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Review

Rising Concern About the Carcinogenetic Role of Micro-Nanoplastics

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Abstract: in the last years, awareness has grown regarding micro-nanoplastics (MNPs) effects on human health. Despite a large body of evidence about the origin and distribution of MNPs in the environment, knowledge regarding their impact on human health remains limited. In this context, there is a significant need to address the potential carcinogenic risk of MNPs, both intrinsic and mediated by their ability to transport carcinogenic chemicals. Currently, evidence of carcinogenicity of MNPs is scarce and heterogeneous, but the reported increase in the incidence of malignant tumors among younger populations, together with the increasing environmental abundance of MNPs, is rising a global concern about the possible role of MNPs in the induction and promotion of cancer. In this review, we aim to provide an overview of the current evidence regarding MNPs in terms of eco-toxicological evidence, methods for identification and characterization of environmental particulate, and health-associated risks, particularly for cancer development. In addition, we will suggest possible routes for future research in order to unravel the carcinogenetic potential of MNP exposure and to dissect prognostic and preventive implications of intratumoral MNPs.

Keywords: microplastics; nanoplastics; ecotoxicology; tumor; cancer; carcinogenic; carcinogenicity; cancerogenesis; cancerogenicity

1. Introduction

Pollution is a main environmental cause of disease in the world [1]. In recent years, concerns on plastic pollution in seas stimulated multiple researches that reported evidence of widespread presence of micro-nanoplastics (MNPs) both in marine and terrestrial environments [2–5]. Historically, the rise of plastics began in the mid-1900s with the large-scale extraction and utilization of oil-based products. Plastic is a synthetic, carbon-based class of different polymers developed through the manipulation of oil components. Plastics revolutionized modern industry by replacing several natural materials that were previously used, with a continuous expansion since the 1960s and a 20-fold increase in its production in 50 years [ref]. Nonetheless, the ubiquitous diffusion of plastics utilization led to severe environmental consequences, as a great amount of mismanaged plastics has been abandoned in the environment. Over time, environmental weathering processes such as ultraviolet radiation (UV photo-oxidation), wind, and sea waves can cause plastic items (macroplastics) to progressively fragment into microscopic particles [6]. The formation of this particulate, defined as MNP particles, constitute an environmental debris that permeate the terrestrial and marine environments and that infiltrated multiple ecosystems. It also recirculates in the water cycle through atmosphere suspension, increasing diffusion, interaction with living beings and humans and continuous ultra-fragmentation via continuous recirculation across biologic systems [7] (see Figure 1).

