EDITORIAL

Can Microparticles Contribute to Inflammatory Bowel Disease: Innocuous or Inflammatory?

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Microparticles in air pollution are well known toxicants, contributing to asthma, cardiovascular disease, and overall mortality (1, 2). Inhalation, however, is not the only route of exposure to microparticles. Significant quantities of titanium dioxide and silicate are swallowed, both as natural contaminants of food and as additives. In fact, more than 10^{12} particles per day are ingested (3). The paper in this issue of the journal by Ashwood *et al*. (4) proposes a reasonable question: are the soils, processed foods, and toothpastes that we swallow as innocuous as we have assumed?

With air pollution particulates, it is the populations at high risk who act as sentinels. People with asthma are especially susceptible to the effects of particulates, experiencing increased hospital visits on days with high particulate levels (1). With microparticles that are ingested, it may be the patients with Crohn's disease who provide early warning of potential toxicities. Crohn's disease, a devastating inflammation of the gastrointestinal tract, can result in a range of complications from nutritional deficiencies to bowel constrictions that require surgery (5). The worst cases can require removal of large portions of the bowel. Currently there is no cure for this disease, only treatments designed to suppress the immune response and manage the complications. Potential contributors to the disease include microbes, genetics, immunologic factors, psychological health, diet—and, as proposed by the current paper, microparticles. Previous work from this group investigated the hypothesis that microparticles may be associated with the disease. Indeed, microparticles do penetrate the gut epithelium, residing in macrophages of the gut-associated lymphoid tissue (6). An initial study of patients showed that a low microparticle diet was beneficial to Crohn's disease patients (7). However, a follow-up study, with a larger group of patients, did not confirm the original findings (8). An electron microscopy study of colon tissue obtained from patients with either cancer or Crohn's disease revealed microparticles in all 18 affected patients. No microparticles were found in samples from three controls (9). The authors suggest that the source of the particles could include dental materials, food, and drugs (9). The materials identified were inorganic, inert, and not obviously toxic. This current paper from the Powell group addresses an important question: How could toxicity arise from such an apparently innocuous group of particles?

The manuscript by Ashwood *et al*. explores a unique hypothesis, as follows: Ingested negatively charged titanium dioxide particles bind metal cations in the gut. Then, this new surface becomes coated with inflammatory bacterial anions. These molecules, recognized by pattern recognition receptors of the immune system, are the ubiquitous by-products of a well-colonized healthy intestine. Normally the defenses of the digestive tract epithelium, including mucus and IgA, prevent penetration of these toxins into the intestinal interstitium. But particulates cross this barrier, and might serve as carriers. The toxins, such as lipopolysaccharide (LPS), are the mediators that cause the septic shock of a systemic bacterial infection. If they do penetrate the gut with a particulate carrier, immune system activation and inflammation will be the result.

As a model, the Ashwood *et al*. paper uses titanium dioxide particulate, calcium as a bridging cation, and LPS as the bacterial inflammatory molecule. They show that indeed titanium dioxide particles mixed with calcium ions will bind LPS. When this conjugate is then introduced to monocytes, the receptor for LPS, CD14, is lost from the cell surface, an indication of uptake by the cells. Then they confirm apoptosis of the monocytes by formation of a subdiploid peak of flow cytometry, indicating that the DNA of the cells is fragmented.

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The most important finding, however, is that inflammation occurs as well. Macrophage inflammatory protein-1 alpha is released because of conjugate exposure, whereas monocyte chemoattractant protein 1 is reduced, suggesting a Th1 type inflammation. Other elevated mediators include interleukin-1β (IL-1β), tumor necrosis factor-α, and interleukin-6—above the levels that could be attributed to calcium and LPS. Finally, the ratio of interleukin-1 receptor antagonist to IL-1β is dramatically reduced.

Thus, the particulates we ingest on a daily basis in processed foods, in toothpaste, and as soil contaminants may cause inflammation in the digestive tract. This may occur or be more important in a susceptible population, for example, in patients with Crohn's disease. The next step is clear: an *in vivo* model to confirm that the inflammation—seen *in vitro*—might contribute to diseases such as Crohn's or cancer.

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