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The Impact of Microplastics on Biological Systems: A Focus on Extracellular Vesicles and miRNA Profiles

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Abstract

Microplastics (MPs) have become a pervasive environmental pollutant, contaminating terrestrial and aquatic ecosystems and making their way into food chains and human biological systems. Their small size and widespread presence in air, water, and soil enable them to be easily ingested or inhaled, leading to bioaccumulation in tissues and organs. Recent research has uncovered that MPs do not merely accumulate passively but actively interact with biological components, including extracellular vesicles (EVs) and microRNAs (miRNAs), both of which play fundamental roles in cellular communication, gene regulation, and homeostasis. MPs have been shown to alter EV cargo composition and disrupt miRNA expression patterns, thereby interfering with key biological pathways involved in inflammation, oxidative stress, and metabolic processes. These interactions raise concerns about MPs' potential contribution to chronic diseases, such as cardiovascular disorders, neurodegenerative conditions, and metabolic dysfunction. This review provides a comprehensive analysis of the current understanding of MPs' impact on biological systems, with a particular emphasis on their interaction with EVs and influence on miRNA profiles. By synthesizing recent research findings, this paper aims to highlight the potential health risks associated with MP exposure, offering insights into emerging mechanisms of toxicity and emphasizing the need for further studies and regulatory interventions to mitigate their harmful effects

1. Introduction

Microplastics (MPs), defined as plastic particles less than 5 millimeters in size, have emerged as pervasive environmental pollutants infiltrating various ecosystems, including marine, freshwater, and terrestrial environments (Vethaak & Legler, 2021). Their omnipresence raises significant concerns regarding their potential impacts on biological systems. Recent research has illuminated that MPs can interact intricately with cellular components, notably extracellular vesicles (EVs) and microRNAs (miRNAs), thereby influencing cellular communication and gene regulation mechanisms.

Extracellular vesicles are membrane-bound particles secreted by cells, encompassing exosomes, microvesicles, and apoptotic bodies, which facilitate intercellular communication by transporting bioactive molecules such as proteins, lipids, and nucleic acids (Babuta et al., 2022). MiRNAs, a class of small non-coding RNAs approximately 18–24 nucleotides in length, play pivotal roles in post-transcriptional gene regulation by binding to target mRNAs, leading to their degradation or translational repression (Babuta et al., 2022). The packaging of miRNAs into EVs is a regulated process, enabling the transfer of genetic information between cells and modulating various physiological and pathological processes (Yue et al., 2020).

Emerging evidence indicates that exposure to MPs can disrupt the normal functions of EVs and alter miRNA expression profiles, leading to adverse biological effects. For instance, studies have demonstrated that prolonged exposure to polystyrene microplastics (PS-MPs) and nanoplastics (PS-NPs) results in significant changes in the miRNA profiles of serum and intestinal exosomes, particularly a reduction in miR-126a-3p. This miRNA is known to regulate the PI3K-Akt pathway, which is crucial for protecting cells from oxidative stress and apoptosis. The observed decrease in miR-126a-3p is associated with compromised intestinal barrier function and increased permeability, phenomena linked to heightened apoptosis and oxidative stress in epithelial cells (Yue et al., 2020).

Additionally, exposure to MPs has been implicated in immune, neurological, and other toxic effects mediated by dysregulated miRNA expression, thereby increasing the risk of neurodegenerative diseases, cardiovascular diseases, and cancer (Chen et al., 2022).

The interactions between MPs, EVs, and miRNAs are complex and multifaceted. MPs can influence the biogenesis, composition, and release of EVs, thereby affecting the EV-mediated transfer of miRNAs between cells. This disruption can lead to altered gene expression and cellular functions, contributing to various pathological conditions. For example, changes in EV miRNA content have been linked to immune responses, inflammation, and tumorigenesis (Babuta et al., 2022). Understanding these interactions is essential for elucidating the mechanisms underlying MP-induced toxicity and for developing potential therapeutic strategies to mitigate their adverse effects.

This review aims to provide a comprehensive analysis of the current understanding of how microplastics impact biological systems, with a particular focus on their interactions with extracellular vesicles and miRNA profiles. By synthesizing recent findings, we seek to elucidate the mechanisms by which MPs influence cellular communication and gene regulation, thereby contributing to the broader discourse on environmental pollutants and human health.

2. Sources and Environmental Distribution of Microplastics

MPs have become pervasive environmental contaminants, raising concerns due to their persistence, bioaccumulation, and potential toxicity. These particles originate from various sources and are distributed across multiple environmental matrices, including marine, freshwater, terrestrial, and atmospheric systems. Understanding the sources and pathways of MPs is essential to evaluating their impact on ecosystems and human health. The sources of MPs can be broadly categorized into primary and secondary sources. Primary MPs are intentionally manufactured in small sizes for specific industrial and commercial applications, including plastic pellets used in manufacturing, microbeads in personal care products, and synthetic fibers released from textiles during washing (Kumar et al., 2021). Microbeads, once commonly used in exfoliating personal care products, have been banned in many countries due to their detrimental environmental impact. However, synthetic fibers remain a significant concern, as laundering a single synthetic garment can release thousands of microfibers into wastewater systems, many of which bypass filtration and end up in water bodies (Hernandez et al., 2017). Secondary MPs, on the other hand, result from the fragmentation of larger plastic debris due to environmental factors such as ultraviolet (UV) radiation, mechanical weathering, and microbial degradation. Common sources of secondary MPs include plastic waste breakdown in the environment, road runoff containing tire wear particles, and industrial emissions (Jiang et al., 2020). Road runoff is a particularly significant contributor, as tire wear particles, which contain synthetic polymers, are generated in vast quantities and eventually make their way into aquatic and terrestrial ecosystems (Wagner et al., 2018).

The environmental distribution of MPs varies across different ecosystems, influenced by factors such as particle size, density, and environmental transport mechanisms. In marine environments, MPs are among the most prevalent pollutants, accumulating in coastal waters,

