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The micro(nano)plastics perspective: exploring cancer development and therapy

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Abstract
Microplastics, as an emerging environmental pollutant, have received widespread attention for their potential impact on ecosystems and human health. Microplastics are defined as plastic particles less than 5 millimeters in diameter and can be categorized as primary and secondary microplastics. Primary microplastics usually originate directly from industrial production, while secondary microplastics are formed by the degradation of larger plastic items. Microplastics are capable of triggering cytotoxicity and chronic inflammation, and may promote cancer through mechanisms such as pro-inflammatory responses, oxidative stress and endocrine disruption. In addition, improved microplastics bring new perspectives to cancer therapy, and studies of microplastics as drug carriers are underway, showing potential for high targeting and bioavailability. Although current studies suggest an association between microplastics and certain cancers (e.g., lung, liver, and breast cancers), the long-term effects and specific mechanisms still need to be studied. This review aimed at exploring the carcinogenicity of microplastics and their promising applications in cancer therapy provides important directions for future research and emphasizes the need for multidisciplinary collaboration to address this global health challenge.

Keywords Micro (nano) plastics, Carcinogenicity, Drug carrier, Cancer therapy

Introduction

Microplastics (MPs, 1 μm-5 mm) and nanoplastics (NPs, < 1 μm) are novel pollutants resulting from the degradation of plastics as well as from commercial production, and these tiny plastic particles can persist in the environment for long periods of time and pose a potential threat to the ecosystem and human health [1–5]. Its particle size ranges from a few nanometers to a few millimeters, and it is a mixture of non-uniform plastic particles of various shapes, which is often difficult to distinguish with the naked eye, and therefore it is figuratively called"PM2.5 in the sea" [6, 7]. Microplastics can be categorized into two main groups, primary microplastics and secondary microplastics, based on their source and formation process [8] (Fig. 1). Primary microplastics mainly originate from industrial production areas such as cosmetics, personal care products, and medical drugs [9]; whereas secondary microplastics are mainly formed from large plastic wastes that are gradually fragmented by physical, chemical, and biological processes under environmental conditions [10, 11]. Microplastics are widely distributed in oceans, freshwater, soil, atmosphere and living organisms [12, 13]. They are difficult to degrade in the environment and are able to migrate around the globe with natural forces such as wind and water currents, causing long-term impacts on ecosystems [14, 15]. Microplastics enter the human body through the food chain, and

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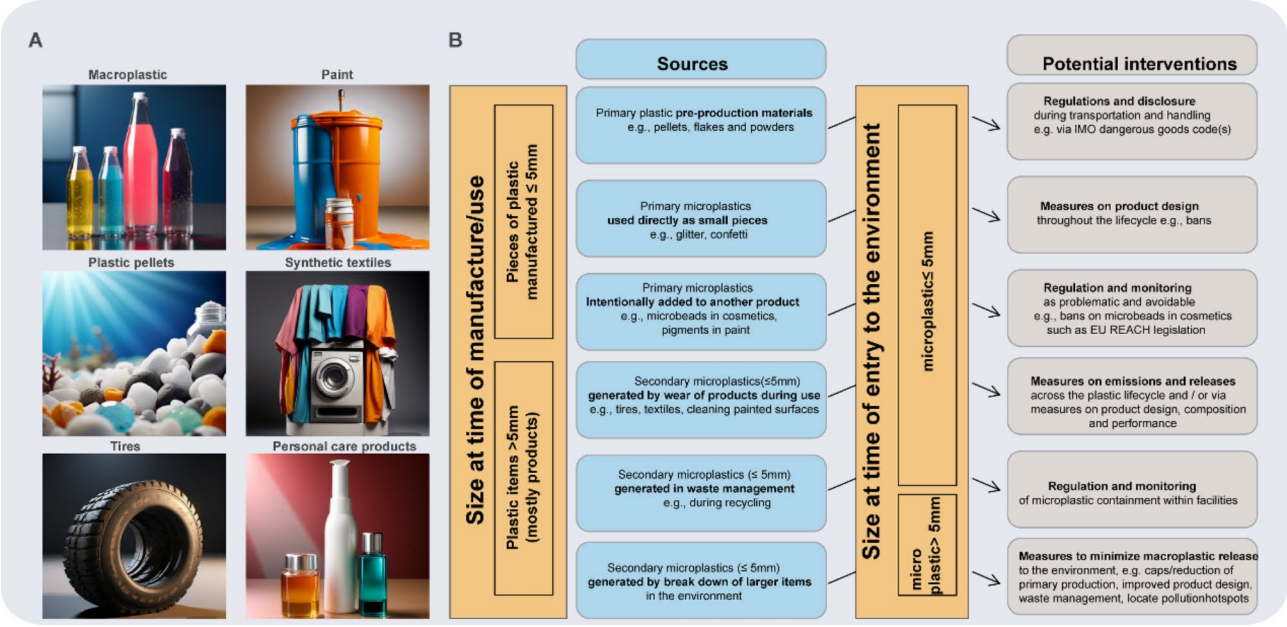

Fig. 1 Sources and categories of micro(nano)plastic. (**A**) Human activities leading to six key sources of microplastics. (**B**) Scheme outlining our proposed nomenclature for microplastic categorization based on origin and size; together with potential interventions

Table 1 Detected types of plastics that pass through human biological barriers or are excreted from the body

Type of MnPs	Placenta	Meconium	Breast milk	Blood	Feces
Polyamide	✓	✓	✓	✓	✓
Polyurethane	✓	✓	✓	✓	✓
Polyethylene	✓	✓	✓	✓	✓
Polyethylene terephthalate	✓	✓	✓	✓	✓
Polypropylene	✓	✓	✓	✓	✓
Polyvinyl chloride	✓	✓	✓	✓	✓
Polyoxymethylene	✓	✓	✓	X	✓
Ethylene vinyl acetate copolymer	✓	✓	✓	X	✓
Polytetrafluoroethylene	✓	✓	✓	X	✓
Chlorinated polyethylene	✓	✓	✓	X	✓
Polybutadiene	✓	✓	✓	X	✓
Polycarbonate	✓	X	X	✓	X
Polystyrene	✓	X	✓	✓	✓
Polymethyl methacrylate	✓	✓	✓	✓	✓
Polylactic acid	✓	✓	✓	X	✓
Polysulfones	✓	✓	✓	X	✓
Nitrocellulose	X	–	✓	X	X
Reference	[136, 142, 143]	[136, 143, 144]	[136, 145]	[133, 134, 146]	[133, 136, 141, 147]

