TME, tumor microenvironment; MPs, microplastics; NPs, nanoplastics; PS, polystyrene; PE, polyethylene; PP, polypropylene; EOC, epithelial ovarian cancer; TOCP, tri-o-cresyl phosphate; NLRP3, NLR family pyrin domain containing 3; N/A, not applicable.

have been extensively studied for their roles in promoting tumor progression (50). Macrophages, as the principal phagocytic cells in mucosal environments such as the gastrointestinal tract and pulmonary system, exhibit modified functionality and viability upon exposure to MPs, a mechanism potentially impacting the TME and tumor progression. In a study by Yang *et al* (51), it was demonstrated using a murine model that oral administration of polyethylene (PE)-NPs or PS-NPs perturbed the gut microenvironment, thereby modulating the adaptive immune response in a manner that promoted the proliferation of pre-existing colorectal tumors. This phenomenon was attributed to the induction of IL-1β-producing macrophages in the colon, instigated by NP-induced lysosomal damage, which subsequently facilitated the differentiation of Tregs and Th17 cells. This process is associated with T cell exhaustion, thus fostering a pro-tumorigenic environment (51).

Moreover, MPs have been reported to exert pro-inflammatory effects on macrophages, which may contribute to chronic inflammation that promotes tumor growth. A study performed using RAW264.7 mouse macrophage cells demonstrated that the production of ROS and nitric oxide, in conjunction with the secretion of inflammatory cytokines, were key mechanisms through which PS-NPs and PS-MPs elicited cytotoxicity and inflammation in macrophages (52). Furthermore, Brammatti *et al* (53) investigated the effects of NPs of different sizes (25, 50 and 100 nm) and concentrations (25-500 μg/ml) on HT29 and U937 cell lines, utilizing a Transwell system to assess macrophage activation and the subsequent progression of the inflammatory response in intestinal cells. The findings indicated that NPs of varying sizes displayed differential permeability in intestinal cells, resulting in alterations in macrophage infiltration and the activation of HT29 cells. This activation led to the upregulation of IL-1β and inducible nitric oxide synthase levels, thereby fostering an inflammatory milieu conducive to the development of a tumor-supportive microenvironment (53).

In terms of cell viability, Merkley *et al* (54) demonstrated that macrophages, upon phagocytosing MPs in a murine model, underwent a metabolic shift towards glycolysis accompanied by a concomitant reduction in mitochondrial respiration. This metabolic alteration was associated with increased expression of the co-stimulatory molecules, CD86 and CD80, on the cell surface, as well as the upregulation of pro-inflammatory cytokine genes (54). These findings are consistent with those reported by Ling *et al* (41) and Collin-Faure *et al* (55). Additionally, Koner *et al* (56) reported that exposure to PS-NPs at concentrations of 50-500 μg/ml markedly reduced the viability of human macrophages. This exposure also induced oxidative stress, inhibited cellular proliferation, decreased mitochondrial membrane potential and resulted in DNA damage (56). Collectively, these findings suggest that MPs disrupt the microenvironment, modulate macrophage infiltration, induce oxidative stress and impair both lysosomal and mitochondrial functions, along with several surface markers integral to immune responses. Consequently, this diminishes macrophage efficiency and disrupts the equilibrium of the innate immune system, thereby facilitating tumor development and the formation of the TME.

Beyond macrophages, Wolff *et al* (57) performed isolation and differentiation or activation of human T cells and dendritic cells, reporting that T lymphocytes exhibited minimal susceptibility to cytotoxic effects induced by MPs. Conversely, phagocytic dendritic cells and macrophages derived from isolated monocytes demonstrated a high sensitivity to raw MPs. Following 24-h MP exposure, marker expression indicated a downregulation of the M2 macrophage-induced inflammatory phenotype and an upregulation of M1 macrophage markers. This shift may compromise the innate immune defense of the host, potentially promoting tumorigenesis and the development of the TME (57). In a related study, Weber *et al* (58) primarily assessed the effects of NP exposure on primary human monocytes and monocyte-derived dendritic cells, reporting that NP exposure induced the secretion of both pro- and anti-inflammatory cytokines in these cells (58). Notably, the results of these two experiments exhibited certain inconsistencies, which may be attributed to Weber's utilization of specific polymers, such as PVC and polymethyl methacrylate or the employment of irregularly shaped particles.

