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Letter

Aggravated Visual Toxicity of Eco-Corona on Micro(Nano)Plastics in Marine Medaka (*Oryzias melastigma*)

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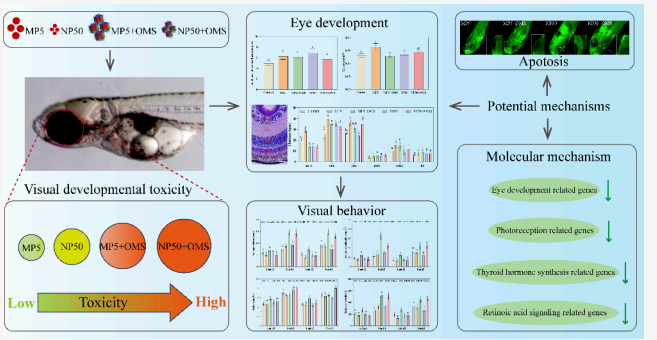
ABSTRACT: In marine environments, micro(nano)plastics (MNPs) and biomolecules will inevitably combine to form eco-corona. However, the presence of eco-corona may change MNP physicochemical properties, thereby impacting their biological effects. This study investigated how eco-corona influenced the visual toxicity and potential mechanisms of MNPs in marine medaka. The results showed that MNPs, with or without eco-corona, can cause eye malformation, retinal damage, eye cell apoptosis, and suppression of visual-related gene expression. Although MNPs caused visual impairments, they did not lead to abnormal behavior during light-dark alternation. Moreover, while 5 μm polystyrene microplastics (MP5) caused eye swelling, 50 nm polystyrene microplastics (NP50) resulted in more severe retinal damage. Regardless of eco-corona, NP50 induced greater activity during dark periods compared with MP5. Notably, eco-corona exacerbated retinal damage and cell apoptosis caused by MNPs, leading to increased activity. The analysis of visual-related genes revealed that eco-corona aggravated the visual toxicity of MNPs, and NP50 exhibited greater visual toxicity than MP5, regardless of eco-corona. Overall, smaller MNPs may pose higher risks to the visual system in real marine environments. This study provides novel insights into the effects of eco-corona in MNP-induced visual toxicity and highlights the importance of considering biomolecules in marine environments.



KEYWORDS: *Micro(nano)plastics, Eco-corona, Marine medaka, Behavior, Visual toxicity*

1. INTRODUCTION

Marine plastic waste breaks down into smaller microplastics (MPs, < 5 mm) and nanoplastics (NPs, < 1 μm).[1] The concentrations of micro(nano)plastics (MNPs) in marine environments vary significantly (Text. S1). However, MNPs persist in marine ecosystems due to their small size and high stability, causing various toxic effects on marine organisms, including developmental toxicity,[2] cardiotoxicity,[3] reproductive toxicity,[4] metabolic abnormalities,[5] neurotoxicity,[6] and immunotoxicity.[7] Biomolecules are abundant in the marine environment and encompass various natural organic substances (NOM).[8] Due to the hydrophobic properties, MNPs inevitably interact with these biomolecules to form unique eco-corona.[9] However, the ecotoxicity of MNPs is strongly influenced by the presence of biomolecules in the marine environment. It is reported that the formation of eco-corona can mitigate oxidative stress and cytotoxicity caused by MNPs in marine microalgae.[10] Another study showed that eco-corona did not alleviate severe cellular stress induced by MNPs in marine diatoms and green algae.[11] However, eco-corona exacerbated oxidative stress and intestinal toxicity caused by MNPs in zebrafish (*Danio rerio*).[9] In brief, the effects of eco-corona on MNP ecotoxicity depend on the composition of eco-corona and the properties of MNPs. Therefore, the effects of eco-corona should be further investigated to comprehensively evaluate the ecological risks caused by MNPs in marine systems.

