Commentaries

H. pylori and Lewis antigens

Lipopolysaccharide (LPS) of many Helicobacter pylori strains expresses Lewis antigens (Le⁺, Le⁻, Le⁺, Le⁻) which are similar to those expressed by gastric epithelial cells ("molecular mimicry"). In addition, H. pylori LPS displays phase variation in these antigens—that is, the high frequency, reversible switching of phenotype; for instance, a strain that expresses Le⁺ may yield variants that express Le⁻. As yet, no definite role has been assigned to these Lewis antigens, nor to phase variation, in the pathogenesis of gastric disease.

In this issue of Gut (see page 18), Zheng and colleagues report that H. pylori strains isolated from Asian peptic ulcer patients express two or more Lewis antigens more often than strains from non-ulcer dyspepsia patients (89.6 vs 73.2%; p=0.035). What could be the link between H. pylori Lewis antigen expression and the development of pathology in the host?

1. Lewis antigens induce pathogenic antibodies. On infection, H. pylori LPS may induce anti-Le⁺ antibodies that bind not only to bacteria but also to host gastric epithelium, followed by complement fixation and tissue destruction. However, although high titres of antibodies to H. pylori LPS are found in the serum of infected patients, these antibodies are not autoreactive and not directed against Le⁺ (see Yokota and colleagues).

2. Lewis antigen mimicry provides persistence through immune evasion. Analogous to ABO blood group antigens, a host that expresses Le⁺ would be able to form anti-Le⁺ antibodies but not antibodies directed at Le⁻. Consequently, Le⁺ positive bacteria infecting a Le⁻ positive host would escape immune attack and be able to persist while an Le⁻ positive strain would not be able to persist. Experimental infection in monkeys confirms this concept: a H. pylori strain isolated from Le⁺ positive monkeys expressed mainly Le⁻; the same strain expressed mainly Le⁺ after colonisation of Le⁺ positive animals. This indicates that expression of the H. pylori Lewis phenotype depends on the host; adaptation can occur by means of phase variation followed by selection through anti-Le⁺ antibodies. Two of three studies in humans, however, failed to demonstrate the existence of a correlation between the phenotypes of the host and pathogen. Moreover, it has been shown that strains expressing Le⁺, and strains expressing Le⁻, can be isolated from the same patient. Finally, a shift in H. pylori Le⁺ antigen expression would be driven by anti-Le⁺ antibodies and there is no evidence that these are formed in infected patients.

3. Lewis antigens are involved in adhesion and colonisation. Expression of Le⁺ is crucial for in vivo colonisation of mice: mutants with inactivated β1,4-galactosyltransferase or α3-fucosyltransferase genes (S L Martin, submitted) expressed no Le⁺ and colonised less well than their Le⁺ positive parent strains.

How would Le⁺ expression affect colonisation? Recent data suggest that Le⁺ plays a role in adhesion. A monoclonal antibody (Mab) specific for H. pylori LPS inhibited adhesion to gastric epithelial cells; this Mab was specific for Le⁺ (B J Appelmelk, H. Yamaguchi, unpublished). Strains knocked out in galE or rfbM, genes involved in the biosynthesis of Le⁺, did not adhere to gastric tissue sections. In addition, synthetic Le⁺ bound to human gastric epithelial cells from some hosts but not from all (T Boren, unpublished). Studies in gastritis patients demonstrated that H. pylori strains that strongly expressed Le⁺ caused a higher colonisation density than strains that expressed Le⁺ weakly. These data suggest that expression of Le⁺ enhances colonisation through increasing adherence. They also predict the existence of a gastric Le⁺ binding lectin. Experimental studies confirmed this: Le⁺ binding polypeptides of 16–29 kDa are found in gastric epithelial cells; the identity of these proteins is unknown. Independent studies have shown that surfactant protein D, a 120 kDa lectin belonging to the innate defence system and expressed in the stomach, can also interact with H. pylori LPS; which part of the LPS is recognised is unknown.