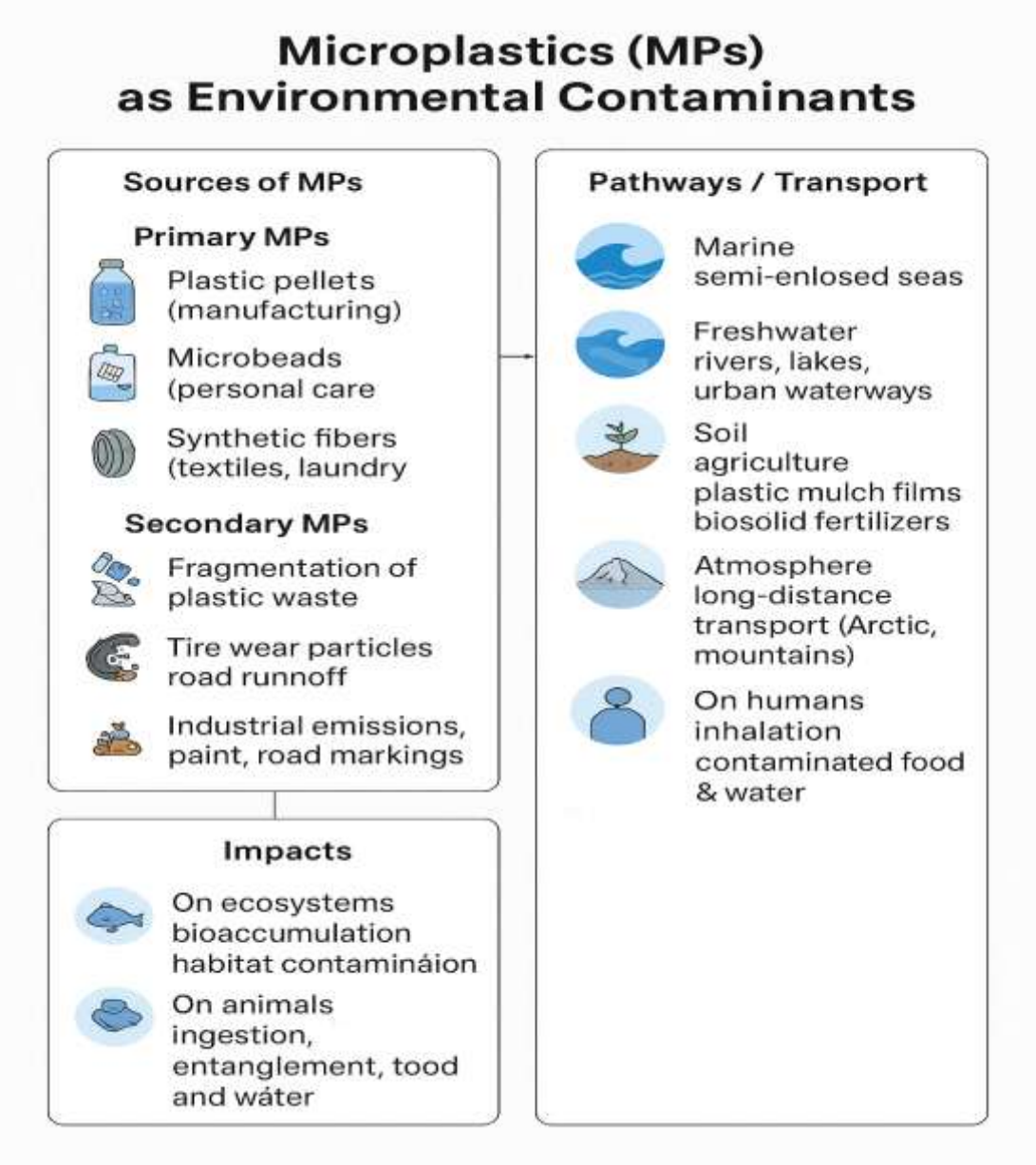

Fig.1: Image showing MPs contaminants sources, pathways/transport and its impact.

semi-enclosed seas, and oceanic gyres. For instance, studies on the Great Pacific Garbage Patch have revealed that MP concentrations reach up to 85,184 plastic particles per square kilometer, with inputs from urban runoff, fishing activities, and mismanaged plastic waste (Lebreton et al., 2018). Rivers and lakes serve as conduits for MPs, transporting them from terrestrial environments to the oceans. Urban waterways, wastewater effluents, and industrial discharges contribute significantly to freshwater MP contamination. Research has shown that even remote mountain lakes are not immune to MP pollution, as airborne MPs can be transported over long distances and deposited through atmospheric fallout (Bergmann et al., 2019). Soil environments are also heavily impacted by MPs, particularly through agricultural activities. The use of plastic mulch films, biosolid fertilizers derived from wastewater sludge, and irrigation with contaminated water introduce MPs into the soil, leading to their accumulation and potential uptake by plants (Rillig et al., 2019) (Fig.1).

The atmosphere represents an increasingly recognized pathway for MP distribution. Wind erosion of plastic waste, industrial emissions, and urban dust contribute to the presence of airborne MPs, which can be inhaled by humans or deposited onto terrestrial and aquatic environments. Recent studies have detected MPs in remote regions, including the Arctic and the Pyrenees, highlighting their ability to travel long distances via atmospheric transport

(Allen et al., 2019). The implications of airborne MPs for human health are concerning, as inhalation exposure may lead to respiratory inflammation and other adverse effects (Prata et al., 2020). Given the widespread distribution of MPs across various environmental compartments, understanding their sources, transport mechanisms, and ecological impacts is critical for developing effective mitigation strategies. Efforts to reduce MP pollution must include improved waste management practices, regulatory policies to limit plastic production and use, and advancements in filtration technologies to prevent MP release into the environment. Addressing MP pollution requires a multi-faceted approach that incorporates scientific research, public awareness, and policy interventions to mitigate its long-term consequences on ecosystems and human health.

3. Microplastics in Biological Systems

3.1. Ingestion and Accumulation

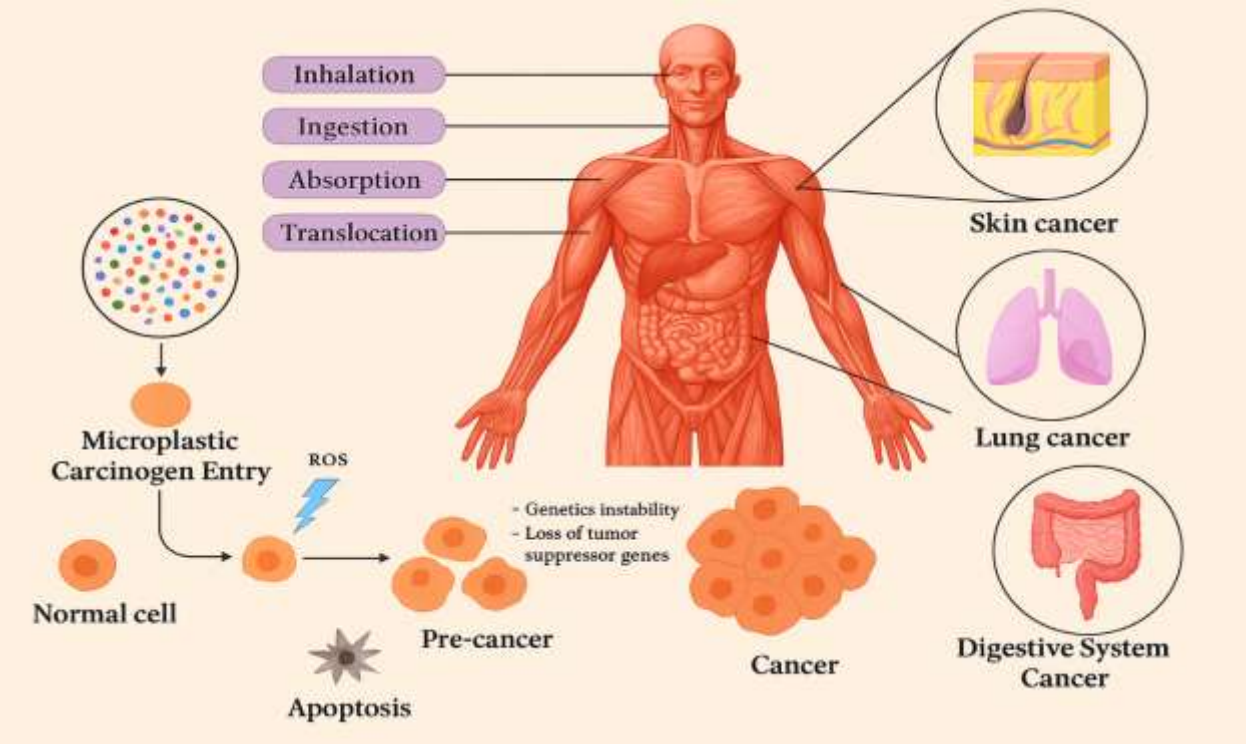

Fig.2: Diagram illustrating the transport pathways of MPs and their role in regulating gene pathways leading to cancer cell development.