The visual system, a vital part of the sensory system, is intricately connected to various behavioral activities. Marine organisms, particularly fish, are more vulnerable to visual system damage due to their lack of eyelids, which leaves their eyes directly exposed to environmental pollutants.[12] Eye differentiation is a critical stage in the early development of fish, essential for feeding, predator avoidance, and spatial cognition.[13] Previous studies have shown that fish visual systems are especially susceptible to direct damage from MNP exposure, as well as chronic effects from long-term

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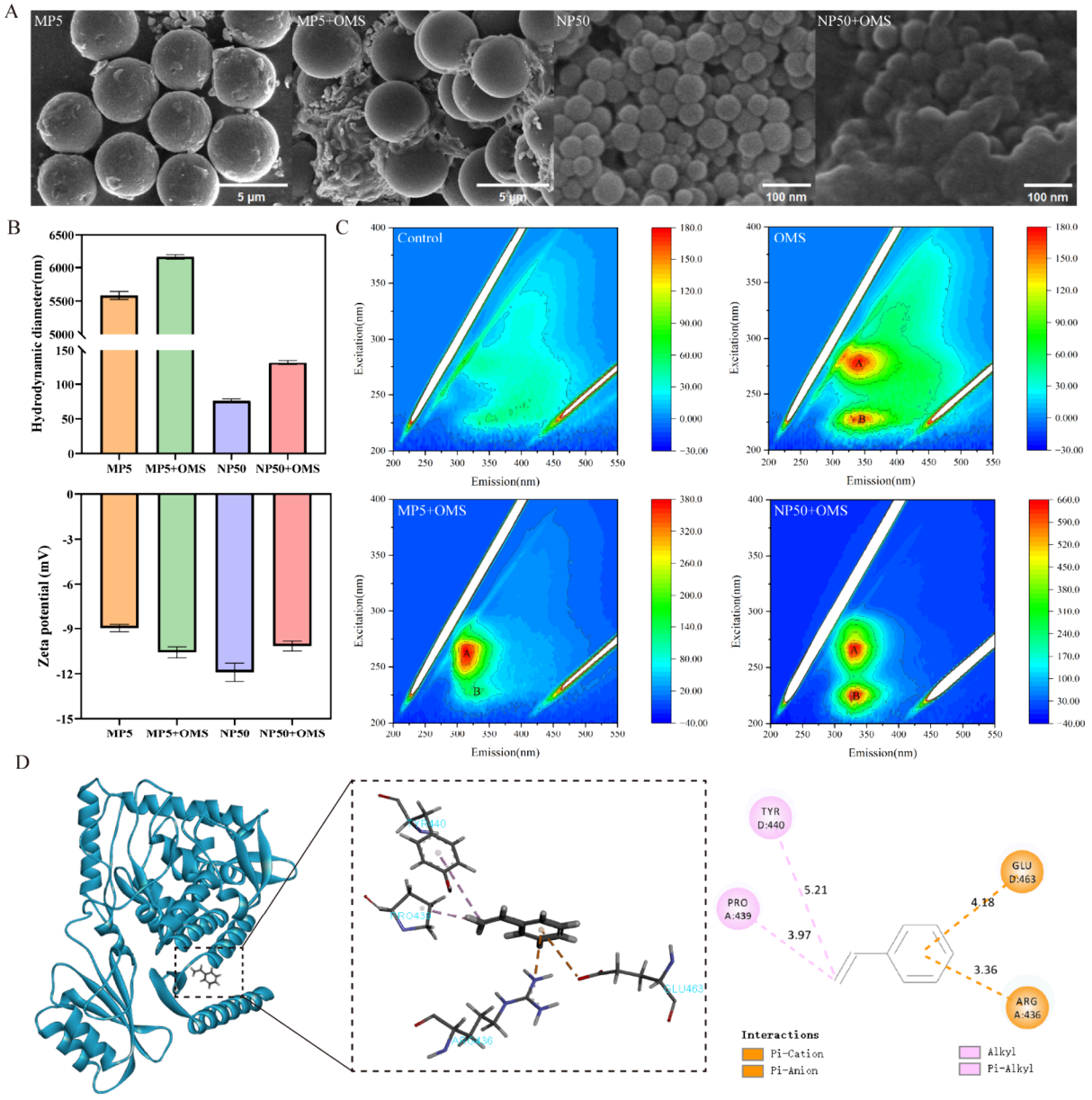

Figure 1. Characterization of MNPs and MNPs+OMS. (A) The SEM images of MNPs and MNPs+OMS. (B) The hydrodynamic diameter and zeta potential of MNPs and MNPs+OMS. (C) The 3D-EEM fluorescence spectra of Control, OMS[25] and MNPs+OMS. Peak A: soluble biological byproducts. Peak B: tryptophan-like proteins. (D) Ribbon schematic representations of the molecular docking of styrene with tryptophan 5-hydroxylase (TPH). The results are presented as mean ± SEM.