"✓" indicates the plastic type has been detected, whereas cells with the dash (**X**) indicate that no evidence of the presence of the MnP type was found in the corresponding medium

aquatic organisms (e.g., fish and shellfish) often accidentally ingest microplastic particles, leading to their accumulation in their bodies and subsequent consumption by humans. Different types of microplastics have been found in human placenta, meconium, breast milk, blood, and feces (Table 1). The ingestion of microplastics may lead to impaired physiological functions in humans [16–18], including growth retardation [19], reduced fertility [20–23], and impaired immune system [3].

In recent years, scientific studies have gradually revealed a possible strong link between microplastics and tumorigenesis [24]. Microplastics may not be directly carcinogenic per se, but as a carrier, they are able to adsorb and carry a variety of toxic chemicals, such as polycyclic aromatic hydrocarbons (PAHs), heavy metals, and plasticizers [25, 26]. The accumulation and release of these harmful substances in organisms may interfere with the normal physiological functions of cells, leading to gene mutations, abnormal cell proliferation, and disorders of the immune system, which in turn promote tumorigenesis.

Particularly in critical organs such as the bone marrow, the accumulation of microplastics can lead to more serious consequences. Bone marrow is an important part of the hematopoietic system and is responsible for the production of key cells such as red blood cells, white blood cells and platelets. After entering the bone marrow [27], microplastics may interfere with the normal hematopoietic process and lead to abnormal proliferation and differentiation of blood cells, thus increasing the risk of hematological system tumors such as leukemia [28]and

lymphoma. In addition, microplastics may be distributed to tissues and organs throughout the body through the blood circulation system (Fig. 2), interacting with various cells and further exacerbating tumor development and progression. Therefore, reducing exposure and intake of microplastics and strengthening environmental regulation and plastic pollution control are important for the prevention of chronic diseases such as tumors.

In summary, there are complex links and potential threats between microplastics and tumorigenesis. This review focuses on the role of micro(nano)plastics in cancer occurrence and development and their potential impact on treatment. We need to address this challenge at multiple levels with integrated measures to protect human health and ecological safety.

The relationship between micro(nano)plastics and cancer

Biocompatibility of micro(nano)plastics

The biocompatibility of micro(nano)plastics is an important indicator for assessing their impact on living organisms, which includes their uptake, accumulation, and toxic effects on cells and tissues in living organisms [29]. Micro(nano)plastics enter the human body through the food chain, leading to their accumulation in the body [30] (Fig. 2). Over time, these particles may lead to cellular dysfunction and chronic inflammatory responses [31], which is widely recognized as one of the risk factors for cancer. The presence of micro(nano)plastics in the body can activate the immune system [32], leading to the release of inflammatory factors [33], which in turn affects the normal physiological functions of the body.

In biocompatibility studies of micro(nano)plastics, their cytotoxicity and relation to tumorigenesis have received much attention. The size, shape and surface properties of microplastic particles affect their behavior inside cells. Significant differences in the uptake and distribution of PS-MNPs of different sizes (0.25 μm, 1 μm and 10 μm) were found in four colon cancer cell lines [24]. Smaller sized (0.25 μm) micro(nano)plastics were more readily taken up by the cells and the smaller sized particles showed higher accumulation rates in all tested colon cancer cell lines in both short- and medium-term accumulation studies [24]. Microplastic treatment, especially