Fibroblasts. Fibroblasts are integral to maintaining tissue homeostasis, as they are involved in the synthesis, degradation and preservation of the ECM. They also serve a role in leukocyte recruitment, angiogenesis and the promotion of chronic inflammation within tissues (59). In the TME, fibroblasts contribute to cancer progression through intricate interactions with several cell types. They influence tumor angiogenesis and metabolism by secreting factors and metabolic products, processes frequently modulated by epigenetic alterations (60). Research on the interaction between MPs and fibroblasts frequently discusses inflammation and stress responses. Wang *et al* (61) reported that fibroblasts are capable of internalizing PS-MPs. When fibroblasts were cultured in a medium conditioned with PS-MPs, there was a notable increase in the production of ROS and proteins associated with endoplasmic reticulum stress, such as activating transcription factor 6, phosphorylated eukaryotic translation initiation factor 2α and inositol requiring enzyme 1. Additionally, there was an upregulation in the expression of proteins related to fibrosis, including plasminogen activator inhibitor-1, collagen type I and connective tissue growth factor (61). Martin *et al* (62) reported that dermal fibroblasts co-cultured with NPs exhibited enhanced uptake of these particles, alongside an upregulation of α-smooth muscle actin and pro-collagen Iα. This suggests a notable differentiation of fibroblasts into myofibroblasts, potentially initiating inflammatory or immune responses (62). Furthermore, several studies propose that MPs may disrupt the homeostasis of the ECM by affecting fibroblast protein expression, which could have a substantial impact on the TME. Eom *et al* (63) elucidated that exposure to PS-MPs in human dermal fibroblasts led to the upregulation of matrix metalloproteinase-1 (64), a collagenase known for degrading type I collagen, and several other ECM proteins. This process of exposure to PS-MPs markedly diminished the expression of adhesion and ECM-related genes (ELN, LAMA, LAMB, LAMC, etc.), thereby weakening the mechanical linkages between the intracellular and extracellular environments and the ECM. Moreover, a downregulation of integrin β subunits (65) was also observed in Eom's study, which are cell surface receptors that mediate cell-matrix adhesion, along with downstream focal adhesion kinase expression.

This downregulation subsequently activates the PI3K/AKT signaling pathway, reducing cell migration and inducing apoptosis (63).

Endothelial cells. Endothelial cells, which constitute a thin layer of cells lining blood vessels, are integral to the regulation of connective tissue cell growth and development, as well as the facilitation of angiogenesis. The formation of new blood vessels is vital for delivering nutrients and oxygen, thus sustaining tumor growth and progression. Therefore, angiogenesis mediated by endothelial cells is a fundamental process in tumor development (66). The influence of MPs on endothelial cells may represent a pivotal mechanism connecting MPs to tumor progression and alterations in the TME. Vlacil *et al* (67) assessed the effects of carboxylated PS microparticles (1 μm) on murine endothelial cells and reported that these PS particles had the capacity to activate endothelial cells, inducing the expression of adhesion molecules. This activation subsequently enhanced leukocyte adhesion and stimulated monocytes to secrete pro-inflammatory cytokines (67). Mobayen *et al* (68) evaluated the effects of irregular PS-MPs, exposing human umbilical vein endothelial cells to PS-MPs for a duration of 24 h. The results demonstrated a marked upregulation in the expression of intercellular cell adhesion molecule-1 and vascular cell adhesion molecule-1, thereby corroborating the activating influence of MPs on endothelial cells. Furthermore, it was reported that MPs induced alterations in endothelial cell phenotypes and shortened the lag time for fibrin formation, consequently heightening the risk of vascular inflammation or thrombosis (68). Mice models were used to assess the relationship between MPs and vascular damage and inflammation. According to a previous study, NP exposure caused structural damage to vascular endothelial cells, triggered inflammatory responses and weakened coagulation, resulting from the activation of the Janus kinase 1/STAT3/tissue factor signaling pathway and inflammatory mediators, such as IL-6 (69).