accumulation. For example, the accumulation of polystyrene nanoplastics (PS-NPs) in zebrafish eyes and brains decreased photoreceptor protein synthesis, impairing retinal development and function.[14,15] Polystyrene microplastics (PS-MPs) can cause visual damage in zebrafish and marine medaka by inducing oxidative stress in the eyes.[16,17] Although these studies have revealed mechanisms by which MNPs cause visual dysfunction in fish, available information on photoreceptive function remains limited. Furthermore, the effects of eco-corona on the visual toxicity of MNPs remain unexplored. Fish rely on visual function to perceive and respond to environmental stimuli, making behavioral observation under light-dark alternations an effective method to assess visual system damage (Text. S2).[18]

This study investigates the effects of eco-corona on the visual toxicity of polystyrene micro(nano)plastics (PS-MNPs) in marine medaka (*Oryzias melastigma*) during early development (Text. S3). A comprehensive evaluation of visual toxicity induced by MNPs and MNPs coated with *Oryzias melastigma*'s secretions (OMS) (MNPs+OMS) will be conducted at individual, tissue, cellular, and molecular levels through morphological, behavioral, histopathological, apoptotic, and molecular biological analyses. We hypothesize that eco-corona will alter the physicochemical properties of MNPs, thereby leading to differences in the visual toxicity between MNPs and MNPs+OMS. This study provides valuable perspectives for evaluating the ecological risks of MNPs in real marine environments.

2. METHODS AND MATERIALS

2.1. Experimental Animals and Materials. Exposure experiment consisted of one control group and five treatment

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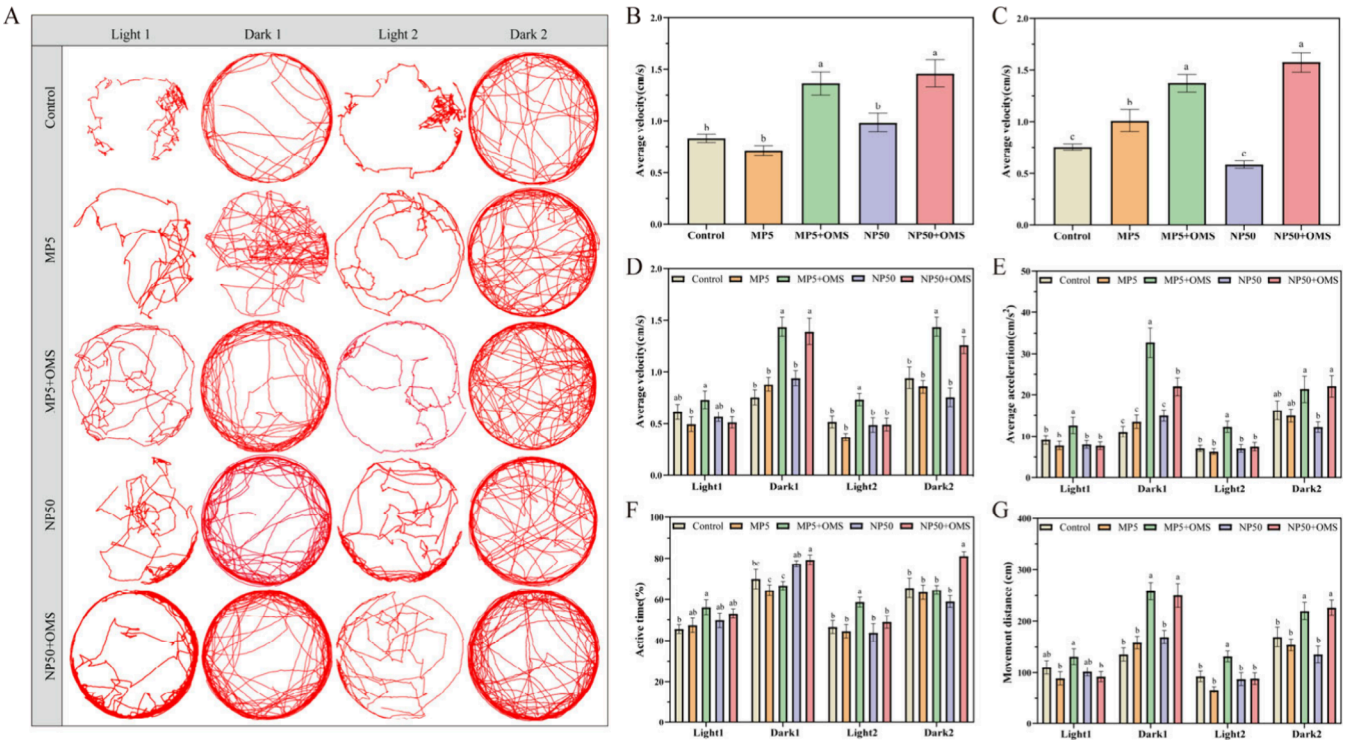