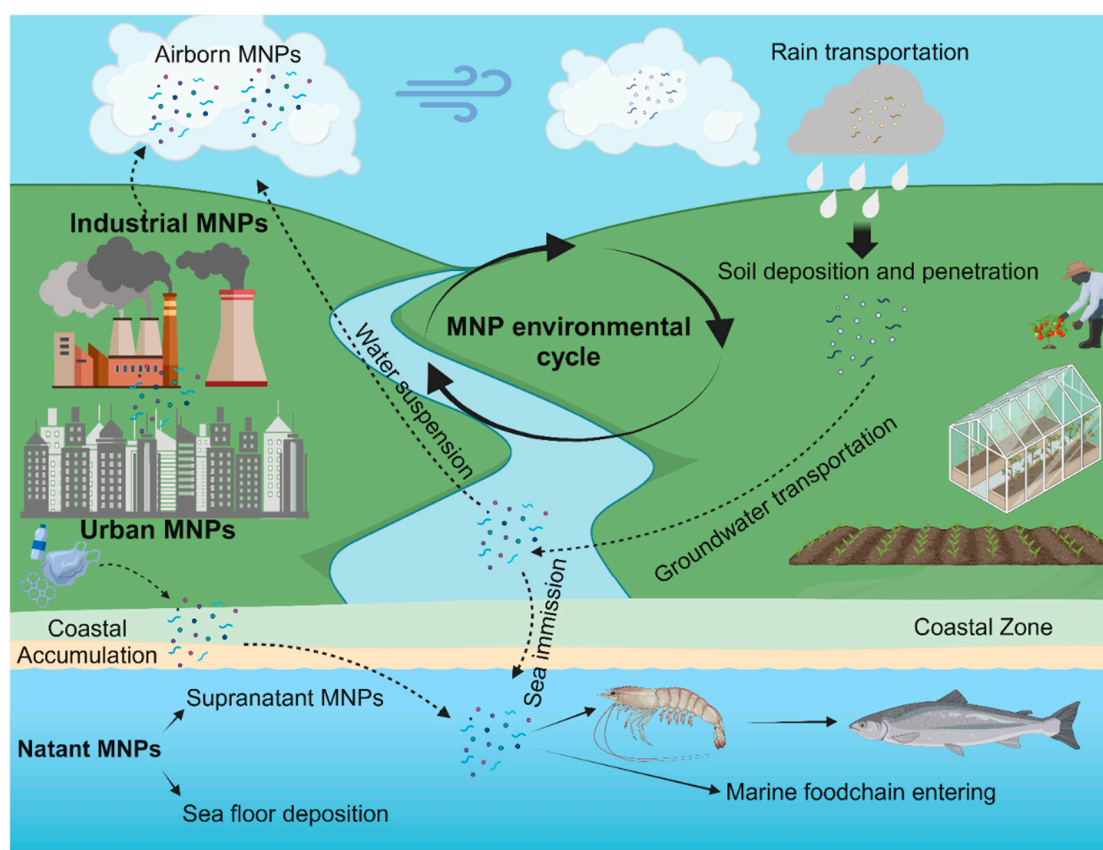


Figure 1. MNP environmental recirculation. Once emitted in the environment, MNPs have the capability to continuously recirculate through air suspension, soil penetration and sea immission, entering in the water cycle. Sea natant MNPs can be ingested by marine organisms, persisting in the marine foodchain. In addition, airborne MNPs can precipitate within rain, penetrating in soil and reaching underwater, rivers and lakes. Created in BioRender. Ruggieri, L. (2024) <https://BioRender.com/h88g872>.

Microplastics (MPs) and nanoplastics (NPs), overall recognized as MNP debris, are already known as environmental pollutants, although definitive conclusions on their impacts are yet to be drawn. MPs are defined as plastic particles ranging between 1 millimetre and 1 micrometre, while NPs range between 1 micrometre and 1 nanometre [8]. Plastic production and mismanagement exponentially increased during the last decades, paralleled by health-risk concerns related to the increasing detection of MNPs in the environment [9]. In 2019 the Scientific Advice Mechanism Group of Scientific Advisors provided the European Commission with a Scientific Opinion on microplastics, concluding that, while MNP pollution does not currently represent a widespread risk, stable emissions at the present rate will potentially cause serious damages within a century, warranting the introduction of preventive measures [10]. Increasing evidence points towards a possible role of MNPs in the etiology of multiple human disease, including cancer [11]. At present, there is still lack of sound epidemiological data to support the association between MNPs and cancer, and MNPs have not been classified for their carcinogenic potential by the International Agency for Research on Cancer (Agents classified by the IARC Monographs, Volumes 1–136)[12]. However, multiple preclinical and clinical studies have recently pointed to a potential link between MNP exposure and cancer development. In this narrative review, we will offer an overall prospect of the current available literature, offering general considerations about eco-toxicology, risks for human health and potential carcinogenic effects of MNPs, providing a future perspective on human health research from a medical oncologist point-of-view.