Humans are continuously exposed to microplastics (MPs) through various pathways, including ingestion, inhalation, and dermal contact, with ingestion being the most significant exposure route. MPs are widely present in food and beverages due to contamination from plastic packaging, food processing, and environmental pollution. A study by Senathirajah et al. (2021) estimated that an average adult consumes approximately 39,000 to 52,000 MP particles annually, with this number increasing to over 100,000 particles when considering inhalation exposure. Certain food items are particularly prone to MP contamination. For example, seafood such as fish, shellfish, and mollusks contain MPs due to their ingestion of contaminated water and food sources (Barboza et al., 2018). Bivalves, such as mussels and oysters, are filter feeders, meaning they directly accumulate MPs from their environment, making them a significant dietary source of MPs for humans. Similarly, table salt, sugar, honey, beer, and bottled water have been found to contain varying levels of MPs, with bottled water containing up to 325 particles per liter (Schymanski et al., 2018).

Inhalation represents another significant route of MP exposure. MPs present in indoor and outdoor air originate from synthetic fibers, urban dust, industrial emissions, and the degradation of plastic waste. Indoor environments, where people spend most of their time, often have higher concentrations of airborne MPs due to synthetic textiles,

carpets, and household dust (Vianello et al., 2019). MPs inhaled through the respiratory system can penetrate the lower airways, potentially leading to lung inflammation and respiratory distress. Studies have shown that inhaled MPs may translocate from the lungs into the bloodstream, further contributing to systemic exposure (Wright & Kelly, 2017).

Once inside the body, MPs can accumulate in various organs, including the gastrointestinal tract, liver, kidneys, spleen, and even the brain. Fournier et al. (2020) demonstrated that MPs have the potential to cross biological barriers, such as the gut epithelium and the blood-brain barrier, raising concerns about their long-term health effects. The small size of MPs allows them to bypass the body's natural defense mechanisms, leading to their accumulation in tissues and organs. The presence of MPs in the liver and kidneys suggests that these organs play a role in the metabolism and excretion of MPs, but prolonged exposure may result in toxic effects, oxidative stress, and inflammatory responses (Prüst et al., 2020) (Fig. 2).

Recent studies have also identified MPs in human blood, providing direct evidence of their systemic circulation. Leslie et al. (2022) detected MP particles in the blood samples of healthy individuals, confirming their ability to travel through the circulatory system and potentially reach vital organs. The presence of MPs in the bloodstream raises concerns about their impact on the immune system, cardiovascular health, and overall physiological functions. MPs may also act as carriers for harmful pollutants, heavy metals, and endocrine-disrupting chemicals, further exacerbating their potential toxicity (Ragusa et al., 2021).

The accumulation of MPs in human tissues highlights the urgent need for further research on their long-term health effects and potential regulatory measures to reduce exposure. Strategies such as reducing plastic use, improving wastewater treatment, and adopting sustainable alternatives in food packaging can help mitigate MP contamination in the environment and food chain. Given the growing evidence of human exposure and potential health risks, addressing MP pollution should be a global priority.

3.2. Cellular and Molecular Effects of Microplastics in biological systems

Microplastics (MPs) pose significant threats to biological systems, primarily through mechanisms that induce oxidative stress, cytotoxicity, and inflammatory responses. These toxicological effects have raised concerns about the potential contribution of MPs to chronic diseases, including metabolic disorders, immune dysfunction, and neurodegenerative diseases. The biological impact of MPs is largely driven by their size, surface properties, and ability to carry hazardous chemicals, which collectively interfere with cellular homeostasis, disrupt membrane integrity, and alter protein expression (Yee et al., 2021).

3.2.1. Oxidative Stress and Cytotoxicity Induced by MPs

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the antioxidant defense system of cells. MPs have been shown to increase ROS production, leading to cellular damage through lipid peroxidation, protein oxidation, and DNA fragmentation (Huang et al., 2022). The surface of MPs can adsorb toxic environmental pollutants, such as heavy metals and persistent organic pollutants, further exacerbating oxidative stress. The oxidative damage caused by MPs has been implicated in various pathophysiological conditions, including cardiovascular diseases, neurodegeneration, and cancer (Rahman et al., 2021). Additionally, MPs can penetrate cells via endocytosis, triggering lysosomal dysfunction and mitochondrial damage, which enhances oxidative stress and induces apoptosis (Fadare et al., 2020). Studies have demonstrated that polystyrene MPs disrupt mitochondrial membrane potential, leading to cytochrome c release and activation of caspase-dependent apoptotic pathways (Xu et al., 2021). The cytotoxic effects of MPs have been observed in multiple cell types, including lung epithelial cells, liver cells, and neurons, suggesting their potential to induce widespread tissue damage.

3.2.2. Inflammatory Responses and Immune Dysfunction

MPs can act as pro-inflammatory agents, triggering immune responses upon interaction with biological tissues. Once internalized, MPs are recognized as foreign particles by immune cells, leading to the activation of macrophages and the release of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1 beta (IL-1β) (Hirt & Body-Malapel, 2020). Chronic exposure to MPs has been associated with low-grade systemic inflammation, which is a major risk factor for metabolic disorders, autoimmune diseases, and cancer (Yong et al., 2020). Studies on animal models have revealed that ingestion of MPs can lead to gut microbiota dysbiosis and intestinal inflammation, which in turn affects immune homeostasis (Jin et al., 2022). Inhaled MPs may also contribute to pulmonary inflammation and respiratory diseases by

inducing oxidative stress and disrupting alveolar macrophage function (Amato-Lourenço et al., 2021). Furthermore, MPs have been detected in human placenta and umbilical cord blood, raising concerns about their potential to influence fetal immune development and increase the risk of allergic diseases and immune dysfunction in newborns (Ragusa et al., 2021).

3.2.3. MPs and Chronic Diseases: Metabolic Disorders, Neurodegenerative Diseases, and Cancer

Emerging evidence suggests that MPs contribute to the development of metabolic disorders by interfering with endocrine signaling and lipid metabolism. MPs have been shown to disrupt the gut microbiome, leading to metabolic imbalances, insulin resistance, and obesity (Chen et al., 2021). Additionally, MPs can act as endocrine-disrupting chemicals (EDCs) by leaching additives such as bisphenol A (BPA) and phthalates, which interfere with hormone regulation and increase the risk of diabetes and metabolic syndrome (Lu et al., 2022). Neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, have also been linked to MP exposure due to their ability to induce neuroinflammation, mitochondrial dysfunction, and protein aggregation in neural tissues (Xu et al., 2021). Studies have demonstrated that MPs can cross the blood-brain barrier, where they may disrupt synaptic function and exacerbate neurodegenerative processes (Fournier et al., 2020). Furthermore, the genotoxic effects of MPs, including DNA damage and chromosomal aberrations, have raised concerns about their potential role in carcinogenesis. MPs may promote tumor formation by inducing chronic inflammation, oxidative stress, and DNA mutations, all of which contribute to cancer progression (Zhang et al., 2022) (Fig. 2).