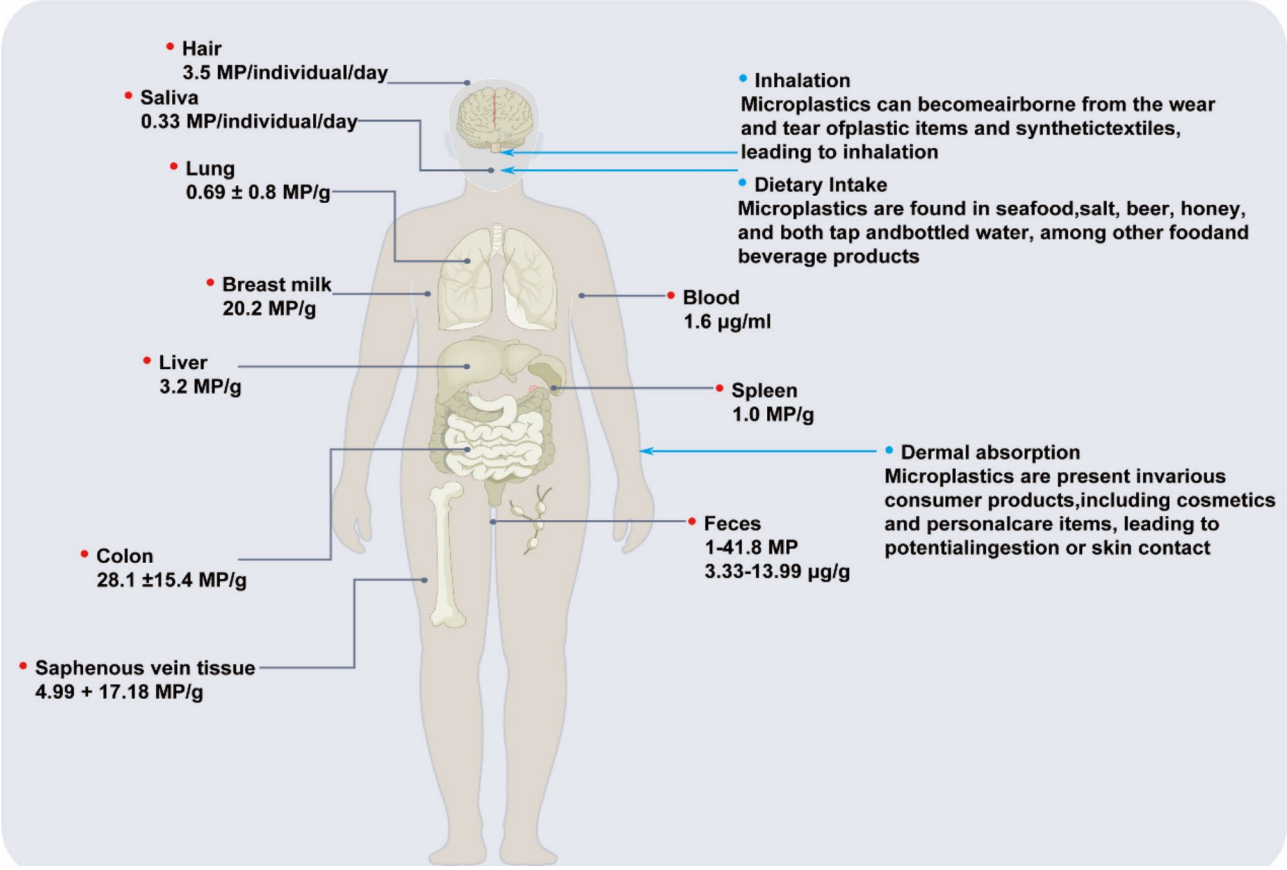

Fig. 2 Locations in the human body where micro(nano)plastics have been reported. Exposure pathways (turquoise labels) and reported quantities (red labels) are shown [131–141]. The quantities presented are as reported in each study and have not undergone additional QA/QC screening for this review. Caution is advised when making inter-study comparisons due to variations in methodologies and units of measurement. Additionally, since some methods do not differentiate between individual particles, it is likely that the quantities reported by mass may include both micro- and nanoparticles

at 0.25 μm, significantly increased the rate of cell migration, which could lead to a metastasis-promoting effect. This finding emphasizes the influence of microplastic size on its biological effects, with small-sized micro(nano) plastics promoting cell migration more significantly than large-sized micro(nano)plastics [24].

Smaller microplastic particles are more likely to be ingested by cells and may lead to oxidative stress upon entry [34] (Fig. 3). Oxidative stress refers to the accumulation of reactive oxygen species (ROS) in the body, which are capable of triggering DNA damage [35], leading to genetic mutations and thus increasing the risk of cancer. In addition, toxic chemicals that may be adsorbed on the surface of micro(nano)plastics, such as heavy metals and persistent organic pollutants (POPs), can exacerbate this toxic effect [36]. These substances, when released inside cells, may further damage cells and lead to cancer. Therefore, the toxic effects of micro(nano)plastics in organisms are closely related to their physicochemical properties, which provides important clues to study the relationship between micro(nano)plastics and tumorigenesis.

Despite the concerns about the toxic effects induced by micro(nano)plastics in the environment and in living organisms, their applications in the medical field are gradually being explored, especially their potential as drug carriers. By modifying micro(nano)plastics, targeted delivery of drugs can be achieved, improving their bioavailability and therapeutic efficacy. However, while conducting these studies, the biocompatibility of micro(nano)plastics and their potential toxicity must be carefully considered, especially for applications in tumor therapy. Future studies should focus on the effects of micro(nano)plastics on cell behavior and the mechanisms of their toxicity in specific biological environments. At the same time, there is an urgent need to establish standardized assessment methods to explore the biocompatibility of micro(nano)plastics in depth so that their safety can be fully evaluated in medical applications. Only through multidisciplinary cooperation and in-depth research can the biocompatibility of micro(nano)plastics and their relationship with tumorigenesis be fully understood.

