

Impacts of Nanoplastics on Molecular Mechanisms within Microglia

Ella Wilce

Otumoetai College, 105 Windsor Road, Bellevue, Tauranga, 3110, New Zealand; ellajwilce@gmail.com

ABSTRACT: The ubiquity of nanoplastics (NPs) in the environment and organisms poses increasing threats to humans. NPs' minuscule size allows them to penetrate biological barriers; NPs have been detected in the human placenta, lungs, and brain. In the brain, NPs are preferentially internalized by surveilling microglia, resident immune cells, for destruction. This uptake of NPs induces physiological changes in microglia, including a transition to an active, pro-inflammatory state and programmed cell death, thereby threatening homeostasis. Damage to microglia is implicated in neurodegenerative diseases such as Alzheimer's, Parkinson's, and Multiple Sclerosis. Therefore, understanding the mechanisms underlying NP-microglia interactions is critical for quantifying the risks NPs pose to humans, informing consumer and manufacturer policies, and developing potential therapeutic interventions. In this review, studies on NPs and microglia are corroborated and analyzed to provide a roadmap detailing how NPs affect these mechanisms. Lysosomal dysfunction induced by NPs is a central trigger for microglia reactivity, causing the release of reactive oxygen species (ROS), calcium ions (Ca^{2+}), and other molecules. These induce metabolic reprogramming and phosphorylation cascades resulting in a pro-inflammatory response and programmed cell death in microglia. Furthermore, NPs elicit structural changes in proteins in the brain parenchyma, resulting in misfolded aggregates that impose an additional burden on microglia. This may contribute to or exacerbate existing disruptions caused by NPs within microglia. These findings suggest that NPs disrupt several essential mechanisms and pose a relevant threat to microglia.

KEYWORDS: Environmental Neurology, Cellular Pathways, Nanoplastics, Microglia, Neuroinflammation.

■ Introduction

Over the last century, more than 10 billion tonnes of plastic have been produced globally.^{1,2} Of these, 29% have been recycled or incinerated,² leaving over 7 billion tonnes of plastic to decompose into micro and nano particles. Nanoplastics (NPs) are defined as particles ranging from 1 to 1000 nm as a result of industrial plastic degradation.³ At this scale, plastic particles are able to infiltrate a wider range of biological barriers impenetrable to larger polymers, including the blood-brain barrier (BBB).⁴ The NPs of nylon, polyethylene terephthalate (PET), high-density polyethylene (HDPE), polyvinyl chloride (PVC), polypropylene (PP), and polystyrene (PS) have been found in the brains of humans.^{5,6} Though less prevalent, polymethyl methacrylate (PMMA) has also been studied due to its high concentration within people with surgical implants.^{7,8} Alarmingly, one study detected a median of 4917 $\mu\text{g/g}$ of NPs in human brains. This concentration is more than 10 times that detected in the kidneys or liver, suggesting that the brain's high lipid content and lack of clearance capacity confer susceptibility to NPs retention.⁵ NPs interact with neurons and proteins in the brain, threatening neural function.⁹ Murine studies found that exposure to NPs, proportional to the amount of NPs humans are exposed to, incurred cognitive deficiencies such as impaired learning and memory in mazes.¹⁰ Therefore, understanding how NPs affect various cells of the brain is imperative.

To clear accumulating NPs in the brain, NPs are engulfed by resting microglia, immune macrophages that maintain neural homeostasis.¹¹ In their resting state, microglia have many

sprawled-out arms, known as processes, with receptors on them, allowing them to constantly survey surrounding brain tissue for signals of unwanted particles.¹² When activated by external stimuli, microglia incur physiological and morphological changes, adopting various phenotypes to elicit an appropriate immune response.^{13,14} These changes are highly dynamic, with microglia regularly alternating between neurodegenerative (M1) and neuroprotective (M2) phenotypes.¹⁵ However, if microglia are in a neurodegenerative state for extended periods of time, excessive inflammation and programmed cell death of microglia can lead to irreversible damage.¹¹