3.2.4. MP-Induced Disruption of Cellular Homeostasis

MPs interfere with cellular homeostasis through multiple mechanisms, including disruption of membrane integrity and alterations in protein expression. The interaction of MPs with cell membranes can lead to increased permeability, membrane fluidity changes, and structural damage, ultimately affecting cellular function and viability (Zhu et al., 2022). MPs have been shown to alter the expression of genes involved in oxidative stress response, apoptosis, and inflammatory pathways, further contributing to their toxic effects (Xu et al., 2021). Additionally, MPs may serve as carriers for toxic contaminants, increasing their bioavailability and exacerbating cellular dysfunction. Recent proteomic studies have identified significant changes in protein expression profiles upon MP exposure, particularly in proteins associated with cellular stress response, metabolism, and immune regulation (Huang et al., 2022).

4. Interaction of Microplastics with Extracellular Vesicles

4.1. Extracellular Vesicles: Structure and Function

Extracellular vesicles (EVs) are a diverse group of membrane-bound vesicles actively secreted by almost all cell types, serving as essential mediators of intercellular communication. These vesicles are classified based on their size, biogenesis, and function into exosomes (30–150 nm), microvesicles (100–1,000 nm), and apoptotic bodies (500–2,000 nm) (van Niel et al., 2018). EVs play a pivotal role in maintaining cellular homeostasis and facilitating molecular exchange between cells, thereby influencing various physiological and pathological processes such as immune responses, tissue regeneration, neurodegeneration, and cancer progression (Yáñez-Mó et al., 2015). Their unique ability to transport bioactive molecules across biological barriers, including the blood-brain barrier, makes them critical players in systemic communication and disease pathology (Kalluri & LeBleu, 2020).

4.1.1. Biogenesis and Composition of EVs

The biogenesis of EVs is a complex process that involves multiple cellular pathways. Exosomes originate from the endosomal system, specifically through the formation of multivesicular bodies (MVBs). These MVBs contain intraluminal vesicles that, upon fusion with the plasma membrane, are released as exosomes into the extracellular space (Kowal et al., 2014). In contrast, microvesicles are shed directly from the plasma membrane through outward budding, whereas apoptotic bodies are formed during programmed cell death. The cargo of EVs is highly dynamic and reflects the physiological and pathological state of the parent cell. They contain a diverse array of biomolecules, including proteins, lipids, nucleic acids (DNA, mRNA, miRNA, and long non-coding RNA), and metabolites (Tkach & Théry, 2016). The selective packaging of these molecules is tightly regulated and influenced by the cellular microenvironment, allowing EVs to function as biomarkers for various diseases, including cancer, cardiovascular disorders, and neurodegenerative conditions (Théry et al., 2018).

4.1.2. EV Cargo and Its Functional Significance

EVs serve as carriers of signaling molecules that modulate recipient cell function. Their protein content includes tetraspanins (CD9, CD63, CD81), heat shock proteins (HSP70, HSP90), and cytoskeletal proteins, which contribute to their structural integrity and facilitate cellular interactions (Jeppesen et al., 2019). The lipid composition of EVs is enriched with sphingolipids, ceramides, and cholesterol, which enhance membrane stability and enable vesicular trafficking (Record et al., 2018). Among the most significant components of EVs are their nucleic acid cargo, particularly microRNAs (miRNAs). These small non-coding RNAs regulate gene expression by binding to target mRNAs, thereby influencing processes such as inflammation, cell proliferation, apoptosis, and metastasis (Zhang et al., 2019). The miRNA profile of EVs can vary depending on cellular stress, disease state, or environmental factors, making them valuable diagnostic and prognostic biomarkers.

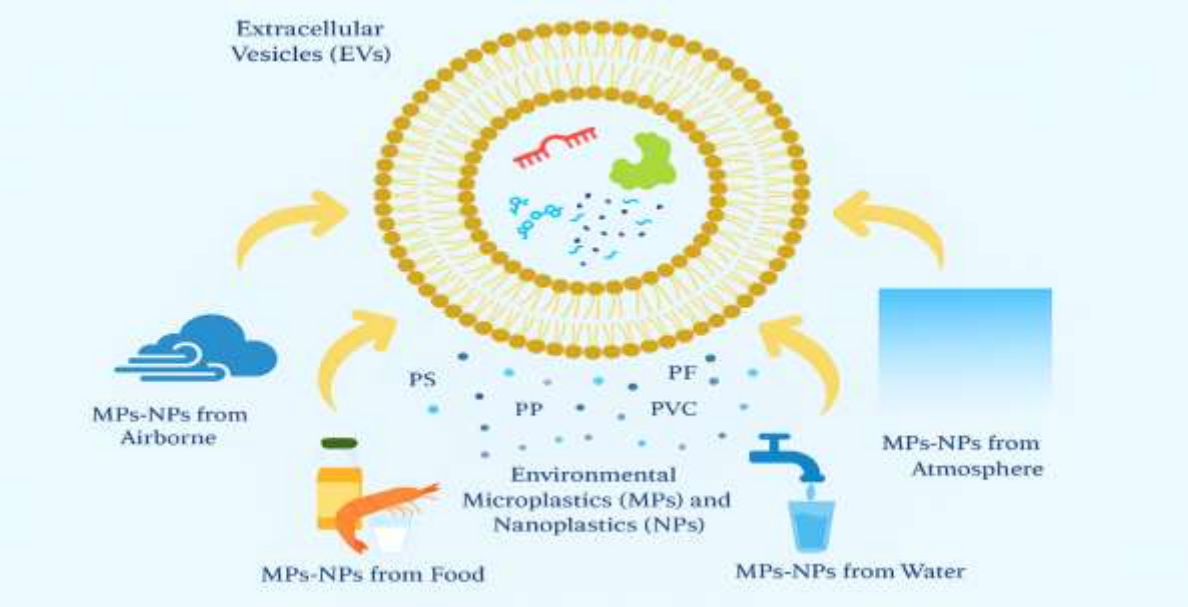

Fig.3: Diagram illustrating the pathways of MPs entry and their impact on extracellular vesicles (EVs) through different environmental routes.

4.1.3. EVs in Health and Disease

The functional role of EVs extends to both normal physiological processes and pathological conditions. Under normal conditions, EVs facilitate immune regulation, tissue repair, and neural communication. For example, mesenchymal stem cell-derived EVs promote tissue regeneration by delivering growth factors and miRNAs that enhance wound healing and angiogenesis (Lai et al., 2019). In the nervous system, EVs participate in synaptic plasticity by transferring neurotrophic factors and neurotransmitter receptors between neurons (Budnik et al., 2016). However, under pathological conditions, EVs can contribute to disease progression by transferring oncogenic proteins and RNAs in cancer, promoting neuroinflammation in neurodegenerative diseases, and facilitating viral transmission in infectious diseases (Whiteside, 2018). In cancer, tumor-derived EVs have been shown to modulate the tumor microenvironment by suppressing immune responses, promoting angiogenesis, and enhancing metastasis through miRNA-mediated gene regulation (Kalluri & LeBleu, 2020). Similarly, in neurodegenerative diseases such as Alzheimer's and Parkinson's, EVs contribute to disease pathology by spreading toxic protein aggregates such as amyloid-beta and alpha-synuclein between brain regions (Saresella et al., 2020).