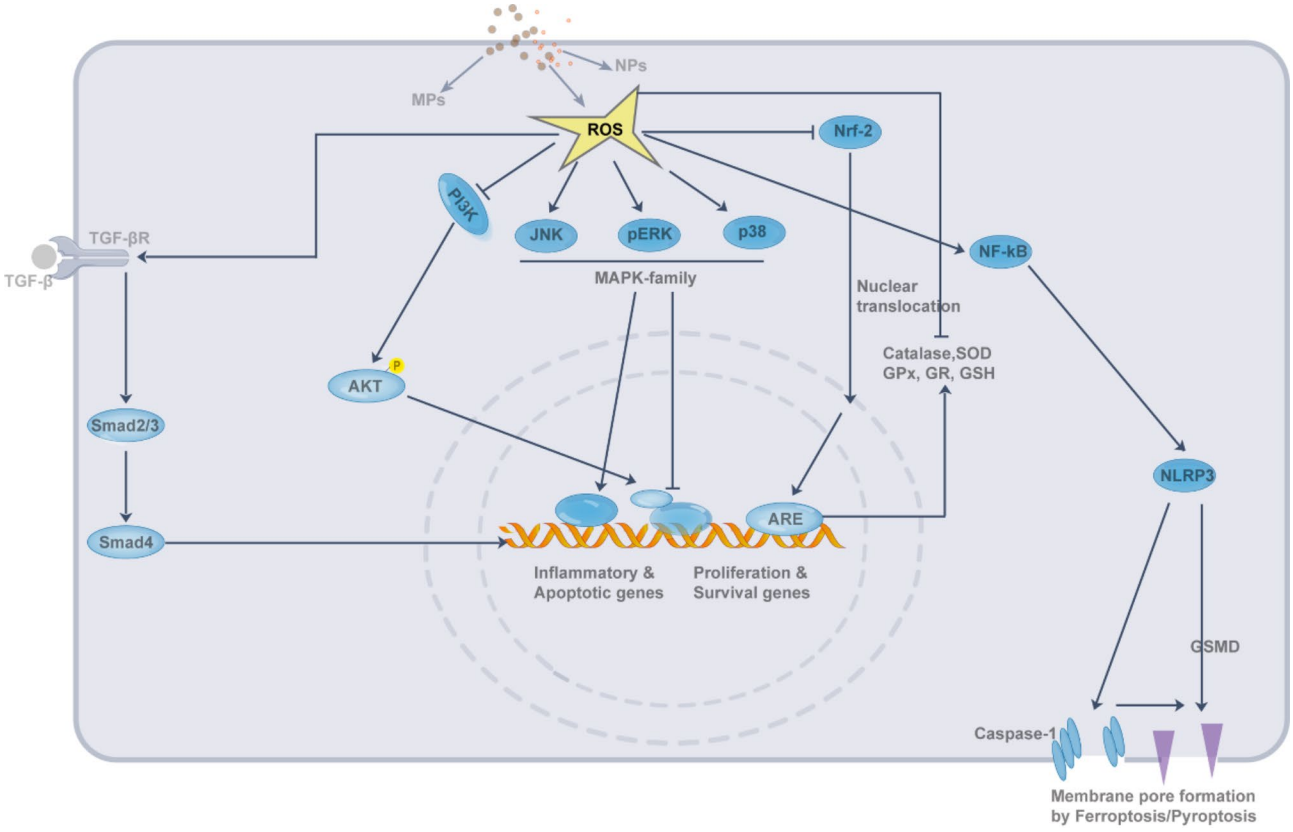

Fig. 3 Micro(nano)plastics-induced ROS regulate multiple signaling pathways. The induction of ROS by MPs/NPs leads to the regulation of various signaling cascades critical to the normal physiological functions of cells. These include the MAPK signaling pathways (JNK, p38 kinase, and ERK1/2), the Nrf2 pathway, the PI3K/Akt pathway, as well as the TGF-β and NF-κB/NLRP3/Caspase-1/GSDMD pathways. Abnormal activation or inhibition of these pathways may lead to cancerous transformation of normal cells. Microplastics (MPs) and nanoplastics (NPs)

The role of micro(nano)plastics in cancer development

Epidemiological studies

An overview of existing epidemiological studies reveals a potentially complex relationship between microplastic exposure and cancer [37, 38]. Although research in this area is still in its infancy, several studies have begun to explore the effects of microplastic exposure on human health [39–42], particularly cancer risk. Epidemiologic studies directly demonstrating that microplastic exposure contributes to the development of specific cancers are still limited. However, laboratory studies have shown that micro(nano)plastics are capable of accumulating in living organisms and may cause cellular damage, which in turn promotes cancer development [43, 44]. Several epidemiologic studies have found that areas with high levels of environmental microplastic contamination have a relatively high incidence of certain cancers in their inhabitants [45]. This suggests that microplastic exposure may be associated with an increased risk of cancer, but the exact mechanism needs to be further investigated.

Microplastic particles in the air may enter the lungs through breathing and be deposited in the lungs [46–48]. Long-term exposure to high concentrations of microplastic particles may cause damage to lung cells, which in turn increases the risk of lung cancer. Several studies have shown that micro(nano)plastics in the food chain may enter and accumulate in the liver through the digestive tract [49, 50]. As an important metabolic organ in the human body, the liver has a high sensitivity to micro(nano)plastics and the harmful substances they carry. Long-term exposure to micro(nano)plastics may lead to pathological changes such as liver cell damage [51], increased inflammatory response and increased oxidative stress, which in turn increases the risk of liver cancer. In addition, additives in micro(nano)plastics (e.g., plasticizers, antioxidants, etc.) have endocrine-disrupting effects [52], which may affect hormone levels and cell proliferation processes, further contributing to the development and progression of liver cancer. Studies have indicated that exposure to microplastics may be linked to the development of cancers other than lung and liver cancers, including breast cancer [53] and prostate cancer [54].

In summary, the existing epidemiologic studies reveal a possible correlation between microplastic exposure and cancer, but the specific mechanisms need to be further investigated.

Animal results

In recent years, with the increased attention to the issue of microplastic pollution, scientists have begun to study the relationship between microplastic exposure and tumorigenesis in animal models. These studies have focused on model organisms such as zebrafish [55] and mice to observe the effects of microplastic pollution in animals by simulating the environmental microplastic pollution.

In the zebrafish model, researchers found that zebrafish exposed to aqueous environments containing micro(nano)plastics had significant changes in the expression of certain genes associated with tumorigenesis [56, 57]. These changes may indicate abnormal cell proliferation or impaired apoptosis in zebrafish, thereby increasing the risk of tumorigenesis. In addition, some studies have further observed the effects of microplastic particles on tumorigenesis in zebrafish by injecting them into the body or allowing them to ingest feed containing micro(nano)plastics [58]. The results of these experiments showed that microplastic exposure could indeed increase the incidence of tumors in zebrafish.

In a mouse model, scientists conducted a similar study. They observed tumorigenesis in mice by feeding them microplastic-containing chow or exposing them to microplastic-containing environments. It was found that polystyrene nanoparticle microplastic (PS-NP) exposure accelerated the growth of epithelial ovarian cancer in mice [44], whereas in in vitro experiments, PS-NPs were able to reduce the relative viability of human epithelial ovarian cancer (EOC) cells in a dose-dependent mode of action [44]. These results suggest that microplastic exposure may be associated with the development of certain types of tumors.

Mechanisms of micro(nano)plastics carcinogenesis

Although the exact mechanisms of how micro(nano)plastics contribute to tumor progression are not fully understood, scientists have suggested some possible pathways.

Pro-inflammatory response

Micro(nano)plastics, as a foreign object, are able to trigger an immune system response when they enter the body [59]. Immune cells such as macrophages and neutrophils rapidly recognize and attempt to remove these microplastic particles. However, due to the tiny size and difficult degradation properties of micro(nano)plastics, they are often difficult to remove completely, thus persisting in the body and triggering chronic inflammation [32]. This chronic inflammatory response leads to a sustained release of inflammatory factors, such as IL-6 and TNF-α, in local tissues, which in turn promotes the infiltration and proliferation of inflammatory cells [60, 61].

