JCI The Journal of Clinical Investigation

In This Issue

John Ashkenas

J Clin Invest. 2001;107(5):531-531. https://doi.org/10.1172/JCI119921.

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ER stress in inflammatory bowel disease (See article on pages 585– 593.) Eukaryotic cells respond to the accumulation of unfolded proteins in the endoplasmic reticulum (ER) through a pathway termed the ER stress response. Although aspects of this pathway differ from yeast to mammals, the role of certain upstream effectors, including the Ire1 proteins, has been conserved, and the pathway in all cases induces the synthesis of protective ER chaperone proteins. The mouse Ire1α protein is ubiquitously expressed and is essential early in development, but Bertolotti and colleagues now show that the related protein Ire1β, which is found in the stomach and intestines, plays a more subtle role. Mice lacking this isoform develop normally, but, taking a cue from the restricted expression of Ire1beta;, the authors examined the mutant mice for a defect in the gastrointestinal tract. The gastric epithelium in Ire1beta;-/- animals appears normal but proves to be hypersensitive to the effects of dextran sodium sulfate, an irritant that induces the ER stress response and provokes inflammatory bowel disease in mice. Epithelial cells in mutant mice show higher base-line levels of the ER resident chaperone protein BiP and of activated MAP kinase, which acts both in the unfolded protein response in the ER and in similar cytoplasmic pathways - phenotypes that might be expected if the absence of Ire1beta; […]

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By John Ashkenas, Science Editor

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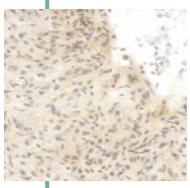
Eukaryotic cells respond to the accumulation of unfolded proteins in the endoplasmic reticulum (ER) through a pathway termed the ER stress response. Although aspects of this pathway differ from yeast to mammals, the role of certain upstream effectors, including the Ire1 proteins, has been conserved, and the pathway in all cases induces the synthesis of protective ER chaperone proteins. The mouse Ire1α protein is ubiquitously expressed and is essential early in development, but Bertolotti and colleagues now show that the related protein Ire1β, which is found in the stomach and intestines, plays a more subtle role. Mice lacking this isoform develop normally, but, taking a cue from the restricted expression of Ire1β, the authors examined the mutant mice for a defect in the gastrointestinal tract. The gastric epithelium in *Ire1β*$^{-/-}$ animals appears normal but proves to be hypersensitive to the effects of dextran sodium sulfate, an irritant that induces the ER stress response and provokes inflammatory bowel disease in mice. Epithelial cells in mutant mice show higher base-line levels of the ER resident chaperone protein BiP and of activated MAP kinase, which acts both in the unfolded protein response in the ER and in similar cytoplasmic pathways — phenotypes that might be expected if the absence of Ire1β leaves the gastric mucosa unprotected in the presence of damaging levels of unfolded proteins in the secretory pathway. Evidently, Ire1α and other sensor proteins can activate unfolded protein responses to some extent, but in the absence of Ire1β they do not allow for normal cellular homeostasis in this tissue.



Genomic analysis of pathogenic and benign gastritis bacteria

(See article on pages 611–620.)

Infection with the mucosal resident bacterium *Helicobacter pylori* can lead to a series of diseases of the gut, culminating in some cases in gastric adenocarcinomas. Still, most long-term *H. pylori* carriers are apparently unharmed by the bacterium, perhaps because they are protected by some genetic or environmental factors or because only a subset of *H. pylori* strains are virulent. Work in a gerbil model of *H. pylori* infection argues for the latter possibility, and Israel et al. have now used whole genome analysis to examine the genetic differences between two strains, B128 and G1.1, that differ in their effects on host cells. When studied in live animals or in culture, B28 consistently induces higher levels of inflammatory cytokines and a greater degree of epithelial cell death than does G1.1. Both strains carry a large chromosomally inserted element called the *cag* pathogenicity island, where multiple genes are found that influence interactions between the bacterium and the host cell. However, by analyzing the two strains with an *H. pylori* gene microarray, Israel and colleagues find that the relatively benign strain, G1.1, carries a large deletion that removes 18 genes from this element. The authors focus on one gene, *cagE*, and show that disruption of this single gene in a B128 background yields a strain whose effects in culture and in vivo mimic those of G1.1. For more on the uses and challenges of genomic analysis of pathogenic bacteria, see the Perspective by Kato-Maeda et al. (in this issue, p.533) and other articles in our ongoing series on bacterial polymorphisms.

Witnessing clonal deletion in action

(See article on pages 555–564.)

Clonal deletion of self-reactive T cells within the thymus represents an important protection from autoimmune disease. Unfortunately, this mechanism depends on the availability of self-antigens in the thymus, so it would seem to be of limited use for developing tolerance to peripherally expressed proteins, and indeed, many disease-related autoantigens are proteins with limited distribution. However, proteins that play their normal physiological roles elsewhere may also be expressed in the thymus, where they can be presented to developing T cells by thymic dendritic cells (DCs) or macrophages. Pugliese and coworkers now report that thymic DCs themselves express and present insulin and other pancreatic proteins that are known autoantigens in type 1 diabetes. Remarkably, these self-antigen–presenting DCs can be seen in histological preparations surrounded by T cells that are undergoing apoptosis, presumably because they are specific for the self-epitope presented by the neighboring DC. One surprise from this work concerns the transcriptional regulator AIRE, which has been implicated in the expression of certain peripheral proteins by thymic epithelial cells. Pugliese et al. find AIRE expressed in other cells in the thymus but not in self-antigen–presenting DCs, suggesting that the this organ uses several cell types and mechanisms to express these proteins and thus to promote tolerance to potentially dangerous autoantigens.