4.1.4. EVs as Biomarkers and Therapeutic Agents

Due to their stability in biological fluids, EVs have emerged as promising biomarkers for disease diagnosis and prognosis. Their presence in blood, urine, cerebrospinal fluid, and saliva allows for non-invasive monitoring of disease progression and treatment response (Zhou et al., 2020). Advances in EV-based liquid biopsy techniques have enabled the detection of cancer-specific EVs, aiding in early cancer detection and personalized therapy

(Hoshino et al., 2020). Beyond diagnostics, EVs are being explored as potential therapeutic agents. Engineered EVs can be loaded with therapeutic molecules, including drugs, siRNAs, and CRISPR/Cas9 components, for targeted delivery to diseased tissues (Alvarez-Erviti et al., 2011). The use of EVs as drug delivery systems offers several advantages, including biocompatibility, low immunogenicity, and the ability to cross biological barriers (Gao et al., 2018).

4.2. Interaction Between Microplastics and Extracellular Vesicles: Implications for Systemic Dissemination and Toxicity

Emerging evidence suggests that microplastics (MPs) interact with extracellular vesicles (EVs), potentially influencing their biogenesis, cargo composition, and function in intercellular communication. MPs, particularly nanoplastics, have been shown to infiltrate biological systems, where they can be internalized by cells and subsequently incorporated into EVs. This interaction raises critical concerns about the systemic dissemination of MPs via EV-mediated transport, potentially exacerbating their toxicological effects. Studies indicate that polyethylene terephthalate (PET) MPs, a common environmental pollutant, can be detected within circulating EVs, suggesting that these particles may exploit the vesicular transport system to reach distant organs and tissues (van Niel et al., 2022).

4.2.1. Microplastic Uptake and Their Association with EVs

MPs and nanoplastics can enter the human body through ingestion, inhalation, or dermal exposure, eventually accumulating in various tissues, including the bloodstream. Once internalized by cells, MPs may be processed and enclosed within multivesicular bodies (MVBs), the precursors of exosome formation, or interact with microvesicles shed from the plasma membrane. This incorporation of MPs into EVs provides a novel mechanism by which these pollutants can evade traditional clearance pathways and persist in circulation for extended periods (Dellar et al., 2022). Furthermore, the size, charge, and surface chemistry of MPs influence their interaction with cellular components, including EVs, potentially altering the normal physiological role of vesicular transport (Xu et al., 2021).

4.2.2. Impact of MPs on EV Cargo Composition

The presence of MPs within EVs has been linked to significant changes in their molecular cargo, particularly in microRNA (miRNA) profiles. MiRNAs play a crucial role in regulating gene expression, and their dysregulation is associated with numerous pathological conditions, including inflammation, cancer, and neurodegenerative diseases (Chen et al., 2021). Studies suggest that exposure to PET MPs alters the miRNA composition of serum-derived EVs, potentially affecting recipient cell function and systemic homeostasis (van Niel et al., 2022). These alterations may contribute to immune dysregulation, metabolic imbalances, and increased susceptibility to chronic diseases. Moreover, the oxidative stress induced by MPs has been shown to modify protein expression within EVs, further impacting their ability to mediate normal physiological processes (Yee et al., 2021) (Fig. 3).

4.2.3. EV-Mediated Transport of MPs and Systemic Toxicity

The ability of EVs to transport MPs throughout the body represents a novel pathway for the systemic dissemination of these pollutants. Unlike free MPs, which may be subject to rapid clearance or local tissue accumulation, EV-associated MPs can traverse biological barriers, including the blood-brain barrier and placental barrier, raising concerns about their role in neurotoxicity and fetal development (Leslie et al., 2022). Once transported to distant organs, these vesicle-bound MPs may elicit cytotoxic, inflammatory, and oxidative stress responses, thereby exacerbating their toxicological effects. For instance, MPs have been detected in human placenta-derived EVs, suggesting potential implications for fatal health and developmental disorders (Fournier et al., 2020).

5. The Role of Microplastics in Altering miRNA Profiles

5.1. MicroRNAs: Key Regulators of Post-Transcriptional Gene Expression

MicroRNAs (miRNAs) are a class of small, non-coding RNA molecules, typically 18–25 nucleotides in length, that play a crucial role in post-transcriptional gene regulation. Since their discovery, miRNAs have been recognized as essential components of gene expression networks, modulating various physiological and pathological processes by binding to complementary sequences in target messenger RNAs (mRNAs), leading to mRNA degradation or translational repression (Nana-Sinkam & Croce, 2014). This regulatory mechanism enables miRNAs to fine-tune protein synthesis, ensuring precise cellular responses to environmental and intracellular cues. Their involvement in gene regulatory pathways makes miRNAs indispensable for maintaining cellular homeostasis, and their dysregulation has been implicated in numerous diseases, including cancer, neurodegenerative disorders, cardiovascular diseases, and immune dysfunction (Hammond, 2015).

5.1.1. Biogenesis and Mechanism of miRNA Action

The biogenesis of miRNAs follows a multi-step process beginning in the nucleus and culminating in the cytoplasm. Initially, miRNAs are transcribed as primary miRNAs (pri-miRNAs) by RNA polymerase II or III. These pri-miRNAs are subsequently processed by the Drosha-DGCR8 (DiGeorge syndrome critical region 8) complex into precursor miRNAs (pre-miRNAs), which are approximately 70 nucleotides in length and possess a characteristic stem-loop structure (Ha & Kim, 2014). The pre-miRNAs are then exported to the cytoplasm by Exportin-5, where they undergo further processing by the Dicer enzyme, yielding mature miRNA duplexes. One strand of this duplex, the guide strand, is incorporated into the RNA-induced silencing complex (RISC), while the passenger strand is typically degraded (Bartel, 2018).

Once incorporated into RISC, the mature miRNA guides the complex to target mRNAs based on sequence complementarity, primarily within the 3′ untranslated region (3′ UTR). If there is near-perfect complementarity, the target mRNA is cleaved and degraded. In cases of partial complementarity, miRNAs induce translational repression, preventing protein synthesis without degrading the mRNA itself (Ameres & Zamore, 2013). This post-transcriptional regulatory mechanism allows miRNAs to exert control over a wide range of biological functions, as a single miRNA can target multiple mRNAs, and a single mRNA can be regulated by multiple miRNAs, forming intricate gene expression networks (Saliminejad et al., 2019).

5.1.2. Role of miRNAs in Biological Processes

5.1.2.1. Regulation of Inflammation

MiRNAs are critical regulators of the immune response and inflammatory processes. They modulate cytokine production, immune cell differentiation, and the activation of signaling pathways associated with inflammation. For instance, miR-155 and miR-146a have been extensively studied for their roles in inflammatory regulation. MiR-155 promotes pro-inflammatory responses by targeting suppressor of cytokine signaling 1 (SOCS1), thereby enhancing cytokine signaling and immune activation (O'Connell et al., 2012). In contrast, miR-146a acts as a negative regulator of inflammation by targeting tumor necrosis factor receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1), reducing NF-κB signaling and dampening excessive inflammatory responses (Taganov et al., 2006). Dysregulation of these miRNAs has been linked to chronic inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease, and sepsis (Neudecker et al., 2017).