Long-term chronic inflammation can significantly alter the tumor microenvironment [62–64]. Areas of chronic inflammation are usually accompanied by changes such as cellular infiltration, stromal remodeling and angiogenesis [65–67]. These changes provide favorable conditions for tumor cell proliferation, migration and metastasis. Specifically, immune cells in the inflammatory

microenvironment, such as macrophages, lymphocytes, and dendritic cells, may promote the growth and survival of tumor cells by secreting growth factors and cytokines. For example, tumor-associated macrophages (TAMs) may promote tumor angiogenesis and enhance tumor nutrient supply by secreting vascular endothelial growth factor (VEGF) [68, 69]. In addition, reactive oxygen species (ROS) and nitrogen oxides (RNS) generated in the inflammatory microenvironment can trigger oxidative damage to cellular DNA [70, 71], thereby increasing the mutation rate and consequently elevating the likelihood of carcinogenesis.

The inflammatory response triggered by micro(nano) plastics is not only the formation of a local tumor microenvironment, but may also alter the body's ability to immunosurveillance against tumors by affecting the systemic immune response. Studies have shown that chronic inflammation may lead to dysfunction of immune cells, preventing them from effectively recognizing and clearing tumor cells [72]. Specifically, the inflammatory response may contribute to the transformation of certain immune cells into an immunosuppressive phenotype, which would weaken the body's immune surveillance of tumors and thus promote tumor development and spread [73, 74]. In addition, chronic inflammation is closely associated with the development of several tumor types, such as liver cancer [75], lung cancer [76], and colon cancer [77]. Therefore, the inflammatory response triggered by micro(nano)plastics promotes the formation of the tumor microenvironment through multiple mechanisms, enhances the survival and development of tumor cells, and provides favorable conditions for tumorigenesis.

Oxidative stress

After entering the cells, micro(nano)plastics may affect the intracellular redox balance through several mechanisms. First, micro(nano)plastics can adsorb a large number of metal ions, such as iron, zinc, and copper [78], which tend to participate in redox reactions within cells [79, 80]. When micro(nano)plastics carry these metal ions into cells, they may inhibit or promote specific redox reactions, thereby disrupting the intracellular redox balance [81, 82]. In addition, micro(nano)plastics may inhibit the activity of intracellular antioxidant enzymes, reducing the ability to combat oxidative stress and further exacerbating redox imbalance. The disruption of redox balance leads to increased intracellular levels of reactive oxygen species (ROS), which are highly reactive molecules capable of damaging biological macromolecules such as cell membranes, proteins, and DNA [83, 84], causing damage to cells. This damage not only affects the normal physiological functions of cells, but also may trigger cellular stress responses and death pathways (Fig. 3).

Disruption of intracellular redox homeostasis is one of the major causes of DNA damage. ROS are able to directly attack DNA molecules, resulting in DNA strand breaks, base damage, and DNA adduct formation [85, 86]. These damages, if not repaired in a timely manner, can introduce errors during DNA replication and transcription and increase the mutation rate. Mutation is one of the important drivers of cancer development. When mutations occur in key genes, they may lead to changes such as uncontrolled cell proliferation, impaired apoptosis, and metabolic abnormalities, which in turn promote tumor formation and development [87]. Thus, micro(nano)plastics indirectly increase the risk of cancer by affecting intracellular redox balance and leading to DNA damage and increased mutation rates.

In summary, the effect of micro(nano)plastics on intracellular redox balance and the resulting increase in DNA damage and mutation rates is one of the important ways to increase cancer risk.

Endocrine disruption

A variety of chemicals are often added to micro(nano) plastics during the manufacturing process to enhance their properties, with plasticizers and antioxidants being two of the more common types. While these additives give micro(nano)plastics specific functions, they may also have adverse effects on human health, particularly through endocrine disruption. For example, phthalate plasticizers are capable of interfering with the normal function of estrogen and androgen, leading to imbalanced hormone levels [88–91]. In contrast, substances such as bisphenol A may mimic the function of thyroid hormones, interfering with their metabolism and signaling [92]. Estrogen plays an important role in the development and progression of breast cancer. Endocrine disruptors such as phthalates can mimic the function of estrogen and promote abnormal proliferation of breast cells, thereby increasing the risk of breast cancer [93]. Androgens play a key role in the growth and development of the prostate. Endocrine disruptors may interfere with the normal metabolism and signaling of androgens, leading to abnormal prostate cell proliferation and cancer [94]. Abnormal changes in these hormone levels may have important effects on cell proliferation.

Cell proliferation is the basis for the growth and development of organisms and an important process in tumorigenesis. When hormone levels are abnormal, it may promote the abnormal proliferation of certain cells, thus increasing the risk of tumorigenesis [95]. Especially those hormone-sensitive cells, such as breast cells and prostate cells, are more likely to be affected by endocrine disruptors and become cancerous.

In summary, additives commonly found in micro(nano) plastics such as plasticizers and antioxidants have

endocrine disrupting effects that can affect hormone levels and cell proliferation processes in the body, thereby increasing the risk of specific types of cancer.

Effect of micro(nano)plastics on cancer therapy

Effect of micro(nano)plastics on therapeutic drugs

Interference of micro(nano)plastics in drug metabolism

The presence of micro(nano)plastics not only affects the environment, but may also alter the behavior of drugs in the body, especially in oncology therapy [96]. Micro(nano)plastics may interfere with the absorption, distribution, metabolism and excretion of drugs through a variety of mechanisms, thereby affecting their efficacy and toxicity responses [97–99].

The size and surface properties of micro(nano)plastics affect the efficiency of drug uptake [100]. Smaller microplastic particles can facilitate drug uptake through cell membranes, whereas larger particles may be rejected. In addition, the surface of micro(nano)plastics can be functionalized [101]to enhance their interaction with specific cells. For example, attachment of targeted ligands to the surface of micro(nano)plastics can enhance their uptake in tumor cells [102, 103]. This enhanced cellular uptake can increase the concentration of the drug in the tumor microenvironment, thereby improving efficacy. However, micro(nano)plastics may also affect the bioavailability of the drug by binding to it, resulting in a reduced release of the active ingredient.