Thus a role for LPS/Le⁺ in adherence seems likely. This role is not absolute: Le⁺ negative mutants can adhere as strongly as their Le⁺ positive parents (T Boren, unpublished), and Le⁺ negative strains colonise human hosts well. Thus an Le⁺-lectin interaction may contribute to adhesion for only some strains and only in part of the hosts. For example, the adhesin BabA is important for adhesion of H. pylori and recognises Leb expressed by gastric epithelium; only H. pylori strains that do not express BabA or strains that colonise humans that do not express Le⁺ might need their Le⁺ antigens for adhesion. In this concept, LPS phase variation allows detachment of bacteria not expressing Le⁺ and hence transmission to another host; subsequently, switch back variants expressing Le⁺ adhere and colonise a new host.

Adhesion of H. pylori has clinical relevance: strains from ulcer patients more often express BabA compared with strains from gastritis patients. What is the link between adherence and development of host pathology? Firstly, increased adherence may lead to an increased bacterial burden. Secondly, studies in mice showed that increased adherence did not necessarily lead to increased colonisation density but to closer contact between bacteria and gastric epithelial cells. A more intimate contact enhances the cross talk between microorganism and host and may lead to activation of transcription factor NF-κB and host signal transduction pathways. This induces IL-8 production and inflammation, and finally, ulceration. This sequence of events is in agreement with data that show that increased Le⁺ expression in H. pylori is associated with increased neutrophil infiltration.

In summary, current data, including those provided by Zheng and colleagues, are in agreement with the hypothesis that H. pylori LPS Lewis antigens play a role in adhesion and inflammation; LPS phase variation may be essential for host-to-host transmission. To conclude, after several years of intensive research on H. pylori LPS structure, genetics, and biosynthesis we may finally start to understand the biological role of H. pylori Lewis antigens.
A little rest and relaxation

In healthy subjects and in patients with mild to moderate gastro-oesophageal reflux disease, gastro-oesophageal reflux occurs mainly during transient lower oesophageal sphincter (LOS) relaxations.1-3 Transient LOS relaxations are a neural reflex, organised in the brain stem, with efferent and afferent pathways travelling in the vagus nerve.4 Distention of the proximal stomach is a major trigger for the reflex to occur, although stimulation of the pharynx or the larynx may also contribute.5 It is clear that the initiation of the reflex requires activation of gastric mechanoreceptors.6

Because of their pivotal role in the occurrence of gastro-oesophageal reflux, the neurophysiology and pharmacology of transient LOS relaxations are topics of intense ongoing research. Atropine is one of the drugs that were recently shown to inhibit gastro-oesophageal reflux by inhibiting transient LOS relaxations.5 It is unclear if atropine is acting at the level of the stomach, by altering the mechanosensitivity of the proximal stomach, or at the level of the brain stem, by interfering with central integrative processing.

In this issue of Gut, Lidums and colleagues7 used a gasometric barostat procedure to study the influence of atropine on proximal gastric tone and on the occurrence of transient LOS relaxations in healthy subjects (see page 30). Atropine caused prolonged relaxation of the proximal stomach after a meal and decreased the rate of transient LOS relaxations. By comparing the effects on proximal gastric tone and on the rate of transient LOS relaxations, the authors concluded that the inhibitory effect of atropine on transient LOS relaxations was most likely at the central level.8

The nature of the fundic mechanical receptors involved in triggering postprandial transient LOS relaxations is still poorly understood. Based on animal studies it has been proposed that mechanoreceptors are positioned either in series or in parallel to smooth muscle fibres. In parallel, mechanoreceptors respond to stimuli that elongate the stomach wall while in series, mechanoreceptors respond to stimuli that increase the tension within the stomach wall.9-11 Figure 1 illustrates the responses of tension mechanoreceptors (in series) and elongation mechanoreceptors (in parallel) to different stimuli (distention, relaxation, and contraction of smooth muscle). In series, mechanoreceptors are activated during distention and contraction and are inactivated during relaxation. In parallel, mechanoreceptors are activated during distention and relaxation and are inactivated during contraction. Animal studies suggest that gastric mechanoreceptors with afferents in the vagal pathways are primarily tension receptors.9-11

