at this time to implicate one specific adhesin–receptor interaction as more relevant than another for understanding pathogenesis, for predicting the outcome of infection in individuals or populations, or for use as a therapeutic target that is generally applicable (e.g. for vaccine production).

We do not know to what extent the *H. pylori* adhesin–Lewis b (Le^b) receptor interaction in our transgenic model simulates interactions that occur in human gastric ecosystems. Nonetheless, we believe the potential value of this type of model is to simplify the ecosystem so that the role of bacterial adhesion in pathogenesis can be assessed under more-controlled conditions. By using a given bacterial strain, a given genetically defined transgenic host with an engineered receptor that recognizes adhesins produced during colonization by that strain, and genetically identical nontransgenic littermates as controls, it becomes possible to address the issue of whether and how attachment affects bacterial and/or host gene expression, as well as disease outcome. For example, DNA microarray techniques can be employed to catalogue whole bacterial and host genome transcriptional responses to attachment. Changes in bacterial gene expression as a function of attachment can be examined using promoter trap strategies[1].

One final point raised by Dorrell *et al.* revolves around the issue of molecular mimicry between epitopes produced by colonizing bacteria and epitopes expressed by host cell lineages. Such mimicry appears to underlie the attachment-related production of antibodies that cross-react with bacterial lipopolysaccharide (LPS) and host parietal cell epitopes in our Le^b model. However, just as adhesin–receptor interactions must not be stereotyped, analysis of the role of molecular mimicry in pathogenes is should not be limited by trying to promote the relevance of a particular epitope to a general population. A more-profound understanding is needed of how attach-ment affects the expression of bacterial and host epitopes and how bacterial epitopes are presented and processed by the, as yet, poorly understood gastric mucosal immune system.

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Reference

1 Valdivia, R.H. and Falkow, S. (1997) *Trends Microbiol.* 5, 360–363

Response from Borén and Arnqvist

The article by Dr Dorrell *et al.* points to the complexity and diversity of *Helicobacter pylori* as the contributing factor in a multitude of gastrointestinal diseases. Macrorestriction patterns have revealed extensive variation in *H. pylori* genomic organization[1]. However, comparison of the *H. pylori* genome sequenced by The Institute for Genomic Research (TIGR)[2] and the second *H. pylori* genome sequenced by Genome Therapeutics/Astra[3] suggests a high degree of gene and sequence conservation. For subsequent host adaptation, *H. pylori* might use systems that favor gene recombination events, possibly aided by the activity of transposons in combination with mechanisms of natural competence for transformation. This is exemplified by the acquisition of the virulence-associated *cag* pathogenicity island (PAI)[4]. A flexible genetic system would also have the potential to select for an optimal set of adherence mechanisms, by phase-variation mechanisms. This scenario would adapt *H. pylori* to the different microecological host environments that it will encounter during the colonization process (e.g. gastric or duodenal epithelial tissues, the mucus layer, cells of the immune systems and connective tissues).

The importance of microbial adherence as a virulence factor, particularly in turbid environments such as the gastrointestinal and urinary tracts, is well established for several microbial pathogens (see Ref. 5 for an update). In gastric biopsy material, ~5–20% of *H. pylori* cells adhere to the epithelial cell surfaces, but the majority of cells are located in the mucus layer that covers the epithelial cells. There is probably an equilibrium between microbial adherence properties (i.e. the different adhesin proteins) and flagellar-mediated motility/chemotaxis that is optimized for the specific individual host environment[6].

Several receptor candidates have been described for *H. pylori* (reviewed in Ref. 7), most of which are present in a variety of vertebrate tissues; however, specific adherence of *H. pylori* to gastric epithelial cells *in vitro* seems to be restricted to human and primate tissue[8]. We identified the gastric surface mucous cell receptor as the Lewis b (Le^b) histo-blood group antigen, which is abundant in the human gastrointestinal lining[9]. The high receptor specificity for this human-specific histo-blood group antigen is intriguing and suggests that the host and tissue tropism for human and primate gastric mucosa is dependent on the receptor–ligand interaction. The *H. pylori*–Le^b antigen interaction also has an unusually high affinity constant (in the range of 10^{10} M^{-1})[10]. Such a high affinity is rare for protein–carbohydrate interactions and suggests that the Le^b receptors are used by the microorganisms for targeted and specific attachment to the surface mucous cells. High affinity binding is also important for obtaining nutrients and modulating immune responses. Once on the cell surface, additional receptors, such as sulfatides and phospholipids, might contribute to the intimate adherence process (reviewed in Refs 5,7).