The presence of micro(nano)plastics may alter drug metabolism pathways. The metabolism of drugs in the body is usually dependent on enzymatic activity in vital organs such as the liver, and micro(nano)plastics may affect these processes by triggering inflammation or interfering with the expression of metabolic enzymes. For example, chronic inflammation can lead to impaired function of hepatocytes [104], which in turn affects the rate of drug metabolism and the production of metabolites. This altered metabolism may lead to a longer or shorter half-life of the drug in the body, thus affecting efficacy.

Interference with micro(nano)plastics may result in reduced efficacy or increased toxicity of the drug. First, binding of drugs to micro(nano)plastics may result in delayed release of the drug, thereby affecting its concentration and duration of action in the target tissue. Second, the inflammatory response triggered by micro(nano) plastics may enhance the toxicity of the drug, leading to normal cell damage or death. For example, in an inflammatory microenvironment, the production of reactive oxygen species is increased, which may exacerbate the side effects of drugs [105].

In addition, micro(nano)plastics may affect drug efficacy by altering the immune response. Chronic inflammation and immunosuppression may make tumor cells more resistant to treatment and reduce drug effectiveness [106, 107]. In conclusion, micro(nano)plastics pose potential risks and challenges to tumor therapy by affecting the absorption, distribution, metabolism, and excretion of tumor drugs, thereby interfering with therapeutic efficacy and toxicity responses at multiple levels.

Micro(nano)plastics as drug carriers

The prospect of combining micro (nano) plastics with cancer therapy is actually a rather challenging topic. First, it needs to be made clear that micro(nano)plastics in the traditional sense (i.e., tiny plastic particles in the environment) are not suitable for direct use in biomedical applications, including cancer therapies, due to the toxic chemicals they may carry and their negative effects on the human body. However, we can explore the promise of micro- and nanotechnology-like materials for use in cancer therapy and how they may play a role in enhancing the effectiveness of cancer treatments.

Nanomaterials have attracted much attention in recent years for their application in targeted drug delivery systems due to their unique physicochemical properties [108–112]. Targeted drug delivery aims to deliver drugs precisely to target tissues or cells to improve therapeutic efficacy and reduce side effects. Improved nanoplastics (Fig. 4), as a tunable drug carrier, have good biocompatibility, modifiability and drug-carrying capacity, which makes them show great potential in drug delivery systems [113].

The properties of micro(nano)plastics make them ideal drug carriers [114–116]. First, the size of micro(nano) plastics can be precisely controlled through synthesis and modification processes, usually in the micrometer to nanometer range, and such sizes facilitate cellular uptake and tissue penetration. Second, the surface properties of micro(nano)plastics (e.g., charge, hydrophilicity, and hydrophobicity) can be modulated by chemical modifications to achieve targeted drug release. For example, micro(nano)plastics with hydrophilic surfaces are more likely to bind to cell membranes and improve drug uptake [117]. In addition, micro(nano)plastics have a high drug-carrying capacity and can effectively encapsulate many types of drugs, including small molecule drugs, proteins, and nucleic acids. These targeting ligands can specifically recognize the receptors on the surface of tumor cells and promote the uptake of micro(nano)plastics, thus improving drug targeting and effectiveness.

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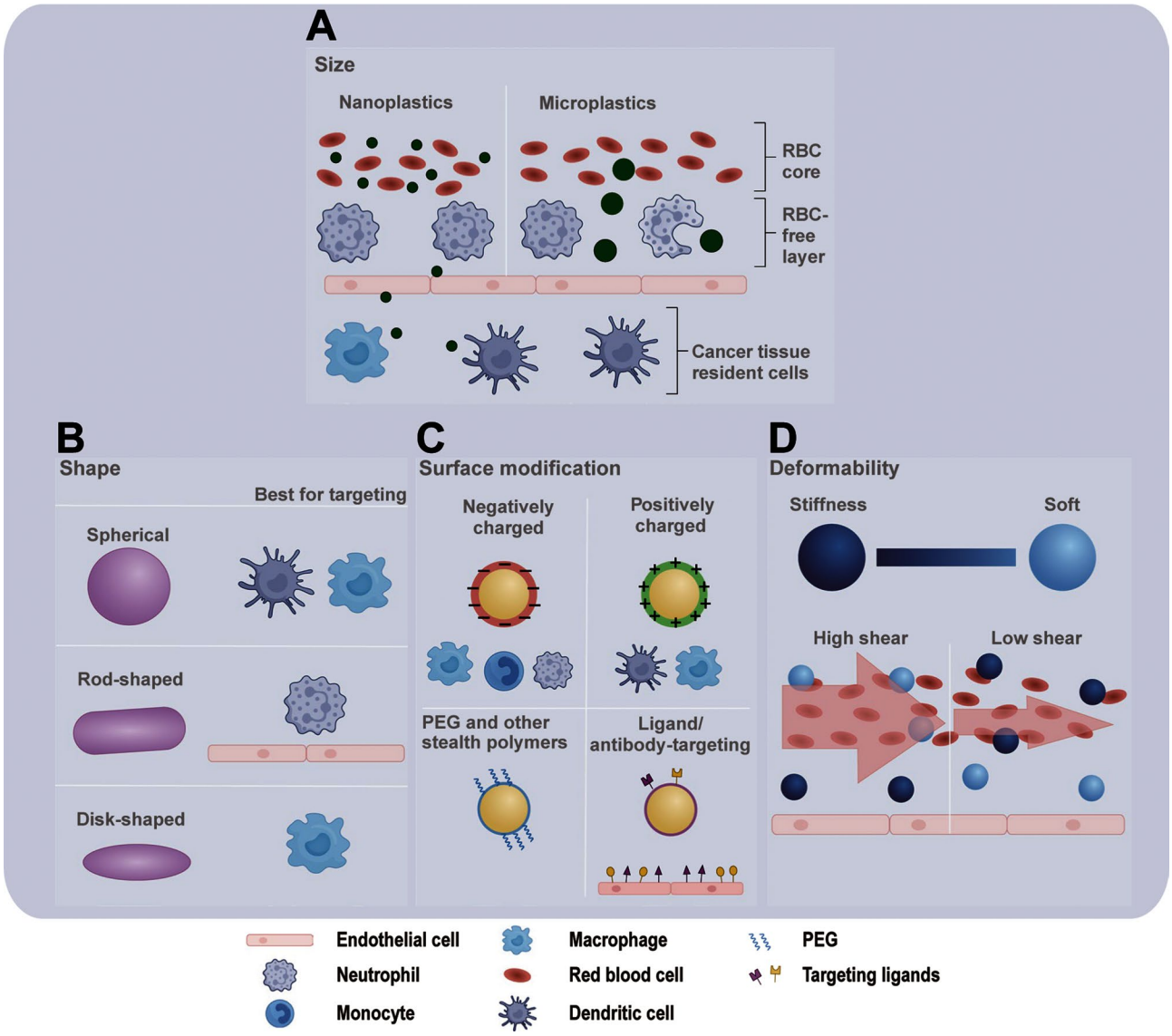