Figure 2. Locomotor activity of marine medaka larvae exposed to 100 μg/L MNPs and MNPs+OMS during a 3 min light or dark period. (A) The representative movement trajectories of larvae in light-dark alternation test. (B) Average velocity of larvae at the first minute after the transition from Light 1 to Dark 1. (C) Average velocity of larvae at the first minute after the transition from Light 2 to Dark 2. (D) Average velocity during the experiment. (E) Average acceleration during the experiment. (F) Active time during the experiment. (G) Movement distance during the experiment. The results are presented as mean ± SEM, and groups with different letters indicate significant differences ($P < 0.05$).

groups: a seawater control and environmentally relevant concentrations[19−23] (100 μg/L) for 5 μm PS-MPs (MP5), MP5+OMS, 50 nm PS-NPs (NP50), and NP50+OMS groups (Figure S1 and Text. S4). Theoretical simulations indicated that the particle numbers for MP5 and NP50 at 100 μg/L are approximately 1.46×10^6 particles/L and 1.46×10^{12} particles/L, respectively. Developmental toxicity assessment of OMS alone in marine medaka showed no adverse effects, indicating that the observed toxicity results from the combination of MNPs and OMS (Figure S2). A semistatic exposure was maintained for 21 d, with the exposure solution replaced every 24 h and dead eggs promptly removed.

2.2. Characterization of MNPs and MNPs+OMS. Scanning electron microscopy (SEM) images, zeta potential, hydrodynamic diameter, three-dimensional excitation−emission matrix (3D-EEM) fluorescence spectra, and molecular docking were obtained for MNPs and MNPs+OMS (Text. S5).

2.3. Light-Dark Alternation Behavior Test. After 3 min of dark adaptation, larval locomotor activity was tracked for 12 min under light-dark alternation conditions (3 min intervals) using the LoliTrack behavioral analysis system, with subsequent analysis of movement parameters (Text. S6).

2.4. Histopathological Observation and Apoptosis Detection of Eyes. Larvae were sliced along the longitudinal axis and then stained with hematoxylin-eosin. The thicknesses of the retinal ganglion layer (RGL), inner plexiform layer (IPL), inner nuclear layer (INL), outer plexiform layer (OPL), outer nuclear layer (ONL), and photoreceptor layer (PL) were measured using ImageJ. Acridine orange (AO) staining was used to detect cell apoptosis in the eyes. Fixed larvae were examined under a fluorescence microscope, where green fluorescence indicated AO-positive apoptotic cells.

2.5. Gene Expression and Biochemical Assays Related to Visual Development. Total RNA and quantitative real-time PCR (qRT-PCR) were performed following previously described protocols, with *18S* used as the internal reference.[3] The relative expression levels of visual development-related genes were calculated using the $2^{-\Delta\Delta Ct}$ method (Text. S7 and Tab. S1). Additionally, thyroxine (T4) levels were measured using an enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions.

2.6. Integrated Biomarker Response (IBR) Analysis. Biomarkers were standardized based on previous methods, and radar plots were created to visualize differences in toxicity levels (Text. S8).[24]

2.7. Statistical Analysis. Data analysis was performed using IBM SPSS Statistics 27.0. Normality and homogeneity of variance were tested by the Kolmogorov−Smirnov test and Levene's test. One-way ANOVA was conducted to determine significant differences among groups, followed by Duncan's multiple comparison test with a significance level set at $p < 0.05$. Data were presented as mean ± standard error of the mean (SEM).

