

Commentary

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Microparticles in Crohn's disease – has the dust settled?

Crohn's disease is likely to be the result of a combination of host and environmental factors. The disease process is becoming better defined and both inherited and acquired determinants of the mucosal immune response are probably important host factors. Thus the gene product of the recently identified disease susceptibility locus on chromosome 16 is an example of the former,¹ while some interesting new results on in utero measles exposure,² are an example of the latter. The predominance of Crohn's disease in developed countries and its increasing incidence suggest a specific environmental trigger. Notably, measles virus and mycobacteria have been proposed, but data on these are inconsistent and largely unsupported by the known epidemiological and anatomical distribution of the disease. A normal gut flora is a prerequisite for intestinal inflammation in animals with genetically altered mucosal immunity,³ while diversion of the faecal stream away from inflamed bowel considerably improves Crohn's disease.⁴ These findings suggest that luminal antigens derived from the intestinal microflora play an important part but while a number of such pathogens could initiate inflammation,^{5,6} it may be their mode of presentation to the mucosa that is the important trigger.

In 1987 Shepherd *et al*⁷ described dark granular pigment cells at the base of Peyer's patch lymphoid tissue as a consistent feature of both healthy and diseased bowel. We have extended this work and recently reported a detailed chemical and ultrastructural analysis of the pigment, which is composed of tiny particles (<0.1–0.7 μm) of highly inert oxides of titanium, aluminium, and silicon.⁸ It turns out to be of dietary origin, much of it from food additives, and many billions of such microparticles are ingested daily. As these microparticles are chemically and biologically undegradable, and are of the correct size to be taken up by the specialised epithelial M cells on the surface of lymphoid aggregates, they progressively accumulate throughout life and remain like tattoos in tissue fixed macrophages at the base of the lymphoid follicles. Although such microparticles were probably first introduced into our diet near the beginning of this century, our exposure to them has greatly increased in the past 50 years, chiefly in the developed world.

In this issue, the study of Lee and colleagues (see page 231) have examined the effects of intradermal administration of inorganic particles to healthy people and to patients with Crohn's disease. The outcome measures were clinical and histological responses, and in either group, there was little tissue reaction. These results suggest that, at least intradermally, the particles are not immunogenic in themselves in either health or Crohn's disease. It is probable however, that the gut immune response to particles differs from that of the skin; for example, the major antigen presenting cells in the gastrointestinal tract are phenotypically phagocytic⁹ while many in the skin are dendritic. Indeed the MALT epithelium of the gut is more closely comparable with that of the lung and particle related diseases are

well described and increasingly recognised as a health risk.¹⁰

The microparticles used by Lee *et al* are present in huge numbers in the gut wall and have two properties that may make them potent adjuvants when given together with antigenic material. Firstly, they have enormous surface areas (for example, 300 m^2/g for food additive titanium dioxide) that are chemically reactive and allow the rapid adsorption of antigen. Secondly, they can protect antigen from normal cellular processing or enzymatic degradation. The super abundance of potential antigens, proinflammatory biomolecules, and metal cations in the intestinal lumen means that a range of molecules are avidly adsorbed to the surface of ingested particles. These modified particles may fundamentally change the intestinal immune response to antigens. Oral tolerance is partly maintained by not processing soluble luminal antigens, which is in considerable contrast with particulates, and hence adsorption of soluble antigen to a microparticle may stimulate an effector immune response.¹¹ Furthermore, only particulate exogenous antigens are processed by phagocytic cells and presented with MHC class I molecules to generate CD8 cytotoxic lymphocyte responses.¹² Finally, the interaction of biomolecules, such as lipopolysaccharide¹³ and immunoglobulin,¹⁴ with specific surface receptor systems during particle phagocytosis can potentially trigger the production of the pro-inflammatory cytokines interleukin 1 and tumour necrosis factor α .

The delivery of antigen loaded on particles has important implications, not only for carrying protein intact through the gastrointestinal tract and delivering it to the mucosa, but also in the subsequent immune response that may be elicited. Rather than placing emphasis on specific antigens, it may be their mode of presentation to people with inherited or acquired sensitivity that is more important.

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