Numerous studies demonstrated that NP exposure is correlated with microglial inflammation and cell death.^{4,7,16} Lysosome damage, signaling pathways, oxidative stress, metabolic changes, and protein misfolding were identified as contributing mechanisms.^{7,17–19} However, the interplay of these mechanisms is yet to be elucidated, with studies tending to focus on a single mechanism or pathway. Many studies focus on the brain-wide effect of NPs on neurodegeneration or solely on the intracellular effects of NPs on neurons. Therefore, there lacks a clear review of how these pathways facilitate microglial responses.

To delineate these pathways, this review first considers entry routes to the brain, as these may influence which brain regions are most affected. Direct uptake of NPs by microglia is then explored, with consideration of lysosomal capacity and function, followed by an analysis of ensuing ramifications to key components of microglial function, such as mitochondria and signaling pathways. Subsequently, the effect of NPs on protein misfolding and the additional burden this imposes on microg-

lia is evaluated. By integrating these mechanisms, this review aims to identify the interconnected pathways that determine the fate and function of microglia exposed to NPs. As NPs induce cognitive impairment in mice and marine organisms, elucidating the mechanisms underlying microglial responses is a critical step towards targeted mitigation and prevention of the cognitive threats posed by NPs.

■ Discussion

Entry Routes to the Brain – Olfactory System, BBB, and Biomolecular Corona:

NPs are internalized by three known pathways: ingestion, inhalation, and dermal exposure.^{20,21} Significant quantities of NPs have been detected in decedent human brains, specifically in the hippocampus,²² prefrontal cortex,^{22,23} and olfactory bulb.²⁴ Though exact routes remain unknown, two key routes are proposed as being exploited: the olfactory system and the BBB.

Airborne NPs likely enter the brain through the olfactory system,^{24,25} a passage that allows the transport of odor molecules into the olfactory bulb. Olfactory neurons originating in the nasal cavity enter the olfactory bulb via multiple holes known as foramina on the cribriform plate.²⁴ Each foramen ranges from around 7.2 mm² to 3.8 mm².²⁶ Odor molecules are internalized by these neurons and transported up their axons into the olfactory bulb.²⁷ This axonal transport pathway is used in nanoparticle drug delivery,²⁸ and offers a plausible route for NPs to gain direct entry to the brain. Supporting this, Micro-Fourier Transform Infrared Spectroscopy revealed microplastics (MPs) in the olfactory bulbs of 8 out of 15 human brains.²⁴ Sixteen distinct polymer particles were identified, with polypropylene comprising 45%, underscoring the need to study a diversity of plastic types.²⁴ Although detection sensitivity was insufficient to confirm NPs' presence, these findings highlight the significance of the olfactory system for ongoing research. As NPs permeate a wider field of biological barriers than MPs, it is likely that NPs would be present in the brains of more people than this study detected. Future research should develop technologies to accurately quantify NP levels across brain regions to better understand health implications.

An alternative route for NPs is the BBB – a semipermeable membrane surrounding the brain that facilitates the movement of molecules and ions in and out of the brain.²⁹ The BBB is lined with endothelial cells sealed with tight junctions composed of structural proteins that regulate paracellular diffusion.³⁰ As small, lipophilic particles, it is likely that NPs bypass tight junctions altogether, instead diffusing transcellularly through endothelial cells to gain direct access to the brain, a process known as transcytosis.³¹

Kopatz *et al.* suggest nanoplastic transport is enhanced through the formation of a lipid corona.³² Computer simulations using polystyrene compared pristine plastic to particles with a corona of lipid (cholesterol) or protein (PDB ID: 1LE1). NPs with a lipid corona were observed to diffuse into the lipid bilayer, where the corona dissociated, leaving the nanoplastic to traverse into the brain via diffusion or aided by a vesicle.³² Conversely, a protein corona did not allow permeation of the