2. Micro-Nanoplastics: Definition and Eco-Toxicology

2.1. Definitions and General Considerations

MNP debris is a highly complex entity, originating from multiple sources. Primary MNPs are manufactured as such for specific purposes, such as plastic micro-beads added to cosmetics; conversely, secondary MNPs originate from mismanaged environmental macroplastics [13]. Secondary MNPs represent the greatest bulk of environmental MNPs, originating from the abrasion or degradation of multiple plastic-based materials, such as synthetic textiles and clothing, car-tyres, plastic coatings and paints, as well as other materials used for insulation that contribute to city dust, in addition to abrasion of marine vessels and fishing gear [13]. Despite this, a quantitative estimate of the proportional contribution of different sources to MNPs spread into the environment is a current challenge, owing to the lack of reliable methods to measure MNPs and to track their origin [13]. Similarly, while MNPs have been found in all environments – including seas, freshwater and land – and are known to recirculate between them, there is no full understanding of their whole “life-cycle” [13]. However, data suggest that the increasing prevalence of plastic use in multiple aspects of daily life in the last decades has been paralleled by a progressive spread of MNPs in the environment. Multiple sources of human exposure have been demonstrated: such as via inhalation of particulate matter and other airborne particles, via exposure to beauty and human care products, and via consumption of contaminated foods and beverages [11,13–17]. Indeed, MNPs have been isolated across most marine environments – both in the abyss and on the coastline, accumulating on the surface of sandy beaches – and in freshwaters, the latter with proportional concentrations in correlation with intensity of human activities in the area [18–25]. MNPs have also been detected in soils across most Continents, both in agricultural fields and in areas not subject to human activities, probably coming mainly from fertilizers and sewage debris, although the study of MNPs in soils is largely hampered by technical limitations in MNP isolation [3,26–30]. Moreover, MNPs are present both in indoor and outdoor air, with 2-fold higher concentrations reported for the former, and higher concentrations in urban environments [31–36]. Finally, wastewaters of urban areas are largely contaminated with MNPs – coming from domestic sources, such as textiles and cosmetics, and to a less known extent from industrial sources – and enter thereby aquatic ecosystems [37–40]. Considering such a widespread diffusion of MNPs, it is not surprising that they have been largely isolated also in water and food intended for human consumption. In fact, MNPs have been isolated both in bottled and tap drinking water, as well as in beer, milk, honey, rice, sea salt and seafood and fish, while some sources point to a possible uptake of MNPs via crops contamination from soils or fertilizers [30,41].

While these data seem to outline an alarming scenario, it should be emphasized that they have been gathered from scattered independent studies focusing on single geographical areas or on single dietary items, providing a highly fragmented picture of the problem. For example, a minority of studies on MNPs diffusion in freshwater come from Asia, while South America and Africa have been hardly considered at all, leaving significant knowledge gaps about some major geographical areas [13]. As a matter of fact, both the Scientific Opinion provided to the European Commission in 2019 and the more recent report on dietary sources of MNPs issued by the World Health Organization in 2022 highlighted the limited amount of available data and the questionable quality of most of these studies, concluding that available evidence is still too limited to draw conclusions about human MNP exposure from environmental sources and to assess related risks [13,41]. However, it is known that persistence and recirculation of MNPs in the environment cause the formation of a biochemical layered structure called eco-corona [42]. These layers develop when MNPs encounter environmental natural organic matter, generally organic polymeric substances such as DNA, proteins, carbohydrates and humus substances, through chemical interactions as hydrogen bonds, Van der Waals forces, and hydrophobic interactions. The eco-corona can enrich the spectrum of bio-physico-chemical interactions between MNPs and living organisms [43]. Given the nature of eco-coronated MNPs, these structures account for additional possible biological hazards of MNP debris, such as formation of micro-organism colonies on the surface, entrapment of toxic chemicals and release of toxic additives [13,44,45]. Thus, predicting MNPs effect in different environmental and biologic

systems, as well as providing a general risk assessment, is extremely complex according to current knowledge [13].

2.2. Routes of Human Exposure

MNPs can enter the human body primarily through ingestion, inhalation and dermal absorption.

2.2.1. Ingestion

MNPs have been found in drinking water, food such as fish and shellfish, table salt and in other numerous foods. When ingested, these particles accumulate in the gastrointestinal tract lumen, where they adhere to the mucous layer. Major size particles interact with M-cells, while particles smaller than 50 μm can be absorbed through enterocytes. Moreover, small particles of various size can cross intercellular spaces [11,46,47]. Penetrating the mucosal layer, MNPs can reach the bloodstream and the lymphatic system [48]. In addition, accumulation of MNPs in the digestive lumen can lead to microbiome disruption, leading to indirect systemic toxicity through gut-organ axes perturbation [49].

2.2.2. Inhalation

airborne MNPs can be inhaled as suspended particles, especially in urban and industrial environments. Particles below 2.5 μm have a higher probability to reach alveolar sacs, depositing in lung tissue or crossing the alveolar-capillary barrier, entering the bloodstream. Alternatively, MNPs are engulfed by alveolar macrophages. Moreover, airborne MNPs can be absorbed through the olfactory bulb, potentially reaching the central nervous system [50].