MPs and the ECM

The ECM functions as an essential scaffold that preserves cellular homeostasis by facilitating cell-matrix adhesion and mediating direct interactions between cells and their extracellular milieu (70). Within the context of tumors, the ECM constitutes a notable component, fulfilling crucial roles, including the provision of mechanical support, the regulation of the microenvironment and serving as a reservoir for signaling molecules (71). Although specific research directly demonstrating the impact of MPs on ECM modulation in relation to tumor growth is currently lacking, Huang *et al* (72) performed a Kyoto Encyclopedia of Genes and Genomes analysis on differentially expressed genes in mice exposed to MPs. The findings identified an enrichment of MPs in the cell adhesion molecule pathway, indicating that MPs can directly influence the ECM. The excessive accumulation of MPs may not only interfere with cell signaling pathways and inhibit the activation of immune responses, but also impact a range of biological processes. These processes include the viability of tissue stem cells, cell differentiation, the regulation of growth factors and potentially the development of cancer (72). These observations underscore important directions for future exploration (Table II).

3. MPs and inflammation

Hanahan *et al* (73) proposed that inflammation notably contributes to the initiation and progression of tumors. Recognized as a hallmark of cancer, inflammation is implicated in every phase of tumorigenesis, encompassing development, malignancy, invasion and metastasis, whilst also interacting intricately with the TME. MPs intensify inflammatory responses by releasing cytokines, triggering inflammatory signaling pathways, inducing oxidative stress and establishing a microenvironment conducive to cancer initiation and progression (Table III) (37,74).

Inflammatory factors are critical in modulating inflammatory and immune responses and notably impact tumor progression within the TME through several mechanisms. These factors establish signaling pathways that mediate the pro-inflammatory effects of MPs and modify the microenvironment. Recent research has demonstrated that PS-NPs exacerbate lipopolysaccharide-induced duodenal inflammation in murine models via ROS-driven activation of NF-κB and NLRP3 (75). NF-κB is a pivotal regulator of pro-inflammatory mediator expression and serves a central role in the pathogenesis of inflammatory diseases. Notably, NF-κB operates in a cell-type-specific manner, facilitating the activation of genes that promote inflammation within the TME (76). The NLRP3 inflammasome contributes to the regulation of inflammatory responses by activating caspase-1, which in turn promotes the secretion of pro-inflammatory cytokines, IL-18 and IL-1β and induces pyroptosis (77). *In vitro* experiments have demonstrated that PS-MPs suppress cell viability via a mitochondria-dependent pathway, leading to increased production of ROS (78). Excessive ROS not only activates NF-κB but also serves as a critical mechanism for the activation of the NLRP3 inflammasome in response to exogenous stimuli (77,79,80). Consequently, the ROS-NF-κB-NLRP3 signaling pathway has emerged as a central focus in research concerning MPs and inflammation. Despite ethical considerations, a notable number of these experiments are performed using animal models. Wen *et al* (81) evaluated the relationship between exposure to PS-NPs and liver inflammation in mice, and reported that PS-NPs exposure markedly increased the expression levels of NLRP3, IL-1β and caspase-1, in addition to activating NF-κB. These results further corroborate the hypothesis that the ROS-NF-κB-NLRP3 signaling pathway is a mechanism through which PS-NPs induce inflammatory damage (81). Similarly, in a study by Zhang *et al* (82), the effects of varying concentrations of PS-MPs on chicken hearts and primary cardiomyocytes were assessed. The findings indicated that PS-MPs induced myocardial pyroptosis, inflammatory cell infiltration and mitochondrial damage via the NF-κB-NLRP3-gasdermin D signaling pathway. This process resulted in the upregulation of factors such as NLRP3, caspase-1, IL-1β, IL-18 and IL-6, thereby exacerbating myocardial inflammation (82). A comparable conclusion was drawn in a previous study evaluating the effects of PS-MPs on thymic inflammation in chickens (83). The study reported that PS-MPs induced oxidative stress in the thymus and activated the nuclear factor erythroid 2-related factor 2/NF-κB, Bcl-2/Bax and AKT signaling pathways. This activation subsequently enhanced the expression of downstream molecules such as IL-1β, caspase-3

Table II. Summary of information on the studies of MPs on stromal cells and ECM.