BBB. It is important to note that a biomolecular corona does not comprise just one molecule, as in the aforementioned simulations. Upon soaking PS and PVC in solutions of human plasma, Abdolahur Monik *et al.* identified 268 proteins in the coronas of PS and PVC.³³ This demonstrates that BBB permeation by NPs exists on a spectrum, increasing in accordance with the proportion of lipids in the corona. As environmental plastics often contain chemical additives, emerging studies are investigating the coronas formed by not only different plastic types but also different chemical additives.^{34,35} Unique results for plastic and chemical variants reinforce the need to study a diverse range of NPs beyond those manufactured in a lab.

NPs Cause Lysosome Permeability and Rupture:

Upon entering the brain, NPs passively diffuse throughout the interstitial fluid, the fluid between neurons and glial cells.⁵ Nanoplastic movement through the brain parenchyma is influenced by the particle's size and structure.³⁶ Microglia are responsible for the degradation of NPs. To do so, NPs are internalized by microglia via phagocytosis.³⁷ Once internalized, NPs may interfere with several key organelles, including lysosomes, mitochondria, and endoplasmic reticulum.

Phagocytosis is a common transport mechanism among cells (for nanosized particles) whereby the plasma membrane of the microglia invaginates, allowing it to engulf the particle in a vesicle, referred to as an endosome.³⁸ The endosome then traffics the nanoplastic to the lysosome, an organelle contained by all cells to facilitate degradation of unwanted particles (autophagy).³⁹ The abundance of lysosomes in microglia and signaling complexity allows for more effective disposal of pathogens in microglia.⁴⁰

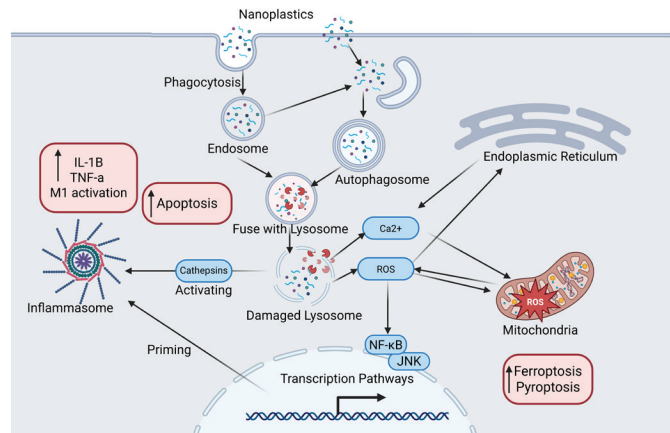


Figure 1: Summary of the intracellular pathways impacted by nanoplastics. Boxes in red indicate microglial responses. Created using BioRender.

NPs may also reside in the microglial cytosol, either by diffusing through the plasma membrane or by escaping endosomes.⁴¹ When this occurs, they are detected by autophagosomes, vesicles with a double-walled membrane. Autophagosomes may fuse with endosomes to form amphisomes, which fuse with lysosomes. These two pathways lead to the majority of phagocytized NPs residing in lysosomes (Figure 1). Yu *et al.* discovered that lysosomal membrane permeability increased in a dose-dependent manner in nanoplastic-treated BV2 microglia cells, indicated by an increase in a marker protein

(Galectin-3) observed via immunofluorescent imaging.⁴² Furthermore, LAMP1, an indicator of impaired lysosomal function, also increased.⁴² Lysosome permeability and rupture release small molecules such as ROS and Ca^{2+} , and larger enzymes such as cathepsins, into the cytosol, respectively.⁴³ These trigger downstream pathways affecting transcription factors, pathways, and metabolic reprogramming (Figure 1). In the above study, this culminated in microglial pyroptosis.