5.1.2.2. Apoptosis and Cell Survival

Apoptosis, or programmed cell death, is a tightly regulated process essential for maintaining tissue homeostasis and preventing the accumulation of damaged or abnormal cells. MiRNAs play a dual role in apoptosis, acting as either pro-apoptotic or anti-apoptotic regulators depending on their target genes. For example, miR-15a and miR-16-1 promote apoptosis by targeting B-cell lymphoma 2 (BCL2), an anti-apoptotic protein that inhibits cell death (Cimmino et al., 2005). Conversely, miR-21 functions as an anti-apoptotic miRNA by targeting phosphatase and tensin homolog (PTEN), leading to increased activation of the PI3K/AKT survival pathway and enhanced cell proliferation (Asangani et al., 2008). Abnormal expression of apoptosis-related miRNAs has been implicated in

cancer, neurodegeneration, and cardiovascular diseases, making them potential therapeutic targets for modulating cell survival pathways.

5.1.2.3. Metabolic Regulation

MiRNAs also play a central role in regulating metabolic processes, including glucose homeostasis, lipid metabolism, and mitochondrial function. In metabolic disorders such as obesity and diabetes, dysregulated miRNA expression can disrupt insulin signaling and energy balance. MiR-375, for example, is crucial for pancreatic β-cell function and insulin secretion, as it directly targets myotrophin (Mtpn), a protein involved in insulin granule exocytosis (Poy et al., 2004). Similarly, miR-33a and miR-33b regulate cholesterol metabolism by targeting ATP-binding cassette transporters ABCA1 and ABCG1, which are responsible for cholesterol efflux and high-density lipoprotein (HDL) formation (Rayner et al., 2011). These findings highlight the significance of miRNAs in metabolic homeostasis and their potential as therapeutic targets for metabolic diseases.

5.1.3. miRNAs in Disease Pathogenesis

Given their widespread regulatory functions, miRNAs have been implicated in various diseases. In cancer, miRNAs can act as oncogenes (oncomiRs) or tumour suppressors. For instance, miR-21 is frequently overexpressed in multiple cancer types, where it promotes tumour growth, invasion, and resistance to apoptosis (Chang et al., 2007). In contrast, let-7 family miRNAs act as tumour suppressors by targeting RAS and MYC oncogenes, inhibiting cell proliferation and inducing differentiation (Johnson et al., 2005). The dysregulation of miRNAs in cancer has led to the development of miRNA-based therapeutics, such as miRNA mimics and inhibitors, for targeted therapy.

Similarly, in neurodegenerative diseases, miRNAs have been found to regulate neuronal survival, synaptic plasticity, and neuroinflammation. MiR-29b, for example, is involved in Alzheimer's disease by modulating the expression of beta-site APP cleaving enzyme 1 (BACE1), which is responsible for amyloid-beta production (Hebert et al., 2008). The dysregulation of miRNAs in neurodegenerative disorders suggests their potential as biomarkers for early diagnosis and therapeutic intervention.

5.2. Microplastic Exposure and Its Influence on miRNA Expression: Insights from Recent Studies

The emerging field of microRNA (miRNA) research has provided critical insights into how environmental pollutants, such as microplastics (MPs), influence gene regulation and systemic health. Recent studies have demonstrated that exposure to MPs can lead to significant changes in miRNA expression profiles across various biological systems, including extracellular vesicles (EVs), which play a pivotal role in cell-to-cell communication. These findings suggest that MPs may contribute to metabolic, inflammatory, and cardiovascular dysfunction by altering miRNA-mediated gene regulatory pathways.

5.2.1. MP Exposure Induces Upregulation of Inflammatory miRNAs

Among the miRNAs identified as being dysregulated due to MP exposure, miR-222 and miR-146a-5p have garnered significant attention for their roles in metabolic syndrome and inflammation. miR-222 is a well-established regulator of insulin resistance, lipid metabolism, and endothelial dysfunction. Elevated levels of miR-222 have been linked to obesity, type 2 diabetes, and cardiovascular diseases due to its ability to impair insulin signaling and promote inflammatory responses (Hsu et al., 2018). Similarly, miR-146a-5p acts as a key modulator of inflammation, targeting signaling molecules such as tumor necrosis factor receptor-associated factor 6 (TRAF6) and interleukin-1 receptor-associated kinase 1 (IRAK1), which are involved in the NF-κB inflammatory pathway (Taganov et al., 2006). The upregulation of these miRNAs in EVs from pigs exposed to polyethylene terephthalate (PET) MPs suggests that MPs may provoke systemic inflammatory responses and metabolic dysfunction by altering miRNA expression profiles (Ortega et al., 2014).

5.2.2. miR-29b Downregulation and Its Implications for Diabetes and Cardiac Fibrosis

While some miRNAs are upregulated in response to MP exposure, others, such as miR-29b, are significantly downregulated. MiR-29b is a critical regulator of extracellular matrix (ECM) homeostasis, glucose metabolism, and fibrosis-related pathways. It directly inhibits the expression of pro-fibrotic genes such as collagen types I and III, fibrillin-1, and TGF-β signaling molecules (Zampetaki et al., 2010). A reduction in miR-29b levels has been associated with increased fibrosis, insulin resistance, and cardiovascular dysfunction, making its downregulation a potential contributor to diabetes and cardiac fibrosis (Roderburg et al., 2011). The observation that PET MP exposure leads to decreased miR-29b expression suggests that MPs may promote pathological ECM remodeling and fibrotic disorders, increasing the risk of diabetic complications and cardiovascular disease

6. Health Implications of Microplastics: Microplastic Role in Metabolic, Cardiovascular, and Neurodegenerative Disorders Through miRNA Dysregulation