First author/s, year	Particle type	Size	Cell/animal model	Aim	Conclusion	(Refs.)
Yang *et al*, 2023	PE-NPs	500 nm	Murine macrophage RAW 264.7 cells	To explore the effects of PE-NPs on the intestinal microenvironment of murine colorectal cancer.	NPs cause lysosome damage in colon macrophages, prompting IL-1β production. This leads to Treg and Th17 differentiation and T cell exhaustion, fostering a tumor-friendly environment in the colon.	(51)
Wang *et al*, 2023	PS-NPs and PS-MPs	80 nm and 3 μm	Murine macrophage RAW264.7 cells	To investigate the effects of 80 nm PS-NPs and 3 μm PS-MPs on murine macrophages RAW264.7 cells.	Exposure to PS-NPs or PS-MPs enhance the secretion of inflammatory cytokines, cause cytotoxicity and pro-inflammatory effect on macrophages and lead to intestinal inflammation.	(52)
Brammatti *et al*, 2023	NPs	25, 50 and 100 nm	Human U937 cells and Caco-2 cells	To assess the effect of different sizes of NPs at the activation of macrophages in a co-culture model with intestinal cells.	Macrophages undergo infiltrative changes. HT29 cells up-regulate IL1-β and inducible nitric oxide synthase levels and the levels of monocyte chemoattractant protein 1 are altered when cells are exposed to NPs.	(53)
Merkley *et al*, 2022	PS-MPs	10 μm	Primary murine macrophages	To examine the metabolic response in macrophages to MP particles.	Macrophage phagocytosis of MPs triggers a metabolic shift to glycolysis, and increases CD80/CD86 markers and glycolysis-related cytokine gene expression.	(54)
Collin-Faure *et al*, 2023	PS-NPs and PS-MPs	100 nm-6 μm	Murine macrophage J774A.1 cells	To investigate how macrophages respond to the ingestion of plastic particles.	Alterations are observed in oxidative stress, lysosomal and mitochondrial functions, along with alterations in immune response surface marker expression.	(55)
Ling *et al*, 2020	MPs	N/A	Murine macrophages	To investigate the effect of MP on macrophage.	Macrophage engulfment of MPs triggers a glycolytic metabolic shift and alters metabolite expression.	(41)
Koner *et al*, 2023	PS-NPs	450 nm	Human macrophages	To examine the differential toxic effects of PS-NPs on human macrophages.	PS-NPs exposure markedly decreases human macrophage viability, triggers oxidative stress, hinders cell proliferation and damages DNA.	(56)
Wolff *et al*, 2023	PS, PMMA and PS-NH_2-MPs	50-1, 100 nm	Human peripheral blood mononuclear cells	To examine the direct effect on immune cells after exposure to MPs sized 50-1,100 nm.	M2 macrophage induction is indicated by reduced inflammatory phenotypes after 24 h of MPs exposure.	(57)
Weber *et al*, 2022	PS, PMMA and PVC NPs	50-310 nm	Human peripheral blood mononuclear cells	To investigate whether NPs exposure induces inflammatory processes in primary human monocytes cells.	NPs exposure can provoke human immune cells to secrete cytokines as key initiators of inflammation. This response is specific to certain PVC and particle shapes.	(58)

Table II. Continued.

First author/s, year	Particle type	Size	Cell/animal model	Aim	Conclusion	(Refs.)
Wang *et al,* 2024	PS-MPs	N/A	Human kidney HK-2 cells	To evaluate how PS-MPs affected tubular cells and fibroblasts.	PS-MP-induced extracellular vesicles lead to ER stress-related proteins, ROS production and fibrosis-related proteins in tubular cells and fibroblasts.	(61)
Martin *et al*, 2024	PS-NPs	100-500 nm	Human dermal fibroblast cells	To investigate the entry of NPs into a human skin system modeling skin with compromised barrier functions.	Trans-epidermal NPs trigger a marked shift from fibroblast to myofibroblast cells, boosting α-smooth muscle actin and pro-collagen Ia production.	(62)
Eom *et al*, 2024	PS particles	N/A	Human dermal fibroblast cells	To examine the 3D behavior of skin-derived cells exposed to PS particles.	MPs affect gene expression linked to ECM and integrin-mediated adhesion.	(63)
Vlacil *et al*, 2022	PS-MPs	1 μm	Murine myocardial endothelial cells	To investigate how carboxylated PS particles affect murine endothelial and immune cells involved in vascular inflammation.	PS-MPs trigger adhesion molecule expression in endothelial cells, leading to leukocyte adhesion in both static and flow conditions and increase pro-inflammatory cytokine expression.	(67)
Mobayen *et al*, 2023	PS-MPs	<5 μm	Human umbilical vein endothelial cells	To determine the effects of MPs exposure on endothelial cells and thrombus formation.	MPs possess the ability to activate the endothelium, reduce the lag time to fibrin formation and maximal turbidity, indicating denser clot formation.	(68)
Wang *et al*, 2023	PS, PS-NH_2 and PS-COOH NPs	80 nm	6-8-week-old male BALB/c mice	To investigate the adverse cardio-vascular impacts of PS, PS-NH_2 and PS-COOH NPs on mice.	NPs can induce injury and dysfunction through the activation of Janus kinase 1/STAT3/tissue factor pathway.	(69)
Huang *et al*, 2023	MPs	5 μm	4-week-old male C57BL/6 mice	TO examine the innate immune response of mice exposed to 5 μm MPs.	MPs disrupt immune receptors and impair cell signaling in the liver and spleen, hindering serum immune signal activation.	(72)

