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Impact of Micro and Nanoplastics on Inflammatory and Antioxidant Gene Expression in the Gastrointestinal System

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Micro and Nanoplastics (MNPs) are emerging contaminants characterized by particle sizes smaller than 5 mm and less than 1 µm, respectively 1. Microplastics (MPs) are categorized into primary and secondary sources of origin 2. Primary MPs are intentionally produced as tiny particles, such as microbeads, in personal care products. Secondary MPs are generated when larger plastic materials degrade owing to factors such as sunlight exposure, biological interactions, mechanical forces, and various environmental conditions 3, 4. MNPs are present in a wide range of ecosystems and affect both marine and terrestrial organisms. They can disrupt the feeding patterns, development, and reproductive processes of various organisms ^{5, 6}. Moreover, MPs can carry harmful pollutants, such as toxic chemicals 7 and antibiotic-resistant bacteria 8, thereby amplifying their negative effects on the environment 9. Recent studies have highlighted concerns regarding the presence of MPs in human tissues and bodily fluids 10. Studies have revealed that MPs are present in various human organ

systems, including the cardiovascular, digestive, reproductive systems respiratory, and Additionally, they have been identified in biological samples such as breast milk, urine, stool, and blood ^{12, 13}. Moreover, MNPs have been detected in a diverse range of food products, including fruits, vegetables, seafood, livestock (such as chicken), and drinking water. MPs contamination has been found in various food products, including beer, honey, sugar, cow's milk, and sea salt. Additionally, more than 220 marine species, such as mussels, oysters, clams, and shrimp, have been reported to contain these particles in their gastrointestinal tracts, making their way into numerous seafood products 14, 15. Therefore, upon ingestion, MNPs interact directly with the intestinal epithelium and are exposed to the local immune system, gut microbiota, and inflammatory bowel disease (IBD)16. IBD, which includes Crohn's disease and ulcerative colitis. affects over 6.8 million people globally, with cases in China projected to exceed 1.5 million by 2025 ¹⁷. Patients with IBD, with their compromised

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intestinal microenvironment, are particularly vulnerable to environmental particulate matter, such as MNPs, which can exacerbate intestinal damage ¹⁸. An in vivo study on mice exposed to MPs (10– 150 μm) at concentrations of 2, 20, and 200 μg/g over five weeks revealed an increase in gut microbial species, bacterial abundance, and flora diversity, along with enhanced secretion of proinflammatory cytokines ¹⁹. These interactions can have significant biological consequences, particularly through the modulation of gene expression ²⁰. Evidence indicates that exposure to MNPs disrupts the regulation of genes related to inflammation, oxidative stress, and gut barrier integrity, raising concerns about their potential effects on human health ^{21, 22}. An initial study found that oral exposure to MPs disturbs redox balance and activates the TLR4/NF-κB inflammatory signaling pathway in the intestines of mice. Consequently, this results in oxidative stress, inflammation, and intestinal epithelial cell apoptosis through the mitochondrial pathway, leading to intestinal barrier impairment, mucosal damage, and intestinal toxicity ²³.

Inflammatory Gene Expression

Studies have demonstrated that MPs can cause inflammatory damage in various murine organs TLRs/MyD88/NF-κB the signaling pathway in in vivo models 24. Prior studies have suggested that MPs may play a significant role in initiating inflammatory gene expression following activation of endogenous molecules released from damaged cells by contributing to intestinal dysbiosis and inflammation triggered by the activation of the Toll-like receptor 4 (TLR4) signaling pathway 19 TLR4, a crucial component of the innate immune system^{25, 26}. Once activated, TLR4 triggers two primary signaling pathways: MyD88-dependent and TRIF-dependent pathways, with the MyD88-dependent pathway mainly activating NF-kB. This activation promotes the production of pro-inflammatory cytokines, such as IL-6, TNF- α , and IL-1 β , as well as chemokines that help recruit immune cells to sites of infection or injury ^{27, 28}. Inflammatory processes contribute to tissue damage and disease progression in the body.

In addition to their inflammatory effects, MPs, such as polystyrene MPs (PS-MPs), exhibit significant cytotoxicity, even at the lowest tested concentrations. PS-MPs increase apoptotic cell counts and reduce cell viability 29. They also disrupt molecular markers, as indicated by elevated levels of LDH, ALT, and AST activity in the supernatants, along with reduced GST activity and SOD and GSH levels in liver organoids 30, 31. Elevated MDA levels further confirmed oxidative stress induced by PS-MPs. Additionally, PS-MPs caused lipid buildup, reduced ATP production, elevated ROS levels, and the release of proinflammatory markers, such as IL-6 and COL1A1. These effects are further intensified by hepatic and increased CYP2E1 HNF4A expression, which heightens the risk of fibrosis and steatosis. These findings highlight the potential of MPs to disrupt cellular and molecular homeostasis and trigger inflammation and oxidative stress, which may exacerbate underlying health conditions ²⁹.

Antioxidant Gene Expression

MNPs can produce reactive oxygen species, causing cellular damage and disturbing cellular balance upon ingestion^{30, 31}. In the gut, oxidative stress plays a crucial role in the activation of antioxidant defense mechanisms, particularly through the Nrf2 (Nuclear factor erythroid 2related factor 2) pathway 32. Under oxidative conditions, Nrf2 is activated and moves to the nucleus, where it attaches to antioxidant response elements ³³ in the promoters of antioxidant genes. These genes include those encoding enzymes such as glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase, which work together to neutralize ROS and protect cells from oxidative damage³⁴. However, the capacity of the gut to mount an adequate antioxidant response to MNP-induced oxidative stress may be insufficient, especially after prolonged or high-level exposure to these particles³⁵.

In addition to their direct effects on cellular

systems, MNPs can antioxidant alter gut microbiota, further influencing oxidative stress and inflammation. MNP-induced dysbiosis can lead to an imbalance in gut bacteria, which may exacerbate oxidative stress and disrupt the regulation of antioxidant gene expression 22. Changes in the microbiome may also affect the production of proinflammatory cytokines, thereby modulating the activation of antioxidant pathways ³⁶. The cumulative effect of these disruptions can impair the gut defense mechanisms, potentially contributing to the development of gastrointestinal disorders, such as IBD, colorectal cancer, and other diseases associated with chronic inflammation and oxidative stress ³⁷.

MNPs pose a significant threat to gastrointestinal health by interfering with the expression of important genes related to inflammation and oxidative stress. Comprehending these molecular interactions is essential for developing approaches to reduce harmful effects and protect human health.

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