2.2.3. Dermal Absorption

airborne MNPs can be absorbed through dermal contact. Indeed, *in vitro* evidence of active micropinocytosis by keratinocytes of keratin-coated MNPs suggests that skin could represent a locus minoris resistentiae through which MNP particles can penetrate the body [51].

3. MNPs: Analytical Methods in Biological Studies

To date, methods of detection, identification and characterization of MNPs in biological studies are heterogeneous, and analytical processes are far from being standardized. Differences in MNPs size definitions and limitations in analytical power hamper the reproducibility and reliability of results, and methods need to be refined. Currently, different approaches could be informative of diverse characteristics of MNPs: for instance cell models to describe cellular uptake and intracellular localization, animal models in order to dissect bioaccumulation tendencies and systemic and local effects, *in vivo* imaging models to track MNP translocations in blood circulation and tissue penetration, and finally *ex vivo* studies to earn real-life information. Here we provide an overview of analytical methods used to characterize the biology of MNPs.

3.1. Surrogate Model Studies

MNPs can primarily recirculate through the bloodstream and lymphatic system, potentially reaching various organs and tissues. To date, human body circulation, distribution, and tissue accumulation are estimated mainly using surrogate *in vivo* animal models, *in vitro* cell cultures, and computational models. *In vivo* animal studies are used to evaluate how MNPs enter the body through ingestion or inhalation. The particles can be tracked using fluorescent dyes, allowing researchers to observe their distribution in various organs like the lungs, liver, and kidneys [52]. On the other hand, cell cultures give a significant opportunity to examine direct interaction of MNPs and human cells. These studies can elucidate different mechanisms of active cell uptake and intracellular processes of MNPs [53]. In recent years, computational models have gained attention for their capability to predict biological and chemical behaviors. Simulations of MNP distribution throughout the body offer

reliable predictions based on available data. These models could inspire the design of more informative future studies that will help to dissect MNP recirculation and accumulation in human tissues.

3.2. *In Vivo Imaging Techniques*

Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are used to monitor the distribution of traceable MNPs in the body in real-time. PET ability to provide real-time imaging enables to track MNP passage through the bloodstream, absorption by organs, and tissue accumulation. This helps distinguish between acute (short-term) and chronic (long-term) exposures, assessing timings of MNP persistence in the body, sites of primary accumulation, and main ways of elimination [54]. Another recent method that aims to dissect MNP interactions with cells and tissues is fluorescent labelling, a technique that can track real-time MNP movements [52].

3.3. *EX Vivo Studies*

Techniques like electron microscopy, fluorescence, Raman spectroscopy and Fourier-transform infrared (FTIR) spectroscopy are employed to visualize and identify MNPs in ex-vivo biological tissues, enabling direct observation of the particles within organs [55–58]. FTIR spectroscopy and Raman spectroscopy are vibrational spectroscopy methods widely used to identify MNPs in human tissues [59–61]. They can assess polymer type, size, shape, and distribution. FTIR spectroscopy is particularly useful to analyse particles larger than 10 μm , while Raman spectroscopy can be used for even smaller particles, down to 1.2 μm . Electron microscopy, as scanning electron microscopy (SEM) and transmission electron microscopy (TEM) are employed to visualize and measure nanoplastics in ex-vivo samples [58]. These methods provide detailed images of particles, allowing researchers to assess their morphology and distribution at the cellular level.

4. Human Health-Risk of MNP Exposure

Evidence is accumulating regarding MNP-related health risks, suggesting multiple molecular mechanisms as drivers, mainly through induced persistent chronic inflammation, oxidative stress, and disruption of other physiological processes. MNPs can induce a variety of cytotoxic effects, mainly through reactive oxygen species (ROS) generation, which can lead to oxidative stress, inflammation, and cellular damage [62]. ROS play a significant role in the disruption of cellular homeostasis, contributing to inflammatory responses by activating multiple molecular pathways [63]. Excessive production of ROS causes oxidative damage to lipids, proteins, and DNA [64]. Studies in both in vitro and in vivo models have shown that exposure to MNPs significantly increases ROS levels, leading to cellular dysfunction and apoptosis [65–67]. Indeed, the imbalance between ROS production and the antioxidant defense system can activate various signalling pathways associated with inflammation, such as the nuclear factor-kappa B (NF- κ B) pathway [68]. This pathway is known to regulate the expression of pro-inflammatory cytokines and can be activated in response to cellular stress caused by MNPs [69]. Prolonged activation of inflammatory pathways may lead to chronic inflammation, which has been linked to a range of pathological conditions, including fibrosis and tissue damage [70]. In addition, MNPs can perturb mitochondrial metabolism, until apoptosis occurs [71]. Furthermore, research showed that MNPs can interfere with autophagy, causing potentially harmful cell damages [72–74].