MPs, microplastics; NPs, nanoplastics; PS, polystyrene; PE, polyethylene; PMMA, polymethyl methacrylate; PVC, polyvinyl chloride; IL, interleukin; MCP-1, monocyte chemoattractant protein 1; ROS, reactive oxygen species; ECM, extracellular matrix; NLRP3, NLR family pyrin domain containing 3; NA, not applicable.

Table III. Summary of information on the studies of MPs and inflammation.

First author/s, year	Particle type	Size	Cell/animal model	Aim	Conclusion	(Refs.)
He *et al*, 2022	PS-NPs	100 nm	8-week-old male C57BL/6 mice	To investigate the inflammatory relationship and molecular mechanisms between PS-NPs and intestinal injury.	PS-NPs exacerbate lipopolysaccharide-induced inflammation and increase duodenal permeability in mice via the ROS-driven NF-κB/NLRP3 pathway.	(75)
Wen *et al*, 2024	PS-NPs	20 nm	6-week-old male mice and AML-12 hepatocytes	To explore the mechanisms of hepatotoxicity and inflammation induced by PS-NPs.	The NRF2-NLRP3 pathway contributes to hepatotoxicity and inflammation induced by PS-NPs.	(81)
Zhang *et al*, 2022	PS-MPs	5 μm	1-day-old chicks	To investigate the mechanism of MPs-induced heart injury in chickens.	Alterations in NF-κB-NLRP3-gasdermin D and AMP-activated protein kinase-PPARG coactivator 1α pathways, driven by PS-MPs and ROS overload, lead to oxidative stress, myocardial pyroptosis, inflammation and mitochondrial and energy metabolism dysfunction.	(82)
Li *et al*, 2023	PS-MPs	5 μm	1-day-old high land broilers	To assess the role of MPs on immune organs (chicken thymus).	Exposure to PS-MPs activates the Nrf2/NF-κB, Bcl-2/Bax and AKT pathways in the thymus, leading to increased downstream signaling that causes inflammation, apoptosis and autophagy.	(83)
Antunes *et al*, 2021	PS-NPs	25, 50 and 100 nm	Human colon adenocarcinoma HT29 cells	To evaluate NP toxicity and their potential to interfere with inflammation-related pathways in HT29 cells.	Increased p50 and p38 expression after PS-NP exposure, indicating activation of the NF-κB pathway.	(84)
Woo *et al*, 2023	PP-NPs	0.66± 0.27 μm	Human alveolar A549 cells and 7-week-old male ICR mice	To study of inhalation toxicity and inflammatory effects of PP particles on the lungs.	PP stimulation elevates phosphorylated-p38 and phosphorylated-NF-κB protein levels *in vivo* and *in vitro*, while PP-induced cytotoxicity in A549 cells is controlled by p38 and ROS inhibition.	(88)
Danso *et al*, 2024	PS-MPs, PP-MPs and PE-MPs	<20 μm	7-week-old male C57BL/6 mice	To examine the toxicity of PP, PS and PE-MP fragments in the pulmonary system of C57BL/6 mice.	PS fragments trigger lung inflammation by activating NF-κB and NLRP3 inflammasomes via the TLR4 pathway.	(89)
Han *et al*, 2024	MPs	Nano-sized	Human- and mouse-derived skin cells	To explore the toxicological effects of nano-sized MPs on the skin.	Nano-sized MPs cause higher inflammation in skin cells, increase absent in melanoma 2 expression based on concentration, trigger IL-1β release, and start an inflammatory response.	(90)

Table III. Continued.