3. RESULTS AND DISCUSSION

The characteristic peaks (I, II, III, and IV) in the Fourier Transform Infrared (FTIR) spectra of MNPs and MNPs+OMS indicated that their main component is polystyrene (PS) (Figure S3). Notably, OMS adhered to the surface of MNPs to form eco-corona, promoting the aggregation of MNPs (Figure 1A). Furthermore, the increased hydrodynamic

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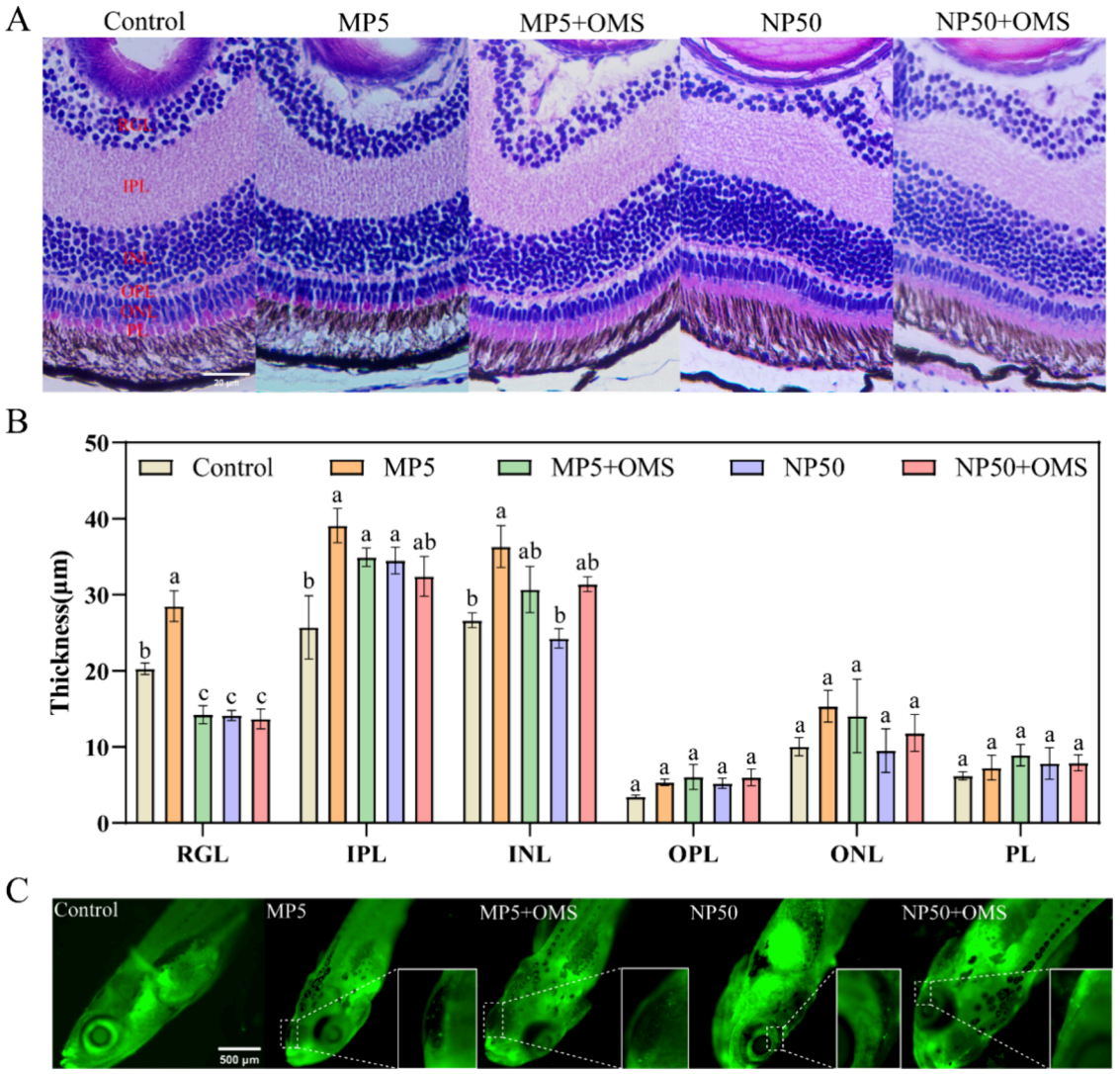

Figure 3. Histopathological analysis and AO staining image of the eyes of marine medaka larvae exposed to 100 μg/L MNPs and MNPs+OMS for 21 d. (A) Retinal histopathological changes in larvae. (B) Thickness quantification of RGL, IPL, INL, OPL, ONL and PL for each group. (C) Apoptosis in the marine medaka larvae eye.[25] The results are presented as mean ± SEM, and groups with different letters indicate significant differences ($P < 0.05$).