4.1. *Digestive Health*

Ingested MNPs tend to be processed by stomach and gut secretion, going through progressive fragmentation [75]. Systemic toxicity of ingested MNPs is mainly related to the disruption of the gut microbiome, leading to perturbation of gut-organ axes and of systemic immunological modulation [49]. Locally, MNPs accumulation in mucosal cells and lymphoid-associated structures of digestive tissue can induce chronic inflammation and direct cell death [76].

4.2. Respiratory Health

Evidence regarding lung toxicity of MNPs in human mainly derives from occupational exposure studies. Workers of the plastic industry exposed to plastic flocks have a reportedly higher incidence of pulmonary fibrosis and pneumoconiosis [77–80]. Preclinical models showed that persistent alveolar macrophage activation and alveolar cell damage are the main underlying mechanisms [81].

4.3. Cardiovascular Health

Recent studies have linked MNPs to cardiovascular diseases. Rats exposed to polystyrene MNPs at incremental environmental concentrations developed proportional grades of cardiac fibrosis through oxidative stress mechanisms [82]. In another mouse model study, inhaled NPs accumulated preferentially in inflamed vascular lesions [83]. A recent pivotal prospective analysis of resected atheromas from carotid endarterectomies showed that the presence of MNPs in macrophages or in the plaques is a negative predictive factor for secondary cardiovascular events and mortality. This was the first study to indirectly prove that MNPs could induce or foster inflammation in humans [58].

5. MNPs' Role in Cancer Development and Progression

The current evidence on the potential role of MNPs in cancer initiation and progression emerge from mainly preclinical studies of in vitro models. These studies have focused on the capability of MNPs to elicit a number of different biological effects potentially linked to carcinogenesis. Key biological processes that influence the induction and promotion of carcinogenesis include tumor-promoting inflammation, oxidative stress, alterations in cellular metabolism, genotoxicity, cytotoxicity, induction of invasive cellular phenotypes, and changes in the local microbiota [84].

5.1. Tumor-Promoting Inflammation

A body of studies assessed MNPs capability of causing a sustained inflammatory response, as a surrogate of their carcinogenicity potential, according to the hypothetic carcinogenetic capacity of chronic inflammation in mammals. Human cancer cell lines significantly increased their production of inflammatory cytokines when exposed to polystyrene MNPs [85–88]. In vivo evidence in mammalian models confirmed the capacity of polystyrene MNPs to induce variegated mucosal inflammatory response [89–93].

5.2. Cancerogenesis Initiation

Different types of alterations in determined cellular processes could initiate the multi-step process of carcinogenesis, generally through loss of apoptotic capacity and anchorage-dependent growth inhibition. Regarding the latter, previous studies demonstrated that exposure of human cancer cell lines to MNPs can lead to anchorage-independent outgrow [94,95]. Immune surveillance is another fundamental mechanism in the prevention of cancerogenesis initiation in mammals. Regarding this, MNPs have shown the potential to polarize immune responses in pregnant mice towards immune tolerance, through a decrease of NK cells and M2 polarization of macrophages [96]. In a similar manner, when Type-1-diabetic mice were exposed to MNPs, apoptosis of CD4⁺ T-lymphocyte increased in favor of an expansion of Tregs and complete reversion of autoimmune response [97]. In addition, MNPs showed genotoxic potential in human blood cells and mammalian cell models in vitro [98–101].

5.3. Cancerogenesis Promotion

Once pre-cancerous cells gained immortalization and escaped the immune system, they need to acquire determined genetic mutations in order to progress in the carcinogenesis process. This phase, called “promotion”, involves a series of alterations in cell proliferation and invasiveness that ultimately result in the development of invasive disease. Different cellular effects of MNP exposure

are related to the dysregulation of cell proliferation [85,94,95,102], potentially fostering the development of cancer. Moreover, in vitro models showed that MNP exposure can induce epithelial-mesenchymal transition in human cell lines [103–106], a process that enhances invasiveness and migration capability of cancer cells.