Released Lysosomal Content Affects Mitochondria and Inflammasome to Reprogram Microglia:

The release of ROS in microglia causes Endoplasmic Reticulum (ER) stress, prompting the release of Ca^{2+} . This creates a self-perpetuating cycle, as Ca^{2+} causes the formation of further ROS in mitochondria.⁴⁴ ROS and Ca^{2+} widen the mitochondrial permeability transition pore, thereby decreasing mitochondrial membrane potential ($\Delta\Psi\text{m}$). To date, no research exists examining the effects of NPs on microglial mitochondria; nonetheless, studies on neurons, neurofibroblasts, and peripheral macrophages offer potential insights as to how microglial mitochondria may be implicated.⁴⁵ Florance *et al.* found that exposure to NPs increased the generation of mitochondrial ROS and decreased mitochondrial membrane potential ($\Delta\Psi\text{m}$) in both human (THP-1) and murine (RAW 264.7) macrophages *in vitro*.⁴⁶ The study used PS NPs treated with anionic surfactants to mimic those commonly found in cosmetics.⁴⁶ A separate study in THP-1 cells using pristine PS NPs similarly demonstrated increased oxidative stress and reduced $\Delta\Psi\text{m}$, hence indicating the potential threat of NPs regardless of surface modifications.⁴⁷ In murine macrophages exposed to 10 μm PS MPs, cells decreased mitochondrial metabolism and $\Delta\Psi\text{m}$, instead utilizing glycolysis, which was demonstrated to support an immunometabolic response.⁴⁸ As microglia share similar functions with macrophages, the risks identified for macrophages hold potential relevance for microglia; however, each has unique responses to internal stimuli adapted to its respective environment that should not be overlooked. Of note, cultured macrophages may exhibit an enhanced response to stimuli, potentially exaggerating the effects of NPs.⁴⁹ A study investigating the roles of microglia and peripheral macrophages in spinal cord injury reported elevated apoptosis and reduced phagocytic efficiency compared to microglia, suggesting microglia maintain a more regulated response *in situ*. Therefore, these results should serve solely as a foundation for future research to build upon through microglia-specific studies using *in vivo* and *in vitro* analysis. If substantiated, this would carry important implications for understanding NPs' role in microglial dynamics.

Glucose metabolism is proposed to exert transcriptional control over microglial activation.⁵⁰ In a resting state, microglia preferentially utilize oxidative phosphorylation to produce energy within mitochondria.⁵¹ However, under inflammatory conditions, such as those caused by NPs, microglia switch to glycolysis, a faster, less efficient process that bypasses the mitochondria, which facilitates enhanced phagocytosis and inflammatory response.⁵² This causes pro-apoptotic signaling,

contributing to cell death in addition to a shift towards chronic microglial activation.^{50,52,53}

Furthermore, ROS act in conjunction with cathepsins released during lysosomal rupture, thereby serving as damage-associated molecular patterns (DAMPs).⁵⁴ DAMPs mediate the second stage of inflammasome activation; the first, priming stage, results from the NF- κB pathway, which will be discussed in the following section regarding transcription pathways.^{55,56} Inflammasomes are protein complexes composed of receptors and adaptors that evoke an inflammatory response by inducing pro-inflammatory caspases and cytokines.⁵⁵ Cathepsin B is predominantly implicated in NLRP3 inflammasome activation; however, a study using various compounds known to induce lysosome membrane permeability further ascertained the involvement of cysteine cathepsins B, C, L, S, and Z released from the lysosome in NLRP3 inflammasome activation.^{57,58} The NLRP3 inflammasome facilitates the maturation of pro-inflammatory cytokines IL-18 and IL-1 β , contributing to sustained microglial activation seen in Alzheimer's disease.