diameter of MNPs+OMS further confirmed this aggregation phenomenon (Figure 1B). However, the zeta potential of MP5+OMS became more negative, while that of NP50+OMS became less negative. This divergence may be attributed to differences in the composition of the MNPs+OMS complex. The 3D-EEM results revealed that NP50 bound more tryptophan-like proteins from OMS than MP5 (Figure 1C). Protein adsorption may reduce the electrostatic repulsion between particles, decreasing the absolute zeta potential value. Moreover, styrene interacted with tryptophan 5-hydroxylase (TPH) through Pi-cation, Pi-anion, alkyl, and Pi-alkyl interactions, and the binding energy indicated a stable complex formation (Figure 1D). The detailed characterization results were provided in Text. S9. Therefore, OMS corona altered the surface properties of MNPs, potentially influencing their toxicity.

Although OMS corona did not significantly affect the eye developmental toxicity of MNPs (Figure S4 and Text. S10), changes in visual function may manifest at the individual behavior level. Under alternating light-dark conditions, larvae in all groups showed higher activity during dark periods and lower activity during light periods, confirming their ability to distinguish light from dark (Figure 2A).[18] Larvae exposed to MNPs+OMS showed significantly increased velocity during the first minute of the dark transition compared with MNPs alone (Figure 2B and C), potentially representing a stress-induced startle response.[26] The enhanced response may result from OMS corona promoting MNP sedimentation,[25] increasing contact with marine medaka embryos and intensifying the startle reaction. However, exposure to MP5 or NP50 alone did not significantly affect larval activity during light-dark transitions (Figure 2D-G). Notably, MP5+OMS exposure significantly increased larval locomotor activity under light stimulation compared with MP5 alone, suggesting that OMS corona heightened sensitivity to light changes and intensified the startle response. Previous studies have shown that early stage larvae exhibit scotophobia and are prone to anxiety.[27] Larvae in the NP50/NP50+OMS groups exhibited significantly longer active times during dark periods compared with MP5/MP5+OMS groups. This was likely related to the ability of NP50/NP50+OMS to passively enter marine medaka embryos (Figure S4). Notably, larvae exposed to MNPs+OMS exhibited

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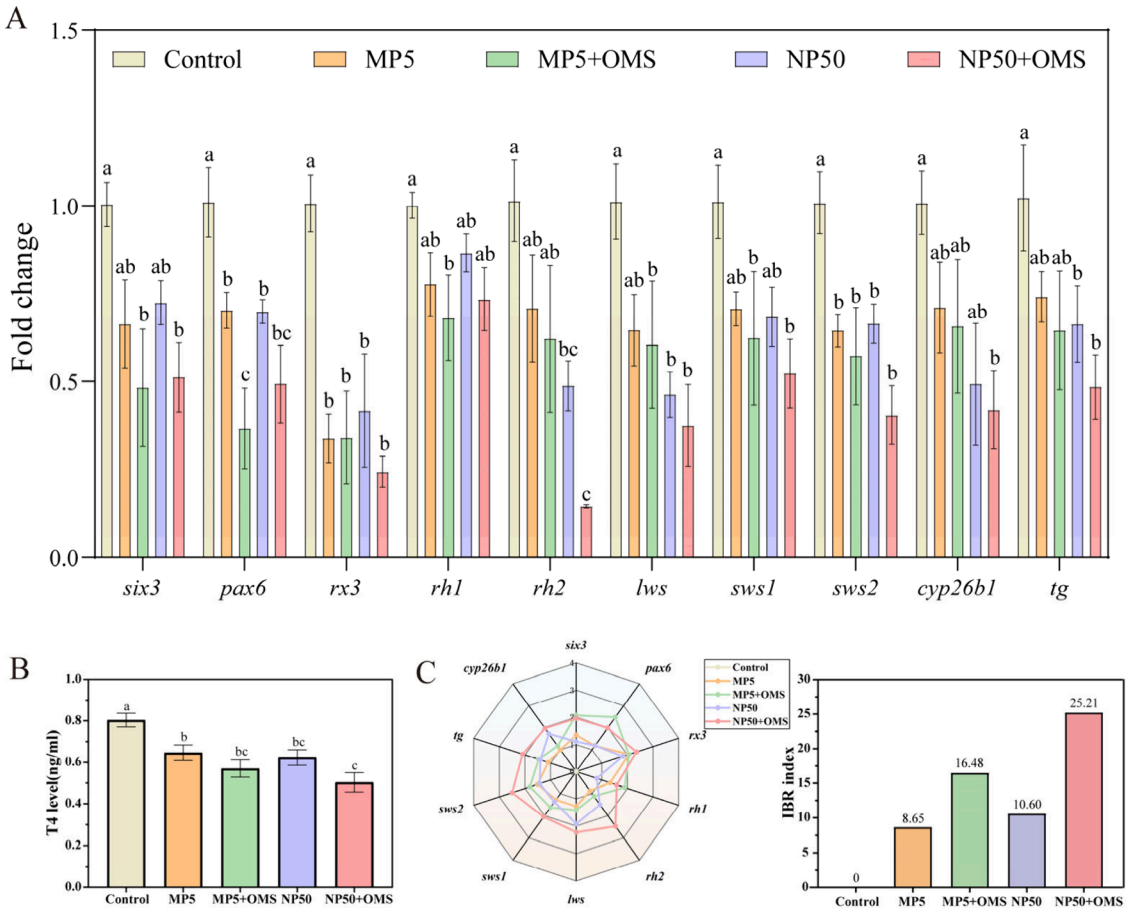

