the points indicated. Dissociation can result from either compression (isothermal) or temperature rise (8). Present modeling of this behavior is phenomenological and is based on treatment of the fluid as an average of pure molecular and monatomic hydrogen equations of state (9). The latter is treated as a metallic fluid with one adjustable parameter designed to reproduce shock data on H_2 and D_2. At present, different theoretical approaches are used to explain the measured isotherm and shock data. A consistent understanding of all available thermodynamic data and the recent conductivity data on H_2 and D_2 under stepwise loading (6) represents an important and exciting scientific challenge.

In principle, the experimental procedures used by Da Silva *et al.* (5) will be valuable for other low–atomic number materials, including energetic compounds. We conclude by noting several important experimental needs: longer pulse durations to examine materials where dissociations or other processes may not be complete in 8 to 10 ns; direct measurements of pressure and particle velocity histories at high energy densities and high compression to provide information about the time evolution of dissociation or other changes; and time-resolved temperature measurements and other spectroscopic data, because these provide important insight into the material processes of interest. For temperature measurements, recent developments using Raman spectroscopy (*10*) can be used to measure temperatures as low as 1500 K by monitoring the intramolecular vibration in H_2 and D_2.

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IMMUNOLOGY

The Chameleon Within: Improving Antigen Delivery

James L. Madara

The spaces inside the gut and the lungs are continuous with the outside world, exposing the adjacent tissues to toxic and pathogenic threats from the environment. The body protects these tissues by lining the airways and intestines with a single layer of epithelial cells, joined cell to cell by gasketlike intercellular tight junctions. This surface barrier protects the organism, but also prevents the efficient uptake of environmental antigens that is required for successful oral vaccination and immunization. Normally, antigens and pathogens in the gut can only penetrate the barrier through infrequent gateway cells called M cells. Now on page 949 of this issue, Kernéis *et al.* (*1*) point the way toward manipulating these essential participants of the immunization process. The authors describe how to stimulate the conversion of the epithelial cells that normally line the intestine (enterocytes) to an M cell lineage, which can efficiently transport antigens across the intestinal barrier to the underlying immune system.

Beneath the epithelial lining of the lungs and gut, bits of lymphoid tissue make up the organized mucosa-associated lymphoid tissue. The rare M cells are located over these subepithelial lymphoid follicles, termed Peyer's patches (*2*). M cells can transport soluble and particulate antigens across their cytoplasm (transcytosis), and use this ability to sample lumenal antigens, which then trigger the induction of secretory immunity—the process by which mucosal surfaces of the gut and lung are bathed with protective antibodies. A basal pocketlike invagination in M cells (see the figure) creates a space in which lymphocytes, macrophages, and possibly dendritic cells gather. Lumenal antigens transcytosed by M cells are thus immediately delivered to these antigen-processing and -presenting cells, which then migrate to antigen-specific lymphocytes in underlying lymphoid follicles and induce their proliferation. This process results in the development of IgA–producing B cells, some of which move into the vasculature and then back to the mucosal surfaces, efficiently seeding specific mucosal immunity (*2*).

Mechanistic study of this M cell–initiated immune response pathway has been limited, because M cells are scattered and few (<0.1% of epithelial cells). Further, the M cell lin-

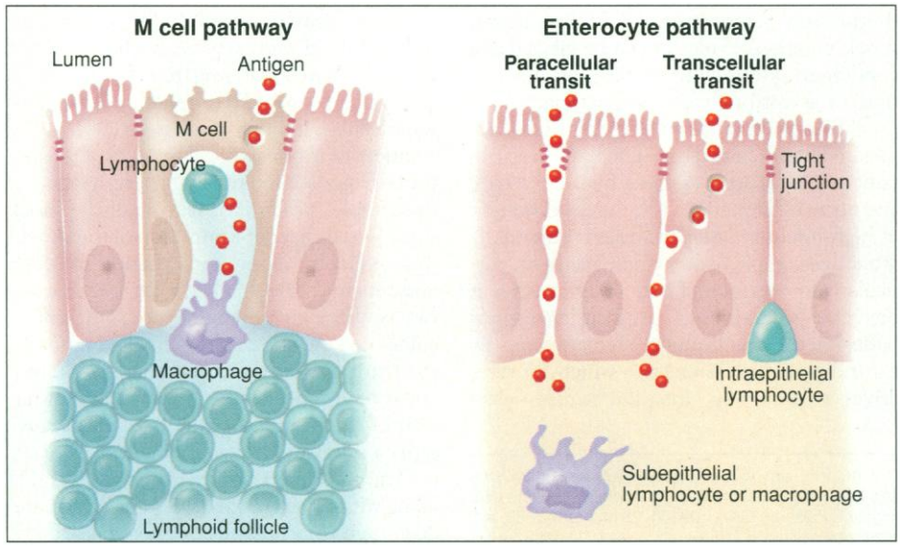

ILLUSTRATION: K. SUTLIFF

Paths across the lining of the gut. Antigens can enter the body from the gut through rare M cells (left), specialized to deliver antigen directly to underlying immune cells, or through the more common enterocytes (right), the epithelial cells that line the gut.