Transcription Pathways Triggered by Nanoplastic-Induced Cytokines and ROS:

Microglial activation is a complex process that can occur through multiple pathways, predominantly triggered by NP-induced ROS.⁶⁰ To determine these specific pathways, existing studies follow a similar structure: first, genes are analyzed across cells exposed to varying levels of NPs. Second, the data are processed, and a common pathway is identified that is shared across all samples. Third, that pathway is suppressed, and proinflammatory markers are measured to validate their findings. Interestingly, activation of pattern-recognition receptors (PRRs) showed minimal increase in microglia exposed to NPs compared to intestinal epithelial cells.⁶¹ This is likely due to microglia containing higher basal levels of PRRs compared to other cells, to facilitate their specialized role in pathogen detection and removal. Despite this, Antunes *et al.* found that N9 microglia exposed to NPs displayed more pronounced cytokine upregulation and cell death than intestinal epithelial cells, suggesting higher vulnerability to NPs.⁶¹ It is therefore critical to understand the signaling pathways specific to microglia, as their response to NPs is distinct from that of other cells.

Studies have shown that nuclear factor κB (NF- κB) is the predominant signaling pathway for nanoplastic-induced microglial activation. NF- κB can be segregated into two pathways: canonical, which utilizes the transcription factor p50/p65, and non-canonical, which uses p52/RELB. A further pathway, atypical NF- κB , induces the same transcription factors as the canonical pathway but uses different upstream mediators. These transcription factors serve to induce an inflammatory response, with the canonical pathway acting immediately and the non-canonical pathway eliciting a slower, sustained response. NPs have been found to increase nuclear translocation of both p50/p65 and p52/RELB via non-canonical and atypical pathways, explained below.

Li *et al.* found that NPs induced nuclear translocation of p50/p65 in BV2 mouse microglia via protein kinase RNA-like

endoplasmic reticulum kinase (PERK).⁶² ROS oxidizes the Harvey rat sarcoma viral oncogene homolog (H-Ras) protein, identified as a central node among overlapping differentially expressed genes (DEGs).⁶² This led to H-Ras activation, which triggers the PERK pathway. Among cells treated with NPs, H-Ras knockdown effectively downregulated the PERK pathway, confirming this correlation. The PERK pathway ultimately inhibits the synthesis of the NF- κ B suppressor I κ B α , thereby freeing NF- κ B to translocate to the nucleus and regulate proinflammatory genes.^{63,64} Removal of I κ B α is the same trigger for NF- κ B in the canonical pathway, where NF- κ B activation is mediated by the direct phosphorylation of I κ B α .⁶⁴ Hence, the same downstream transcription factors, p50/p65, are produced, eliciting the same acute inflammatory response as the canonical pathway.

Another study found NPs triggered the non-canonical NF- κ B pathway. Lu *et al.* performed transcriptome sequencing analysis (RNA sequencing) of the prefrontal cortex of mice that had been fed different amounts of PS NPs.⁶⁵ Four DEGs were present across all concentrations of NPs: Pbx3, Ecell, Crb1, and Ngb. ROS also increased, although it is unclear whether ROS mediated these genetic changes. Regardless, these DEGs upregulated the NIK/NF- κ B (non-canonical) signaling pathway by stabilizing the protein NF- κ B-inducing kinase (NIK), which is normally degraded.^{65,66} NIK functions in conjunction with inhibitor of NF- κ B kinase α (IKK α) to phosphorylate the NF- κ B2 precursor protein (p100) in the cytosol.⁶⁶ This causes p100 to split into RelB/ p52 (types of NF- κ B), which then translocate to the nucleus to transcribe pro-inflammatory genes.^{65,66} Supporting this, the same transcriptome analysis showed significant upregulation of TNF α and IL-1 β , two prominent cytokines in inflammation.⁶⁵ The p52 pathway is slow and sustained compared to the canonical NF- κ B pathway, contributing to chronic inflammation. This highlights a potential for NPs to contribute to neurodegenerative diseases.