Gastric distention, the best studied trigger of transient LOS relaxations in humans, results in elongation as well as increased wall tension of the stomach. Hence it is unclear which of these two types of mechanoreceptors initiates the afferent limb of the reflex. Administration of atropine prolongs relaxation and thus elongation of the proximal stomach after a meal. Hence if the mechanoreceptors involved in triggering transient LOS relaxations were elongation receptors, atropine should have enhanced transient LOS relaxations.6

The influence of administration of atropine on activation of tension receptors in the gastric wall after a meal is less clear. Attempts have been made to differentiate tension from elongation following the law of Laplace:

\[ T = \Delta P r^2 \]

where \( T = \) wall tension, \( P = \) pressure, and \( r = \) radius.8 In the present study, intragastric pressure was kept constant by

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the barostat device, and postprandial intrabag volume, and thus the radius, was maintained higher after atropine. If calculated according to the simplified law of Laplace, a higher wall tension after a meal results from administration of atropine. However, use of the Laplace formula requires a number of assumptions that are not necessarily fulfilled under the given circumstances: the wall of the stomach is infinitely thin, the intragastric balloon and stomach are assumed to have a perfect spherical shape, and the pressure external to the stomach is known and is evenly distributed. Most importantly, wall tension in the proximal stomach has both passive and active components. The Laplace formula, most suitable in a passive tension model, do not take into account the modulatory effects of changes in the contractile state of the proximal stomach which may occur reflexly or in response to neurohumoral or pharmacological modulation. During a process of gastric relaxation, such as that which occurs during accommodation of a meal or after administration of atropine, wall tension is likely to fall because of diminution in the active component of wall tension. In the presence of an intragastric barostat bag, keeping intragastric pressure constant and above the level of intra-abdominal pressure and thus providing a continuous drive for low level distension, it is impossible to estimate the true effect on wall tension. However, it seems reasonable to assume that, under the conditions of the present study, wall tension was not decreased after a meal in the presence of atropine. Consequently, if the mechanoreceptors involved in triggering transient LOS relaxations were tension receptors, atropine should have enhanced transient LOS relaxations in the present study.

Based on these underlying assumptions, the authors correctly state that whatever the mechanoreceptors involved, under the conditions of the present study, relaxation of the proximal stomach would be expected to increase the rate of transient LOS relaxations. In support of this notion, fundic relaxation induced by sumatriptan was associated with an increased rate of transient LOS relaxations and gastro-oesophageal reflux. Furthermore, slow infusion of lipids into the duodenum induces gastric relaxation and increases the rate of transient LOS relaxations, both of which are prevented by pretreatment with a cholecystokinin receptor antagonist. Hence atropine induced inhibition of transient LOS relaxations is most likely due to its action at the level of the central nervous system. This does not preclude the possibility of influencing the occurrence of transient LOS relaxations through an effect on proximal gastric tone. A successful peripherally acting approach would, however, require knowledge of the type of mechanoreceptor involved in triggering transient LOS relaxations. In the case of a tension receptor, relaxation of the proximal stomach should decrease the occurrence of transient LOS relaxations. In the case of an elongation receptor, enhanced gastric emptying or redistribution of a meal to the distal stomach should decrease the rate of transient LOS relaxations. Identification of the type of mechanoreceptor involved in triggering transient LOS relaxations in humans is likely to require an innovative approach, avoiding the undistinguishing influence of gastric distention.

J TACK
D SIFRIM

Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, University of Leuven, Leuven, Belgium

Correspondence to: Ditect J Tack, Department of Internal Medicine, Division of Gastroenterology, University Hospital Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium. Email: Jan.Tack@med.kuleuven.ac.be

6 Painal A. A study of gastric stretch receptors: their role in the peripheral mechanism of satiation of hunger and thirst. J Physiol (Lond) 1954;126:255–70.
diagnostic biopsy. Secondly, expression of various MMPs and TIMPs correlated with the histological degree of intestinal inflammation, but did not depend on its aetiology.