Fig. 4 Optimization of nanoplastics carriers. (**A**) Microplastics may be phagocytosed and target blood vessel walls, while nanoplastics may penetrate blood vessels. (**B**) Nanoplastics can be formulated into a variety of shapes to target specific cell populations. (**C**) Functional groups on nanoplastics can be conjugated with targeting ligands or stealth polymeric chains. In addition, the nanoplastics can be positively or negatively charged. (**D**) The stiffness of the nanoplastics can be varied to selectively target specific tumor cells in the bloodstream. Soft particles are better suited for distribution along the edge of the endothelium in the bloodstream than stiff particles. RBC, red blood cell; PEG, polyethylene glycol

can be modulated by chemical modifications to achieve targeted drug release. For example, micro(nano)plastics with hydrophilic surfaces are more likely to bind to cell membranes and improve drug uptake. In addition, micro(nano)plastics have a high drug-carrying capacity and can effectively encapsulate many types of drugs, including small molecule drugs, proteins, and nucleic acids. These targeting ligands can specifically recognize the receptors on the surface of tumor cells and promote the uptake of the micro(nano)plastics, thus improving the targeting and effectiveness of the drugs.

In addition, controlled release of drugs can be achieved by regulating the release kinetics of nano micro(nano) plastics [118]. For example, designing bilayer or multilayer microplastic structures enables the gradual release of drugs under specific physiological conditions (e.g., pH, temperature, or the presence of enzymes) [119–121], resulting in long-term effective therapy. Polylactic acid-glycolic acid copolymer (PLGA) is a common thermoplastic with excellent biocompatibility and biodegradability. It can be used as a drug carrier to target malignant tumors. Studies have confirmed that long-lasting stable and slow release of drugs can be achieved using PLGA nanoparticles loaded with anticancer drugs [122]. In addition, the desired drug release behavior can be obtained by regulating the degradation cycle of PLGA.

Therefore, PLGA nanoparticles can be used as ideal drug carriers for long-acting chemotherapy.

Potential applications of micro(nano)plastics in cancer therapy

Research on targeted therapy

In recent years, the use of micro(nano)plastics as drug carriers in targeted cancer therapy has attracted widespread attention. Researchers have explored different types of microplastic carriers for more efficient drug delivery and better therapeutic effects. Poly (lactic acid) (PLA) micro(nano)plastics were modified to improve their targeting properties. One study prepared PLA-Cy7-SM5-1 to explore its targeting properties on HCC-LM3-fLuc cells [123]. Subsequently, PLA-5FU-SM5-1 with PLA-5FU was developed for the treatment of HCC-LM3-fLuc tumor-bearing mice. Compared to PLA-5FU and 5-FU, PLA-5FU-SM5-1 exhibited higher tumor growth inhibition in both subcutaneous and liver tumor models (45.07% and 53.24%, respectively). In addition, the three-dimensional location of mouse hepatocellular carcinoma was reconstructed by an algorithm, which verified the effectiveness of PLA-5FU-SM5-1 in inhibiting tumor progression.

In addition, it has been found that combining PLGA nanoparticles with PD-L1 checkpoint inhibitors not only stimulates the immune response in the organism, but also reduces the expression of intracellular P glycoproteins, which further enhances the performance of the nanoparticles in reversing tumor multidrug resistance. Under the monitoring of photoacoustic imaging, the multifunctional nanoparticles successfully inhibited the growth of drug-resistant tumors and improved the survival rate of mice [124]. In addition, the researchers developed a PLGA-PEG (si-circ_0008315#1) NPs targeting circ_0008315, which was found to be effective in inhibiting gastric cancer proliferation and cisplatin resistance without significant side effects [125].

The application of microplastic carriers in targeted cancer therapies shows good promise. By optimizing the physicochemical properties of micro(nano)plastics, researchers were able to achieve efficient drug delivery and targeted release. These research cases show that microplastic carriers can not only enhance drug accumulation in tumor cells, but also effectively inhibit tumor growth and reduce toxic side effects. Future studies should further explore the modification of different types of micro(nano)plastics and their safety and efficacy in clinical applications, to provide more precise solutions for cancer treatment.

Potential for combining immunotherapy

With the continuous and in-depth research on cancer therapies, immunotherapy, as an emerging therapeutic strategy, has demonstrated good clinical effects [126]. However, the complexity of the tumor microenvironment and immunosuppressive mechanisms often limit the effectiveness of immunotherapy [127]. As a novel drug carrier, micro(nano)plastics have gradually attracted attention for their application in cancer immunotherapy, especially for their potential in enhancing immune response.