First author/s, year	Particle type	Size	Cell/animal model	Aim	Conclusion	(Refs.)
Zeng *et al*, 2024	PS-MPs	0.1, 1 and 5 μm	Human colorectal adenocarcinoma Caco-2 cells and 6-week-old male C57BL/6 mice	To investigate the molecular mechanisms contributing to MP-induced intestinal barrier dysfunction.	PS-MPs cause intestinal inflammation and barrier dysfunction through the ROS-dependent NF-κB/NLRP3/IL-1β/MLCK signaling pathway.	(91)

MPs, microplastics; NPs, nanoplastics; PS, polystyrene; PE, polyethylene; PP, polypropylene; IL, interleukin; NLRP3, NLR family pyrin domain containing 3; MLCK, myosin light chain kinase; ROS, reactive oxygen species; toll-like receptor 4; NRF2, nuclear factor erythroid 2-related factor 2.

and Beclin1, culminating in thymic inflammation, apoptosis and autophagy (83).

In addition to the ROS-NF-κB-NLRP3 signaling pathway, other studies have suggested that toll-like receptor 4 (TLR4), p38 and p50 may also serve a role in mediating the pro-inflammatory effects of MPs. Antunes *et al* (84) performed an experiment in which the human colorectal cancer HT29 cell line was exposed to PS-NPs. The results demonstrated that HT29 cells exhibited an upregulation of p50 and p38 expression, along with an increase in TLR4 expression. Notably, p38, a member of the MAPK family, is implicated in several signaling cascades, including those related to inflammatory responses, and is responsive to environmental stressors (85). TLR4 functions as a membrane protein in the pattern recognition receptor (PRR) family. The activation of TLR4 can lead to the synthesis of pro-inflammatory cytokines and chemokines (86), as well as the activation of the classical NF-κB pathway and p38, thereby promoting inflammatory responses (87). Consistent results were reported in a study by Woo *et al* (88), where exposure of mouse lungs and A549 cells to PP-NPs resulted in a marked increase in the number of inflammatory cells, ROS production and levels of inflammatory cytokines and chemokines both *in vivo* and *in vitro*. This was accompanied by elevated levels of phosphorylated p38 and NF-κB proteins. In A549 cells, the inflammation induced by PP exposure was regulated by inhibitors targeting p38 and ROS. These results suggest that PP-NPs can promote inflammation through p38-mediated NF-κB signaling pathways (88). Additionally, Danso *et al* (89) administered 5 mg/kg MP fragments intratracheally to mice over a period of 14 days to assess the pulmonary toxicity and inflammatory effects associated with MPs. Compared with the control group, the lung tissues of mice administered with PS-MP fragments exhibited an increased presence of inflammasome components, including NLRP3, apoptosis-associated speck-like protein containing a caspase recruitment domain and caspase-1. This observation supports the conclusion that lung inflammation induced by PS microplastic fragments is mediated via TLR4 activation of the NF-κB and NLRP3 inflammasome pathways (89).

Although the pro-inflammatory pathways triggered by MPs in numerous experimental studies exhibit variability, they consistently implicate the NLRP3 inflammasome, underscoring its critical role in MP-induced inflammation. Contrarily, in the study by Han *et al* (90) on nano-sized MPs and their induction of inflammatory responses in skin cells, activation of the NLRP3 inflammasome was not detected. Instead, the study reported that nano-MPs upregulated the 'absent in melanoma 2' PRR in a concentration-dependent manner, thereby promoting the release of IL-1β and initiating the inflammatory response (90). This enhances the comprehension of inflammation induced by MPs.