Figure 4. Effects of MNPs and MNPs+OMS on gene expression related to visual development in marine medaka. (A) The transcriptional expression levels of visual development-related genes. (B) T4 content in different groups. (C) Graphical representation of IBR analysis. Radar plots (left) and IBR index (right) of biomarker data in different groups. The results are presented as mean ± SEM, and groups with different letters indicate significant differences ($P < 0.05$).

significantly increased locomotor behavior during dark periods compared with MNPs alone. This increased activity suggested that OMS corona intensified MNP-induced hyperactivity, potentially indicative of retinal damage.[18,28] Analysis of behavioral parameters indicated that smaller particles, such as NP50/NP50+OMS, more strongly influenced visually mediated behavioral responses in marine medaka larvae. Additionally, OMS corona exacerbated the effects of MNPs on visually mediated behaviors, leading to increased larval activity, potentially driven by enhanced retinal damage. The detailed behavioral results were provided in Text. S11.

Fish retinas consist of several distinct layers, including the RGL, IPL, INL, OPL, ONL, and PL (Figure 3A). Notably, the RGL thickness of larvae exposed to NP50 and MNPs+OMS significantly decreased, suggesting that visual signal transmission might be suppressed, thereby impairing vision (Figure 3B). However, the RGL and INL thicknesses in the MP5 group significantly increased. Moreover, the IPL thickness in larvae exposed to MNPs and MNPs+OMS all increased. These observed thickness increases may reflect a compensatory mechanism mediated by Müller glial cells to restore normal retinal functions,[29] as they can proliferate throughout retinal layers[30] and differentiate into progenitor cells for tissue repair.[31] The greater increases in RGL and INL thicknesses in the MP5 group compared with NP50 group may indicate that MP5 triggered physiological compensatory mechanisms that reduced retinal damage. However, OMS corona significantly reduced the RGL thickness in the MP5+OMS group, indicating that OMS corona exacerbated the retinal developmental damage caused by MP5. This may be because OMS corona enhanced the bioavailability of hydrophobic MPs, increasing their interaction with larval eyes.[25] Furthermore, fish behavioral responses typically depend on a fully developed retina, as structural changes can impair light sensitivity and lead to abnormal behaviors.[32,33] Compared with MP5, prolonged active time induced by increased scotophobia in larvae exposed to small particle sizes of NP50 may be associated with more severe retinal damage. Moreover, OMS corona may aggravate retinal damage, leading to vision impairment and hyperactivity in larvae exposed to MNPs.[18] Notably, the observed lens size increase may be linked to NP50 and NP50+OMS exposure, supported by their early developmental accumulation in the eyes (Figure S4) and prior evidence on nanoparticle-related lens changes.[34−36] These findings suggested a potential impact on lens development, highlighting the need for further investigation into the underlying morphological, molecular, and cellular mechanisms associated with MNP and MNP+OMS exposure. MNPs and MNPs+OMS induced apoptosis in the eyes of larvae, potentially causing vision impairment and other negative effects (Figure 3C).[37] Therefore, exposure to MNPs and MNPs+OMS may impair visual development by inducing apoptosis in the eyes of larvae. In particular, OMS corona may exacerbate the damage to visual function by increasing eye

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apoptosis, thereby altering behavioral responses. The detailed eye tissue results were provided in Text. S12.