Sun *et al.* identified an additional pathway for NPs in microglia cells, whereby ROS activated c-Jun N-terminal kinase (JNK), an enzyme that phosphorylates transcription factors that upregulate heme oxygenase (HO-1).¹⁸ HO-1 is an enzyme that breaks down heme into iron (and CO and bilirubin). In small amounts, iron can be used as a signal; however, if it is not stored by FTH1, iron can lead to cell death (ferroptosis),⁶⁷ which was seen in the study by Sun *et al.* JNK can also be activated as a downstream pathway of NF- κ B, representing a potential flow of pathways.

These pathways represent opportunities for genetic modification to suppress the effects of NPs. However, cross-talk between pathways in regard to NPs is unclear, and it is likely that many more pathways exist that have not yet been tested. Future research should continue to explore signaling pathways.

Protein misfolding caused by NPs activates microglia:

NPs penetrate brain cells and interfere with protein folding,^{68–71} culminating in protein aggregates and fibrils.⁷⁰ These cannot be digested by microglia, so incur chronic microglial activation, mirroring the pathology of Alzheimer's Disease. Protein misfolding likely results from bonds between NPs and

the free ends of proteins that have yet to be folded.^{68–71} Studies to date have used in silico computer simulations, which provide a baseline to be supported with future *in vitro* studies.

To elucidate the nature of these interactions, Holl  czki and Gehrke used discrete molecular dynamics (DMD) simulations to explore polyethylene (PE), polypropylene (PP), polyethylene terephthalate (PET), and nylon-6,6 (N66) in aqueous solution in the presence of various amino acids.⁶⁸ They identified Phenylalanine and Tryptophan as being highly prone to adsorption on the NPs' surface due to nonpolar attractions.⁶⁸ Further DMD simulations utilized by Wang *et al.* to pinpoint the interactions between amyloid- β and Polystyrene NPs similarly revealed adsorption of Phenylalanine and Tryptophan.⁷¹ Side chains of the amyloid- β that contained amino acids with rings on their side chains (known as aromatic amino acids), specifically Phenylalanine, Tyrosine, and Tryptophan, formed π - π interactions with the benzene ring of PS NPs.⁷¹ This strengthened hydrogen bonding, which occurred between the polar amino acids on the N-terminus (initial free amino group of the polypeptide) of amyloid- β and the hydroxyl groups of NPs.⁷¹

An initial misfolded protein acts as a template for other proteins, thereby spreading the malformed structure to surrounding proteins. These misfolded proteins form small clusters known as oligomers. As oligomers further accumulate, they form strong, insoluble amyloid fibrils.⁷² These can include amyloid- β peptides, the prion protein, α -synuclein, tau, and β 2-microglobulin.⁷⁰ Increased amyloid formation may accelerate the effects of neurodegenerative diseases.⁷¹ Amyloid fibrils cannot be phagocytized by microglia. Instead, microglia digest amyloid fibrils extracellularly via digestive exophagy, whereby tightly sealed regions called lysosomal synapses are formed between the microglia and amyloid fibril through which lysosomal contents are released to degrade the fibrils.⁷³ In a resting state, the pH of microglial lysosomes is $\sim$ 6; this decreases to $\sim$ 5 in active microglia,⁷⁴ the upper limit of the pH at which amyloid- β is degraded.⁷⁵ Therefore, lysosomal alkalization resulting from direct nanoplastic uptake may limit the clearance of these fibrils, contributing to further recruitment and activation of microglia. Together, these result in sustained M1 inflammation of microglia, contributing to diseases such as Alzheimer's and Parkinson's disease.⁷⁶

Limitations and Future Directions:

The past 5 years have seen a marked increase in research on the health implications of NPs. However, technical challenges remain a block in the progression of research, in particular, detection and quantification methods. As such, future research should work on developing these technologies.