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eage exhibits an overall structural-functional phenotype, but has no completely specific marker. Consequently, there is no in vitro or in vivo model of M cell development available for study. Kernéis *et al.* (*1*) now lead us forward on two fronts: They identify a system in which enterocytes can be induced to switch to an M cell phenotype; and they demonstrate that the information available for this phenotype switch is provided by lymphocytes derived from the Peyer's patches that underlie M cells. The next step will be the identification of the triggering molecule or molecules, which could be used to transiently augment mucosal antigen uptake, an ability that could have a major impact on methods and efficiency of oral vaccination.

Although M cells are committed samplers of lumenal antigen at mucosal surfaces, other pathways for transepithelial delivery of ingested antigen exist as well. Enterocytes normally constitute most of the surface area of the intestine, and it is possible that antigen is shuttled directly across (transcellular) or between (paracellular) this major cell population (see the figure). For example, transient, reversible increases in tight junction permeability to lumenal peptides occur naturally as a consequence of activation of certain apical membrane transport systems (*3*). For example, enhanced peptide permeability of the paracellular pathway by activation of an apical glucose transporter can successfully enhance immune responsiveness to specific lumenal antigens in a model of mast cell–mediated mucosal anaphylaxis (*4*). Other forms of short-term perturbation of the tight junction barrier, for example, by a cholera-derived toxin (ZOT), are likewise capable of enhancing delivery of peptides by way of the paracellular pathway (*5*).

Antigen movement across the enterocyte may also be a regulated event. Using cholera toxin as a model by which movement of an apically bound protein can be traced biochemically, Lencer *et al.* have demonstrated that model enterocytes are capable of direct transcytosis of apically bound cholera toxin B subunit (*6*). In addition, this B subunit, which directs its own transcytosis, is a potent adjuvant for orally delivered antigens (*7*). Indeed, under certain conditions, enterocytes themselves can directly present antigen (*8*). Together, these observations suggest that delivery of oral vaccines might also be enhanced by harnessing the transcellular pathway of the major enterocyte population for antigen delivery and perhaps even initial antigen processing.

A key consideration concerning antigen delivery either across enterocytes converted to the M cell phenotype, or by the paracellular or transcellular routes of unmodified enterocytes, is the immunologic microenvironment of the immediate subepithelial space (see the figure). It is doubtful that induction of new M cells alone, without parallel induction of underlying lymphoid follicles, would have the same functional consequences for antigen delivery as would a normal M cell–lymphoid follicle organization. Additionally, because intestinal immune responses may be cellular or secretory and can result in both inflammation and tolerance, consideration of the underlying immunological microenvironment to which an antigen is delivered will be critical. For example, transgenic animals in which the junctions of enterocytes have been disrupted (by expression of a targeted, dominant-negative mutation of the critical junctional organizing protein E-cadherin) develop a morphologically detectable cellular immune response when junctions in both the superficial (villus) and deep (crypt) mucosa are affected (likely permitting paracellular leak of antigen throughout the mucosa) (*9*). In contrast, similar perturbations restricted to the superficial mucosa display no comparable induction of an immune response. These studies imply that exposure to lumenal antigen may have markedly different consequences depending on the mucosal subcompartment in which exposure takes place and emphasize the importance of the subepithelial microenvironment in determining immunological responses.

Cytokines and other soluble or cell surface signals can drastically modify the function of enterocytes, as well as the expression of enterocyte surface molecules thought to be integral to epithelial–immune cell interactions (*10*). If the trigger for the enterocyte to M cell conversion shown by Kernéis *et al.* is a cytokine, it may turn out that lymphocyte-derived mediators alone can redirect vesicular trafficking pathways in epithelial cells, potentially providing another way to improve the efficiency of oral vaccination. Strategies that expand this efficiency enough to allow bulk movement of antigen may follow, a feature that would also permit improved oral drug delivery.

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MOLECULAR BIOLOGY

Telomerase and Retrotransposons: Which Came First?

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Evolution is opportunistic. New cellular mechanisms can evolve from any genetic material available within a cell. This adaptability means that self-replicating genetic elements, such as transposable elements or viruses (cellular parasites), could be recruited for important cellular functions. But this opportunism could work both ways. A gene that supplies a cellular function could become a parasite, if given the ability to self-replicate. An important key to our understanding of which scenario applies to telomeres—specialized structures at the ends of chromosomes—is provided on page 955 of this issue (*1*) and in a previous issue of *Science* (*2*). Because conventional DNA polymerases cannot complete the synthesis of both strands of a blunt-ended DNA template, early eukaryotes adopted the telomere as a mechanism to stably maintain the ends of linear chromosomes. The new reports provide a clear connection between telomerases, the enzymes that synthesize telomeres, and retrotransposons, small elements of DNA that can autonomously move from one part of the genome to another.

Eukaryotic telomeres are composed of tandem arrays of short nucleotide sequences (*3*). The probable mechanism of telomere sequence addition was first revealed by identification of the RNA subunit of telomerase and the demonstration that this RNA provides the template for nucleotide addition (*4*). A short region of the RNA subunit is repeatedly copied with the 3′ hydroxyl at the DNA terminus as a primer. Because the puta-

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