Previous studies show inhibiting *six3*/*rx3* causes fish eye loss,[38,39] and *pax6* deficiency worsens eye defects in rats.[40] The significant downregulation of *six3*, *pax6*, and *rx3* expression in larvae exposed to MNPs and MNPs+OMS may impair retinal development (Figure 4A). Notably, OMS corona significantly reduced *pax6* expression in MP5-exposed larvae, exacerbating retinal developmental damage and potentially increasing light sensitivity-induced hyperactivity. Furthermore, rod cell protein (*rh1*) and cone cell proteins (*rh2*, *lws*, *sws1*, and *sws2*) genes were suppressed by MNPs and MNPs+OMS, suggesting impaired photoreceptor function and reduced sensitivity to light stimuli, which may contribute to behavioral abnormalities.[41,42] Hyperactivity observed in the larvae may be due to anxiety induced by scotophobia, exacerbated by photoreceptor damage. Since photoreceptors are predominantly located in the ONL layer of the retina, the downregulation of opsin genes may disrupt retinal development and function.[15] Previous study has indicated that thyroid hormones regulate the development of photoreceptors and color vision by binding to receptors in the ONL layer of the retina.[18] The expression of the thyroid hormone synthesis-related gene *tg* was significantly downregulated in larvae exposed to MNPs and MNPs+OMS, potentially impairing retinal function and triggering behavioral changes.[43] Meanwhile, Exposure to MNPs and MNPs+OMS significantly reduced T4 levels, indicating potential disruption of thyroid hormone synthesis, with OMS exacerbating the adverse effects of MNPs (Figure 4B). Moreover, retinoic acid (RA) signaling is critical for visual function as it regulates retinal polarity, the arrangement and orientation of retinal cells.[44] The downregulation of *cyp26b1* in the MNPs and MNPs+OMS groups may act as a compensatory mechanism in response to reduced photoreceptive protein production, aiming to restore RA signaling and photoreception.[18] This may explain why larvae exposed to MNPs+OMS displayed hyperactivity despite reduced light sensitivity. The IBR values of NP50/NP50+OMS groups were higher than those of MP5/MP5+OMS groups, suggesting that smaller NP50/NP50+OMS caused more severe visual toxicity in larvae (Figure 4C). Additionally, the high integrated response values show that eye development genes are key pathways for MNPs and MNPs+OMS (Tab. S2), regulating early development, while opsin genes control photoreceptor function later. Meanwhile, thyroid function and RA metabolism further affect eye development indirectly. The IBR values of MNPs+OMS groups were higher than those of MNPs groups, indicating that OMS corona exacerbated the molecular-level visual toxicity of MNPs. Thus, OMS corona may exacerbate visual toxicity by directly suppressing eye development genes and indirectly disrupting RA signaling, impairing thyroid hormone synthesis, and compromising opsin function. The detailed gene expression results were provided in Text. S13.

In conclusion, this study revealed that MNPs and MNPs+OMS induced retinal damage, cell apoptosis, and downregulation of visual development-related genes, explaining the observed eye malformations and visually mediated behavioral abnormalities in larvae. The differences in physicochemical properties between MNPs and MNPs+OMS contributed to their varying toxic effects on the visual system. Specifically, NP50/NP50+OMS exhibited greater visual toxicity than MP5/MP5+OMS, potentially due to their smaller size, enabling passive entry into the embryos. Additionally, OMS corona exacerbated MNP-induced visual toxicity by intensifying behavioral abnormalities, retinal damage, cell apoptosis, and the downregulation of visual development-related genes. This enhancement may be attributed to the increased bioavailability of MNPs facilitated by OMS corona. This study provides the first evidence that eco-corona amplifies MNP-induced visual toxicity in marine medaka (Text. S14).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.estlett.5c00289.

> Distribution of MNPs in marine environments, materials and solution preparation, characterization of MNPs and MNPs+OMS, behavioral test parameters, specific process of qRT-PCR, IBR analysis, eye developmental toxicity, additional result details, research limitations and future directions (PDF)

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Notes

The authors declare no competing financial interest.

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