On the other hand, beyond their pro-inflammatory effects, inflammatory factors have the potential to disrupt cellular junctions, alter the microenvironment and potentially contribute to malignant transformation. Zeng *et al* (91) reported that exposure of the human colorectal cancer Caco-2 cell line to PS-MPs resulted in increased permeability of tight junction proteins within the cultured Caco-2 monolayer. This effect is likely attributable to the induction

of oxidative stress and the activation of NF-κB and the NLRP3 inflammasome by PS-MPs in Caco-2 cells, which subsequently elevated the expression of inflammatory factors, such as IL-6, IL-8, TNF-α and IL-1β (91). Notably, IL-1β is known to activate the NF-κB/myosin light chain kinase (MLCK) signaling pathway (92), whereas TNF-α stimulates IL-8 secretion, thereby promoting intestinal inflammation and MLCK expression (93). Consequently, PS-MPs elicit inflammatory responses and compromise colonic epithelial tight junctions through the ROS-dependent NF-κB/NLRP3/IL-1β/MLCK signaling pathway. This process enhances mucosal barrier permeability and perturbs the intestinal microenvironment (91).

4. Conclusions

MPs have become deeply embedded within human society, establishing themselves as a major global pollutant. Their persistence, mobility, high production volume and wide range of applications have led to their ubiquitous presence in the natural environment. Consequently, MPs are increasingly encountered by the human body, posing potential health risks and potentially elevating the likelihood of disease and cancer (94). Research has reported that under conditions characterized by high concentration, extended exposure and heightened individual susceptibility, MPs may exert cytotoxic effects through mechanisms such as chronic inflammation, oxidative stress, DNA damage, immunotoxicity and the delivery of toxic substances. It potentially culminates in malignant transformation (95). Furthermore, previous studies have broadened the scope of understanding regarding the effects of MPs, demonstrating their influence not only on tumor initiation but also on tumor progression by modulating the TME (39). Despite the nascent stage of research in this field and the limited scope of existing literature, the present review offers a systematic analysis of contemporary studies examining the interactions between MPs and several components of the TME. These elements include tumor cells, immune cells (with a focus on macrophages), endothelial cells, fibroblasts, ECM and inflammatory factors. The primary conclusion is that MPs within the TME markedly contribute to the proliferation and metastasis of tumor cells. They achieve this by modulating the immune cell status to enhance tumor activity, inducing structural changes in vascular endothelial cells, facilitating the activation of fibroblasts and the expression of associated proteins and directly influencing the ECM and inflammatory mediators. We hypothesize that these theoretical foundations will enhance the comprehension of the role of MPs in carcinogenesis and offer novel research trajectories for future scholars. Furthermore, they may identify new diagnostic and therapeutic targets for individuals whose health is compromised by MPs, including patients with cancer.

Similarly, carbon nanomaterials (CNMs) exhibit distinctive physical and chemical properties due to their nanoscale dimensions. CNMs present novel opportunities for cancer therapy by specifically targeting cancer cells and components of the TME (96). The present review serves as an impetus for the investigation into the application of MPs within the context of the TME. Nonetheless, the current understanding of the interaction between MPs and the TME represents merely the tip of the iceberg. Consequently, further research is imperative to elucidate the intricate relationship between MPs and cancer development, establishing it as a crucial area of study.

It is important to recognize that the present review revealed considerable variability in experimental outcomes, attributable to disparities in research methodologies, sample types, the physical properties of samples as well as exposure concentrations and durations. These inconsistencies present challenges in comparing and categorizing study findings. Therefore, future research on MPs and the TME should incorporate several MP types, concentrations and exposure durations, in both *in vitro* and *in vivo* settings, alongside rigorously designed control groups. Whilst this approach may increase the complexity of experiments, it will enhance the reliability and accuracy of the data and conclusions.

In summary, the study of MPs, tumors and the TME necessitates sustained research investment and the adoption of multidisciplinary methodologies. As the present review progressively unravels the complex web of interactions among these elements, the resulting insights will contribute to the development of more efficacious preventive measures, facilitate earlier detection and enhance therapeutic strategies for individuals affected by MPs.

Acknowledgements

Not applicable.

Funding

The present research was supported by the educational research project of Nanjing Medical University (Nanjing, China; grant no. 2023YJS-LX011 and 2023YJS-LX012), the National Natural Science Foundation of China (grant nos. 82203216 and 82102073) and the Natural Science Foundation of Jiangsu Province (grant no. BK20220724).

Availability of data and materials

Not applicable.

Authors' contributions

YC drafted and revised the manuscript. ZZ, KJ, QZ, LQ and CY collected the relevant papers and helped to revise the manuscript. ZZ and QZ designed the tables and charts. CY and LQ reviewed the article. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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