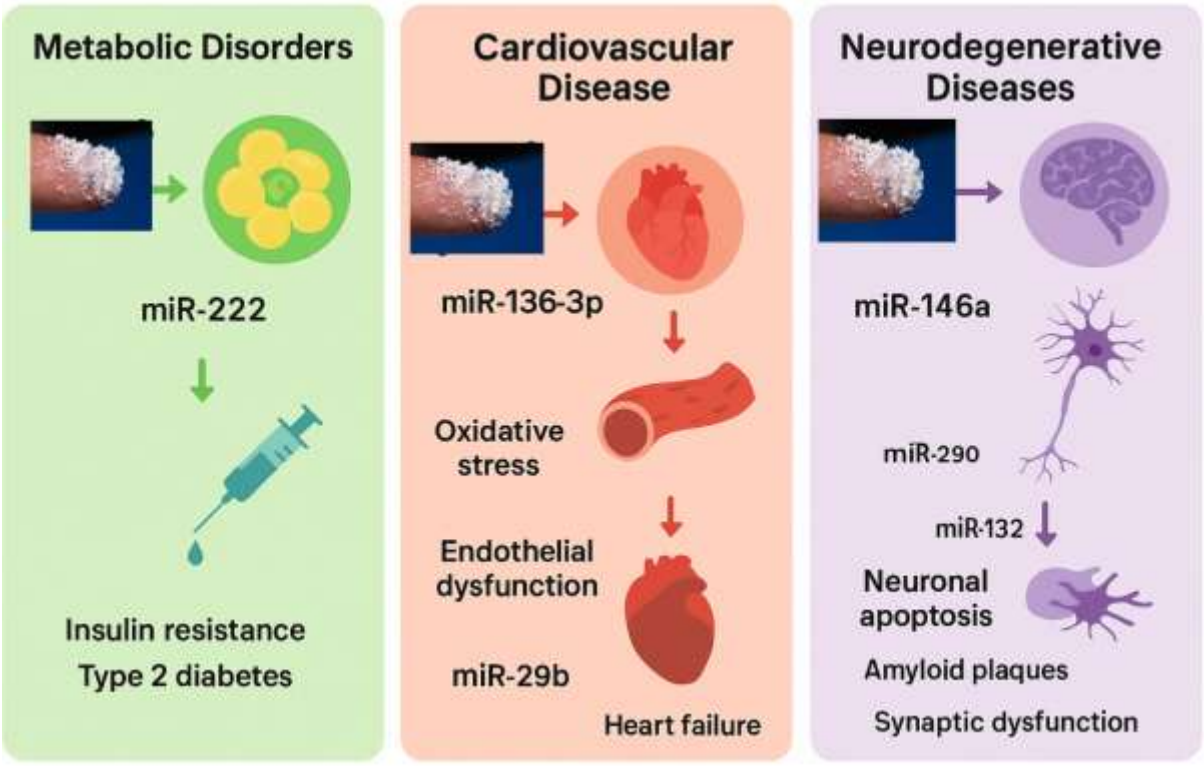

Fig.4: Diagram illustrating the impacts of microplastics on metabolic, cardiovascular, and neurodegenerative pathways, highlighting miRNA dysregulation and disease progression

Microplastic (MP) exposure has emerged as a potential environmental risk factor contributing to metabolic, cardiovascular, and neurodegenerative diseases. MPs have been shown to interfere with cellular homeostasis, leading to oxidative stress, inflammation, and dysregulation of critical molecular pathways. One of the key mechanisms through which MPs exert their toxic effects is by altering microRNA (miRNA) expression, which in turn disrupts essential biological processes, including insulin signalling, cardiovascular function, and neuronal integrity (Fig.4).

6.1. MP-Induced Metabolic Dysfunction: Insulin Resistance, Obesity, and Type 2 Diabetes

Growing evidence suggests that MPs may contribute to the rising prevalence of metabolic disorders such as insulin resistance, obesity, and type 2 diabetes. One of the primary miRNAs implicated in MP-induced metabolic dysfunction is miR-222, which plays a crucial role in regulating insulin signalling and glucose metabolism (Deiuliis, 2016). miR-222 is known to negatively regulate insulin receptor substrate-1 (IRS-1) and other components of the insulin signaling pathway, impairing insulin-stimulated glucose uptake in muscle and adipose

tissues (Hsu et al., 2018). The upregulation of miR-222 in response to MP exposure can therefore lead to insulin resistance, a hallmark of type 2 diabetes. Additionally, MPs may act as endocrine disruptors by interfering with hormonal homeostasis, further exacerbating metabolic dysfunction (Wang et al., 2019).

MPs may also contribute to obesity by altering lipid metabolism and promoting adipogenesis. Studies have shown that MPs can induce inflammation in adipose tissues, leading to chronic low-grade inflammation, which is closely associated with obesity-related complications (Fournier et al., 2020). The dysregulation of metabolic miRNAs in response to MPs suggests a complex interplay between environmental pollutants and metabolic diseases, necessitating further research into the long-term health implications of MP exposure.

6.2. MPs and Cardiovascular Disease: The Role of miR-136-3p and miR-29b

MP exposure has also been linked to cardiovascular dysfunction, including atherosclerosis, hypertension, and cardiac fibrosis. Among the miRNAs associated with these conditions, miR-136-3p and miR-29b have been identified as key regulators of cardiovascular health (Deng et al., 2017). miR-136-3p and miR-29b are two critical microRNAs involved in cardiovascular health, both of which have been found to be dysregulated in response to microplastic (MP) exposure. miR-136-3p plays a significant role in oxidative stress and endothelial dysfunction, both of which are major contributors to the development of atherosclerosis and hypertension. Studies indicate that the upregulation of miR-136-3p in response to MPs may lead to excessive production of reactive oxygen species (ROS), impairing nitric oxide (NO) signalling, which is essential for maintaining vascular tone and endothelial function. This dysregulation ultimately results in increased vascular inflammation, further exacerbating endothelial damage and promoting the progression of cardiovascular diseases (Deng et al., 2017). Similarly, miR-29b is a crucial regulator of cardiac fibrosis and extracellular matrix (ECM) remodelling, serving as an antifibrotic agent by inhibiting collagen synthesis and fibrotic signalling pathways. Under normal physiological conditions, miR-29b prevents excessive collagen deposition and maintains cardiac tissue elasticity. However, studies have shown that MP exposure leads to the downregulation of miR-29b, triggering an increase in collagen accumulation, enhanced myocardial stiffness, and a heightened risk of developing heart failure (Zampetaki et al., 2010). These findings suggest that MP-induced alterations in miRNA expression contribute significantly to cardiovascular dysfunction, especially in populations with pre-existing conditions such as diabetes or hypertension and highlighting the need for further investigation into the long-term effects of environmental pollutants on heart health.

6.3. Neurodegenerative Diseases: MP-Induced Inflammation and miRNA Dysregulation in the Brain

Emerging evidence indicates that microplastics (MPs) may play a significant role in the onset and progression of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and other cognitive disorders. MPs are capable of crossing the blood–brain barrier (BBB), where they accumulate in neural tissues and trigger inflammation, oxidative stress, and protein misfolding all of which are recognized hallmarks of neurodegeneration (Xu et al., 2022).