As Dr Dorrell *et al.* indicated, we identified and purified the adhesin

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protein BabA (blood group antigen binding adhesin) by the novel ReTagging technique, which uses multifunctional affinity-tagged cross-linkers[10]. The corresponding gene belongs to a family of related outer membrane proteins (OMPs), which have been described by TIGR. Another interesting group of potential adhesin proteins, the Alp proteins[11], is also a member of this OMP family and might be the result of recombination events and subsequent phase variation/shift in the fine receptor specificity, as discussed above. These results support the notion that *H. pylori* strains with different degrees of virulence exist, as suggested by the Type 1 (VacA and CagA positive) and Type 2 definitions, because the Le^b-antigen binding activity strongly correlates with the presence of the *cag* PAI (Ref. 10) [i.e. the virulent (ulcer-associated) Type 1 strains].

For future vaccine strategies against *H. pylori* and acid peptic diseases and gastric cancer, it has been suggested that the virulent Type 1 strains should be targeted[12]. From this perspective, biologically conserved structures, such as the carbohydrate-binding domains of adhesin proteins, such as BabA, have an interesting potential as vaccine candidates[13].

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References

1 Jiang, Q. *et al.* (1996) *Mol. Microbiol.* 20, 833–842
2 Tomb, J.F. *et al.* (1997) *Nature* 388, 539–547
3 Hancock, R.E.W. *et al.* (1998) *Nat. Biotechnol.* 16, 216–217
4 Covacci, A. *et al.* (1997) *Trends Microbiol.* 5, 205–208
5 Karlsson, K-A. (1998) *Mol. Microbiol.* 29, 1–11
6 Kirschner, D.E. and Blaser, M.J. (1995) *J. Theor. Biol.* 176, 281–290
7 Ilver, D. *et al.* (1997) in *Pathogenesis and Host Response in Helicobacter pylori Infections* (Moran, A.P. and O'Morain, C.A., eds), pp. 16–27, Normad Verlag
8 Falk, P., Borén, T. and Normark, S. (1994) *Methods Enzymol.* 236, 353–374
9 Borén, T. *et al.* (1993) *Science* 262, 1892–1895
10 Ilver, D. *et al.* (1998) *Science* 279, 373–377
11 Odenbreit, S., Till, M. and Haas, R. (1995) *Mol. Microbiol.* 20, 361–373
12 Blaser, M.J. (1997) *Lancet* 349, 1020–1022
13 Langermann, S. *et al.* (1997) *Science* 276, 607–611

Command, control and communication in bacterial pathogenesis

Stephen C. Winans

As recently as a few years ago, it was thought that the exchange of chemical signals between bacteria was the exception rather than the rule. A few examples of interbacterial signaling had been well described, including the bioluminescence regulatory systems of *Vibrio fischeri* and *Vibrio harveyi* (which are astonishingly dissimilar at the molecular level), the conjugal transfer system of *Enterococcus faecalis*, the development of multicellular fruiting bodies of *Myxococcus xanthus* and the production of antibiotics by *Streptomyces* spp.[1] However, most other bacteria were assumed not to use intercellular signals. Furthermore, although these regulatory systems were fascinating subjects of research, none seemed terribly fundamental to human health and welfare.

In the early 1990s, many new examples of interbacterial signaling systems were reported in rapid succession. Some of these systems use acyl homoserine lactones, similar to the 3-oxohexanoyl homoserine lactone signal used by *V. fischeri*[2], as pheromones. In this family, the pheromone, called an autoinducer, is usually synthesized by a protein related to LuxI and binds to a receptor protein that resembles LuxR. Receptor–pheromone complexes are thought to bind to target promoters to activate their transcription. Gram-positive bacteria have not yet been reported to use autoinducer-based signaling systems, but many of these bacteria use oligopeptide pheromones for interbacterial signaling[3]. These pheromones are synthesized by ribosomes and are generally made as pro-proteins containing signal sequences that guide export from the cytoplasm and are then removed by signal peptidases. Some peptide pheromones bind to the periplasmic domains of transmembrane receptors, whereas others are imported by ABC-type uptake systems and bind to cytoplasmic receptors. Pheromone-based bacterial regulatory systems have been termed 'quorum sensing' systems,

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