However, there are many explanations for the obviously quite different matrix metabolism in UC and CD. mRNA and protein quantification do not allow us to draw conclusions as to the biological activity of the MMPs, the majority of which are secreted as inactive proenzymes that have to undergo a complex proteolytic processing to become fully active. MMP processing is brought about by plasmin, furin-like proteases, or MMPs themselves (with MMP-3 and MMP-14 playing prominent roles as proactivators of other MMPs), with the proactivators again being tightly regulated.4 Furthermore, matrix degradation is usually restricted to small cell membrane associated compartments whereas the great mass of MMPs remains inactive and complexed to TIMPs. Thus mere quantification does not tell us anything about the temporospatial expression of the various MMPs or TIMPs.

Fortunately, the cell types responsible for MMP expression in normal and inflamed intestine in vivo are fairly well defined, thanks to several studies using in situ hybridisation, in part in combination with cell type specific markers.16 Although this knowledge may allow some extrapolation, determination of the focal proteolytic activity of individual MMPs in vivo defies current technology. The picture is further complicated by promi-

What determines the partly divergent evolution of the lesions in UC and CD? Are there differences in the overall or localised expression of other MMPs, MMP proactiva-

The usefulness of corticosteroids and immune suppressive s such as azathioprine which act mainly on lymphocytes underscores the relevance of activated T cells, and the often dramatic improvement in complicated CD with TNF-α blockade may derive, at least in part, from inhibition of MMP activation favouring for example, closure of fistulas. TNF-α blockade does not appear to be equally effective in UC where in contrast, interferon alpha (IFN-α), a TH1-like cytokine, may be promising. The domain for quantification of MMPs, as exemplified in the two present reports, may be to monitor such therapies and, by extension of the spectrum of the molecules analysed, to find better and more specific predictors of disease activity in UC and CD. A novel therapeutic approach could be blockade of certain MMPs, such as MMP-3, by local or systemic application of synthetic MMP inhibitors. Much industrial research effort has been invested in the development of such compounds for treatment of tumours or osteoarthritic joint destruction.
Heparin and inflammation: a new use for an old GAG?

Since its discovery in 1917, heparin has been a fascinating, and in a way elusive, molecule. Heparin is a glycosaminoglycan (GAG) formed by repeated sulphated oligosaccharide units. Natural preparations of heparin (usually obtained from bovine lung or porcine intestinal mucosa) can vary in the length of the polymeric unit and therefore have different molecular weights. As such, the biological actions of this GAG can vary quantitatively between different batches of the molecule. The initial activity ascribed to heparin was its capacity to prolong the biological actions of this GAG can vary in the length of the polymeric unit and other genes involved in mucosal remodelling may be found that more specifically reflect the underlying aetiology. Their use in future therapeutic trials is awaited with much interest.  

D SCHUPPAN  
E G HAHN

Department of Medicine I, Gastroenterology and Hepatology, University of Erlangen-Nuernberg, Germany

Correspondence to: Dr D Schuppan, Department of Medicine I, Division of Gastroenterology, Hepatology and Infection, University of Erlangen-Nuernberg, Krankenhausstr. 12, 91054 Erlangen, Germany.  
Email: detlef.schuppan@med1.med.uni-erlangen.de


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not with CD62L or CD11a/CD18. The authors concluded that heparin blocks CD11b mediated cellular events such as firm adhesion and in this manner this GAG can effectively interfere with the process of leucocyte extravasation that is central to the host inflammatory response. The observation of Salas and colleagues' will undoubtedly give impulse to this line of research.

In conclusion, the novel study published in this issue of Gut has shed further light on the biological activities of heparin. Fragments of this natural product may in the future lead to the development of novel drugs with a wide range of clinical uses in the treatment of inflammatory diseases, including those of the gastrointestinal system.

M PERRETTI

Department of Biochemical Pharmacology,
William Harvey Research Institute,
St Bartholomew’s and the Royal London School of Medicine and Dentistry,
Charterhouse Square, London EC1M 7BQ, UK

C P PAGE

Sackler Institute for Pulmonary Pharmacology,
5th floor Hodgkin Building,
Guy’s King’s and St Thomas’ School of Biomedical Sciences,
King’s College London, Guy’s Campus, London SE1 9RT, UK

Correspondence to: Dr M Perretti. Email: M.Perretti@qmw.ac.uk

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