Micro(nano)plastics can be designed to carry immunomodulators (e.g., cytokines, tumor vaccines, etc.) to enhance the body's immune response. By modifying the surface of micro(nano)plastics, targeted delivery to specific immune cells can be achieved. For example, researchers prepared DINP by coupling aPD1 and aOX40 onto polyethylene glycol poly (lactic acid) glycolic acid copolymer (PEG-PLGA) nanoparticles [128]. It was found that T cell activation was maximal when T cells were able to bind both aPD1 and aOX40. However, if the treatment was performed solely with free antibody, the probability of T cells binding to both aPD1 and aOX40 was relatively small, resulting in suboptimal T cell activation, therapeutic efficacy, and immune memory formation. the DINP platform improves the spatiotemporal precision of co-transmission of aOX40 and aPD1 to the T cells, thereby facilitating simultaneous dual treatment binding events. Improved T-cell activation, enhanced therapeutic efficacy, and increased immune memory [128]. This targeted delivery system is effective in increasing the local concentration of immune factors, antibodies, or proteins, thereby enhancing the body's immune response to tumor cells.

Micro(nano)plastics can also enhance immune response by altering the tumor microenvironment. A lipid/PLGA nanocomplex (RDCM) that activates antitumor immunity by remodeling the immune microenvironment was reported [129]. The complex was modified by the PD-L1 inhibitors DPPA and RGD, and loaded with the photosensitizer Ce6 and the IDO inhibitor 1MT to achieve the synergistic effect of photodynamic therapy (PDT) and immune checkpoint blockade. RDCM kills tumor cells and induces immunogenic death through PDT of Ce6; 1MT inhibits IDO and relieves immunosuppression of T cells; DPPA blocks PD-1/ PD-L1 binding and activates T cell immune effects [129]. An in vivo study showed that RDCM promoted dendritic cell maturation, recruited cytotoxic T cells and triggered immune memory, effectively preventing tumor metastasis [129], providing a new strategy for photo-immunotherapy of colon cancer. Another study demonstrated that the degradable STING agonist release system constructed by PLGA particles improved patient drug compliance, reduced injection cost and tumor metastasis risk, and enhanced the effect of cancer immunotherapy [130]. This system extends the therapeutic range to difficult-to-reach

tumors, prevents postoperative recurrence, and contains only one excipient, PLGA, in a single injection, which has a good prospect for clinical translation. The modular design provides flexible drug delivery and supports multi-drug combinations and temporal modulation, providing a new strategy for the treatment of multiple diseases [130].

The combination of micro(nano)plastics and cancer immunotherapy shows good prospects. By optimizing the physicochemical properties of micro(nano)plastics, the immune response can be effectively enhanced and the tumor microenvironment can be improved. These mechanisms provide new directions to enhance the effectiveness of cancer immunotherapy. However, future studies need to focus on the safety, durability and immune tolerance of micro(nano)plastics in vivo to ensure their effectiveness and safety in clinical applications. With further research, micro(nano)plastics are expected to become an innovative and effective tool in cancer immunotherapy.

Conclusions and perspective

In summary, micro(nano)plastics, as an emerging environmental pollutant, are closely related to the development of cancer. Exploring the occurrence, development and treatment of cancer from the perspective of micro(nano)plastics is of great scientific significance and social value. Future studies should further reveal the toxicity mechanisms of micro(nano)plastics and their effects on cell division, migration and endocrine system; meanwhile, interdisciplinary cooperation and technological innovation should be strengthened to promote the application and development of micro(nano)plastics in cancer therapy. Through in-depth research and active response to the problem of microplastic pollution, we can make a greater contribution to the protection of human health and ecological environment. Here are the future research directions of micro(nano)plastics:

Strengthening basic research and clarifying toxicity mechanisms

Currently, much remains unknown about the specific mechanisms of toxicity of micro(nano)plastics to living organisms, especially human cells. Future research should focus on revealing how micro(nano)plastics interact with cells, including how they enter cells, how they are distributed within cells, how they affect cell function and ultimately how they lead to cell damage or cancer. This will require an in-depth investigation of the mechanisms through the comprehensive use of multidisciplinary tools such as molecular biology, cell biology and toxicology.

Focus on long-term exposure effects and conduct epidemiological studies

At present, most studies on the relationship between micro(nano)plastics and cancer remain at the laboratory stage, lacking large-scale, long-term epidemiological investigations. In the future, the monitoring of the level of microplastic exposure in the population should be strengthened, especially for high-risk groups (such as those living in areas with serious plastic pollution and occupationally exposed people), and the association between microplastic exposure and cancer incidence should be assessed through long-term tracking surveys, to provide a scientific basis for the formulation of relevant policies.

Promoting technological innovation and developing effective governance strategies

To address the problem of microplastic pollution, there is a need for continuous technological innovation and the development of efficient and economical management strategies. This includes improving the production process of plastics to reduce the production of primary microplastics; optimizing the recycling and reuse system for plastic waste to reduce the formation of secondary microplastics; and developing new materials and technologies to replace traditional plastic materials to radically reduce plastic pollution. At the same time, there is a need to strengthen international cooperation to jointly address the global challenge of microplastic pollution.

Exploring the potential applications of micro(nano)plastics in cancer therapy

Although there are still many challenges to the direct application of micro(nano)plastics in cancer therapy, their unique physicochemical properties provide new ideas for cancer treatment. Future applications of micro(nano)plastics as drug carriers, targeted delivery systems or immunomodulators can be explored. Through precise design and modification, micro(nano)plastics can be safely and effectively enriched and release drugs or immunostimulatory factors at the tumor site, thus realizing precise cancer treatment. However, this needs to be supported by in-depth basic research and rigorous safety assessment.

Raising public awareness and promoting green lifestyles

Finally, it is also crucial to raise public awareness and consciousness of the microplastic pollution problem. Through education and publicity, policy guidance and other means, we should advocate green lifestyles and consumption habits, reduce the use and waste of plastic products, and minimize the production of micro(nano) plastics at the source. At the same time, public knowledge and education on cancer prevention should be

strengthened to enhance people's health awareness and self-protection capabilities.

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L. Z. and X. Y. D. wrote the main manuscript text and Y. J. G. and X. Y. D prepared Figs. 1, 2, 3 and 4; Table 1. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

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The authors declare no competing interests.

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