PS NPs comprise 94 percent of studied NPs, yet comprise just 8.5 percent of environmental NPs.⁷⁷ Furthermore, many studies use spherical polystyrene beads, which have the lowest possible surface area, thus distorting nanoscale interactions. Given the structural diversity of environmental NPs, future research should prioritize developing the technology needed to adequately assess a range of NP types, shapes, and sizes. Koo *et al.* exemplified this in an *in vitro* study of microglia ex-

posed to PS, PP, or PMMA, where PMMA showed the most pronounced effects on the expression of chemotactic migration and microglia recruitment.⁷ As PMMA comprises a low percentage of environmental plastics, it is rarely studied. This reinforces the need to examine a range of plastic types, as, beyond this, PMMA has not been used in neurotoxicity studies.

Type diversity is of particular relevance to protein misfolding, due to the differential bonds that form. For instance, the benzene rings of PS NPs reinforced hydrogen bonds with amino acids; however, PS and PET are the only NPs that contain a benzene ring, so the precise interactions of other nanoplastics are unclear. All studies to date use *in silico* analysis, which cannot fully account for the multitude of background bonds formed by the environment; future studies should utilize a combination of *in vitro* and *in vivo* methods to confirm these findings.

A further limitation is that this study focused predominantly on the intracellular effects of NPs on microglia; therefore, it did not account for the effects of cross-talk on microglia. Prior studies have highlighted the plausibility of cytokine signaling in macrophages outside the brain, affecting microglial activation via the gut/brain axis.^{78,79} As NPs have been shown to affect these regions (e.g., LPS in macrophages), one may speculate that cross-talk plays a significant role in exacerbating their effects. Future studies should examine cross-talk among regions, especially those where an immune response has previously been identified, such as the intestines,^{80,81} colon,⁸² liver,⁸³ and lungs.⁸⁴ Similarly, this study has not gone into the depths of how cross-talk with neurons or astrocytes implicates disease, a field worth future research.

Considering these limitations, future research should prioritize utilizing more accurate detection techniques, different types, additives, and shapes of NPs that mimic environmental NPs, more microglia-specific studies, and pathways not yet explored. Developing technology that can reliably isolate NPs in the environment would particularly benefit understanding the type and additive differences. Once specific risks have been established, research should turn to therapeutic strategies. The microglial response highlighted in this paper shares pathologies with those observed in Alzheimer's Disease; therefore, strategies relevant to Alzheimer's, such as the use of inhibitor proteins to block signaling pathways triggered by NPs,¹⁸ may apply to NPs. In addition, nanorobots are currently being explored as a targeted drug delivery mechanism for brain cancers and neurodegenerative disease,⁸⁵ and may offer a solution for the removal of NPs from the brain.⁸⁶

■ Conclusion

NPs represent an emerging ecological threat demonstrating potential neurotoxicity. The ubiquity and environmental persistence of NPs, combined with the toxicity to microglia outlined in this review, highlight the urgent need for future research. In humans, NPs enter the brain via multiple routes of exposure, with their size and structure facilitating absorption, diffusion, and infiltration across biological barriers. This review explored a pathway by which NPs cause chronic microglial activation and cell death. It found that NPs in the brain's in-

terstitial fluid are selectively phagocytosed by microglia, which transport them intracellularly to lysosomes. Because lysosomes are incapable of degrading NPs, lysosomal membrane permeabilization and rupture occur, releasing cathepsins, metals, and ROS into the cytosol. These impair mitochondrial and ER function, altering the physiological state of the microglia. NF- κ B was identified as a key signaling pathway that facilitates microglial apoptosis, with JNK also implicated. These pathways share commonalities with neurodegenerative diseases, underscoring the potential threat of NPs. Outside of microglia, NPs impair protein folding and support amyloid fibril aggregation, placing further burden on inflammatory microglia. Together, these findings provide a pathway for understanding how NPs interact with microglia, establishing a foundation for future research to further identify mechanisms, quantify NP risk, and develop therapeutic strategies to mitigate potential neurological threats.

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■ Author

Ella Wilce is an aspiring scientist with a passion for genetics, neuroscience, and environmental sustainability. She hopes to pursue a related field at a top university with a focus on understanding the ecological effects of environmental pollutants.