5.4. MNPs' Presence in Cancer Tissue

To date, available studies showed that MNPs in human cancer tissues are generally more abundant compared to non-cancerous tissues. In an historical study, MNPs were more commonly detected in lung cancer compared to normal lung tissue [107]. In a more recent case-control study, MNPs were significantly more concentrated in colorectal cancer tissue compared to non-tumoral tissues [108]. In another recent study, the abundance of MNPs in tumor and para-tumoral tissues of human prostate cancer were compared, showing that particles were significantly more concentrated in cancer [109]. Underlying mechanisms should be unravelled, and realistic hypotheses could be hard to propose. Since MNPs can be inherited by cell division and actively absorbed by cancer cells, the higher concentration in tumor tissue could be related to a higher absorption rate of circulating and tissue MNPs. Common alterations in the intratumoral circulation and microenvironment could be responsible for an increased diffusion of MNPs within the tumor, together with a possible fostered pinocytosis of cancer cells. In this scenario, the abundance of MNPs in the tumor tissue is merely representative of their specific bioaccumulation tendencies and overall individual exposure. On the other hand, MNPs' capability to foster carcinogenic events could influence clonal evolution, favoring the proliferation of cells with more effective pinocytosis processes. Extensive characterizations of MNP presence and concentration in tumor, para-tumoral and normal tissues are needed in order to solve these interpretation issues.

6. Discussion

The increasing abundance of environmental MNPs and their capability to recirculate, infiltrate and deposit into various ecosystems, including the human body, has raised significant concerns about their long-term health effects in the recent years. Although the related body of evidence has progressively expanded in the last decade, knowledge about MNP-related health risks, especially as a carcinogen, remains limited to date. Researchers have pointed out a potential to foster inflammation and oxidative stress in living beings and humans, indicating a hypothetical role in cancer initiation and progression. Fragmented and rather initial evidence suggests that MNPs can trigger several biological processes that are strongly linked to carcinogenesis, as tumor-promoting inflammation, oxidative stress and ROS production, direct and indirect genotoxicity (being MNPs carriers of genotoxic chemicals), alterations in immune response, and disruption of gut microbiota (Figure 2). On the other hand, there is an important lack of large-scale epidemiological studies evaluating the impact of human MNP exposure on cancer incidence and mortality. In fact, the IARC has not ever mentioned MNPs as a potential carcinogen for humans, and most specific plastic polymers that have the potential to give origin to secondary MNPs have been listed in group 3, i.e. “not classifiable as to its carcinogenicity to humans”, according to IARC monographs (see <https://monographs.iarc.who.int/list-of-classifications>).