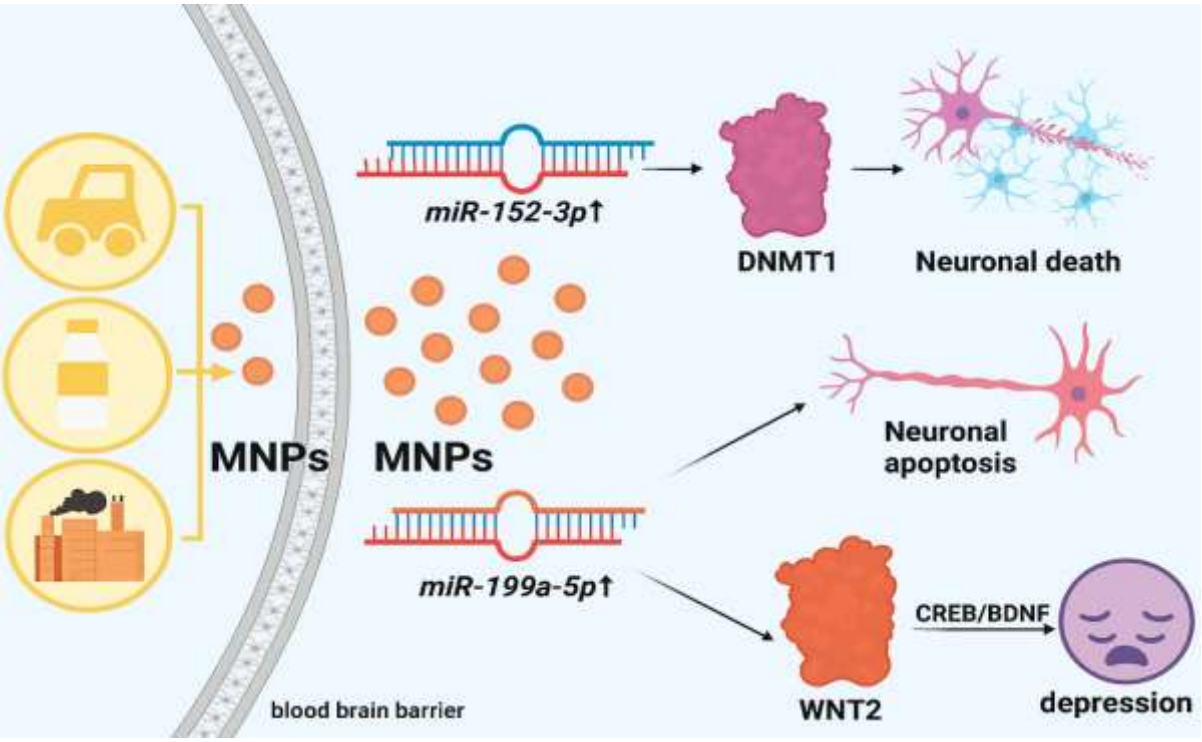

Fig.5: Microplastic Exposure and Gene Pathway Dysregulation in Neurodegenerative Disorders

One of the primary mechanisms by which MPs exert neurotoxic effects is through the dysregulation of microRNAs (miRNAs), which are key regulators of neuronal survival, synaptic plasticity, and inflammatory responses. Several miRNAs have been found to be altered following MP exposure. For instance, miR-146a, a critical regulator of neuro-inflammation, is often upregulated in AD patients. Elevated expression of miR-146a under MP exposure may suppress anti-inflammatory signalling while enhancing pro-inflammatory cytokine release, thereby worsening neuro-inflammatory conditions (Cipollini et al., 2020). Similarly, miR-29b, which is essential for neuronal survival and synaptic plasticity, has been shown to be downregulated after MP exposure. Reduced miR-29b expression is associated with neuronal apoptosis and amyloid-β plaque accumulation, both of which are pathological markers of AD (Zhao et al., 2013). In addition, miR-132, a miRNA crucial for synaptic function and neuroprotection, is also negatively impacted by MPs. Lower levels of miR-132 can impair neuronal connectivity, leading to cognitive decline and memory deficits (Xu et al., 2022).

Beyond these, recent findings suggest that miR-152-3p and miR-199a-5p are also key mediators of MP-induced neurotoxicity. miR-152-3p normally provides neuroprotection by regulating genes involved in neuronal differentiation, DNA methylation, and oxidative stress balance (Chen et al., 2024; Subramanian et al., 2024). Suppression of miR-152-3p under MP influence may increase neuronal susceptibility to DNA damage, impair synaptic signalling, and heighten neuro-inflammatory responses, all of which contribute to AD and PD progression. On the other hand, miR-199a-5p is central to maintaining neural homeostasis by regulating pathways such as mTOR signalling, HIF-1α activation, and extracellular matrix remodelling. Dysregulation of miR-199a-5p in response to MPs can promote neuronal apoptosis, mitochondrial dysfunction, and hypoxia-driven injury within brain tissue. These changes disrupt synaptic integrity and accelerate protein aggregation and neurodegenerative cascades.

Taken together, the dysregulation of miRNAs including miR-146a, miR-29b, miR-132, miR-152-3p, and miR-199a-5p demonstrates how MPs may exacerbate neuroinflammation, oxidative stress, and synaptic dysfunction, thereby elevating the risk of neurodegenerative disease development (Chen et al., 2024; Ni et al., 2024). These insights emphasize the urgent need for deeper investigation into the neurological consequences of MP exposure and the potential for therapeutic strategies to mitigate their harmful effects on brain health.

7. Future Research Directions

Despite growing evidence on the harmful effects of microplastics (MPs) on biological systems, further research is essential to fully elucidate the complex interactions between MPs, extracellular vesicles (EVs), and microRNAs (miRNAs). One of the most pressing areas for future investigation is understanding the long-term health effects of MP exposure in humans. Although animal and in vitro studies have demonstrated the toxicity of MPs, the extent to which chronic exposure contributes to human diseases, including metabolic disorders, neurodegenerative conditions, and cardiovascular dysfunction, remains unclear. Longitudinal human studies are necessary to assess MP accumulation in tissues and its association with disease progression. Additionally, more research is needed to explore the role of EVs in MP-mediated toxicity. Since EVs play a critical role in intercellular communication, their ability to transport MPs and MP-altered miRNAs raises concerns about systemic dissemination of toxicity. Investigating how MPs influence EV biogenesis, cargo composition, and functional properties may reveal novel pathways through which MPs exert harmful effects at the cellular and tissue levels. Another crucial area of study is identifying potential biomarkers for MP exposure using miRNA profiling. Given that miRNAs regulate inflammatory, metabolic, and neurodegenerative pathways, their dysregulation in response to MPs could serve as an early indicator of MP-induced toxicity. Establishing miRNA signatures associated with MP exposure could provide a non-invasive diagnostic tool to assess the biological burden of MPs in human populations. Finally, there is an urgent need to develop effective strategies to mitigate MP contamination in the environment. This includes efforts to reduce plastic production, improve waste management, and enhance filtration systems to prevent MPs from entering food chains and water sources. Furthermore, exploring biodegradable alternatives to conventional plastics and investigating bioremediation techniques using microorganisms capable of degrading MPs could help minimize environmental and biological risks. Addressing these key research gaps will not only improve our understanding of MP-related health risks but also pave the way for preventive and therapeutic interventions to safeguard human and environmental health.

8. Conclusion

Microplastics (MPs) have emerged as a major environmental and public health concern, with increasing scientific evidence indicating their potential to disrupt fundamental biological processes. One of the most alarming findings is their ability to alter extracellular vesicle (EV) function and microRNA (miRNA) expression, both of which play crucial roles in cellular communication, immune response, and gene regulation. The presence of MPs in human biological systems, including blood, organs, and even neural tissues, raises serious concerns about their long-term health implications. Their ability to cross biological barriers and accumulate in tissues suggests that MPs may contribute to the pathogenesis of metabolic disorders, cardiovascular diseases, and neurodegenerative conditions. Given the potential risks associated with MP exposure, there is an urgent need for stricter environmental regulations aimed at reducing MP contamination in air, water, and food sources. Additionally, further research is essential to fully understand the mechanisms through which MPs influence cellular and molecular pathways, particularly their interactions with EVs and miRNA profiles. By identifying these mechanisms, scientists can develop targeted strategies to mitigate the harmful effects of MPs, including biomonitoring approaches, early diagnostic biomarkers, and potential therapeutic interventions. Addressing the issue of MP pollution requires a multidisciplinary approach, combining scientific research, policy implementation, and public awareness to safeguard both human health and environmental sustainability.

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