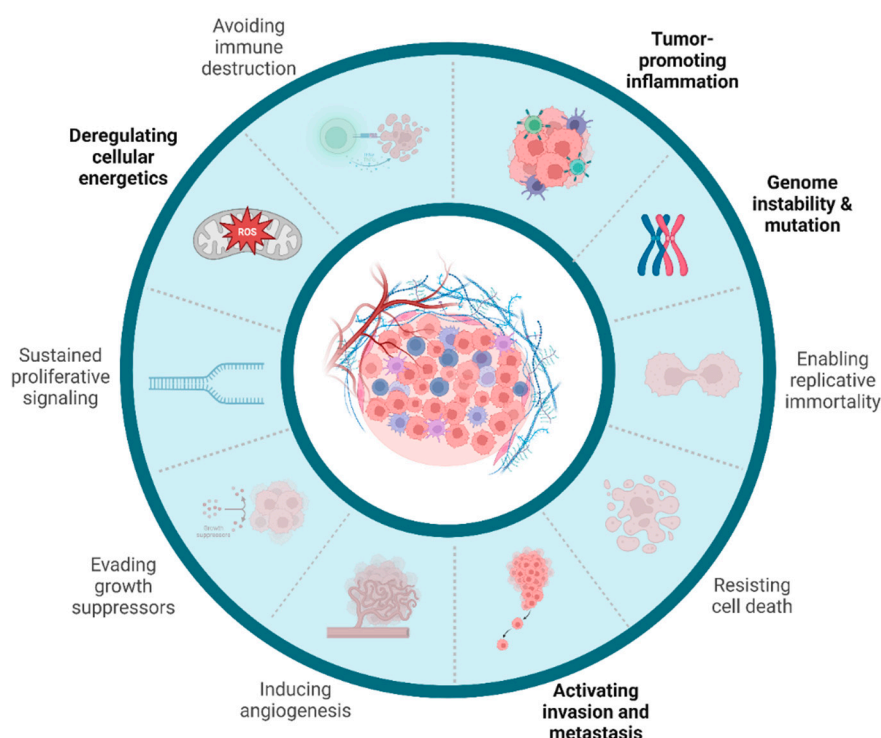


Figure 2. Hallmarks of cancer related to MNPs. Current evidence regarding the role of MNPs in cancer initiation and promotion is linked mainly to the capability of MNPs to induce metabolic stress through the induction of ROS, fostering immune infiltration and chronic inflammation since their persistence in cancer cells and macrophages. The inability of intracellular lytic enzymes of mononuclear phagocytes to process MNPs induces a “frustrated” phenotype that can bring to uncontrolled cell death, further sustaining inflammatory processes. Moreover, MNPs exposed cancer cell showed augmented capacity of invasion and metastatization in preclinical models. Finally, genomic instability could be the results of intricate cytotoxic and genotoxic damage triggered by the presence of MNPs, that need to be further elucidated.

Current basic research is hampered by the incomplete refinement of analytical methods, and heterogeneity of MNPs in their sizes, shapes, polymer structure, chemical properties, nature and composition of the eco-corona further complicate experimental result interpretations. At the ecotoxicological level, human exposure potentially depends on geographical location, weather and soil properties, density of MNP emissions, type of diet and daily habits. Reasonably, dissecting the abundance of different MNPs in indoor environments could refine MNP exposure estimation.

At the current state of knowledge, health risks related to MNP exposure, in particular as a potential carcinogen, remain poorly understood. Preclinical evidence showed major biological effects of MNP exposure, but dose expositions are significantly higher in experimental models compared to real-life cellular exposures, thus results are seldom reliable.

In our view, in order to expand the knowledge regarding MNPs effects, some major areas of further development can be implemented:

- First, standardization in analytical methods for MNP detection in biological specimens will be essential to achieve reproducible and reliable results, and to provide the basis for building consistent evidence from different scientific groups.
- Studies employing mammalian model should evaluate MNP bioaccumulation in tissues over time, thanks to innovative *in vivo* techniques, as well as unravel the real genotoxic potential of MNPs. In this regard, human organ-specific models could further elucidate tissue-specific effects, and provide information on risks specific to different routes of exposure.

- Translational research should effortlessly characterize the presence, distribution and abundance of MNPs in normal and cancer tissues, aiming at investigating potential prognostic and molecular implications. In the near future, the integration of advanced analytical techniques, computational tools, and multi-omics approaches could unravel MNPs role as a carcinogen.
- At a more complex level, MNPs could have a range of interactions with fundamental body-wide entities, such as microbiota, systemic immunity, and nervous signals, which have to be further elucidated.
- To date, there is an urgent need of robust epidemiological data evaluating the correlation of MNPs exposure and disease development at a population level. Longitudinal epidemiologic studies should determine the cancer risk for populations at higher probability of MNP exposure, as in industrial and metropolitan areas or in coastal locations. Moreover, epidemiological data would be extremely valuable in order to generate hypotheses in basic science and further elucidate the underlying mechanisms.

5. Conclusions

In the last years, MNPs raised public health concerns since their ubiquitous nature as environmental pollutants. Currently, the scarcity of knowledge regarding MNP-related health risks hampers the development of regulatory policies and public health strategies aimed at controlling human MNP exposure.

In the field of oncology, many significant advances were achieved in the last decades, especially in the characterization of cancer (epi)genic, metabolic, immunological and microenvironmental features. Meanwhile, environmental and behavioral causative factors are rarely identified, since the complex interplay between different risk factors in multifactorial carcinogenesis. Indeed, in recent years, epidemiological data showed a potential increase in early onset cancers [110,111], and this could be paired with the potentially increased human MNP exposure for new generations. For these reasons, the scientific community will have to put intensive research efforts in order to unravel the real carcinogenic role of MNPs. This knowledge will be fundamental to inform global regulatory ecological and health policies.

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