Chapter 6
Helicobacter pylori, Experimental Autoimmune Encephalomyelitis, and Multiple Sclerosis

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Abstract *Helicobacter pylori* (*H. pylori*) is a common human pathogen which has been implicated in the pathogenesis of peptic ulcer disease and stomach cancer. *H. pylori* colonizes the stomach of about half the globe's population, and its decline in the developed world coincided temporally with an increase in autoimmune and inflammatory disease. The hygiene hypothesis or "old friends" hypothesis have been proposed to explain this inverse link. Indeed, while *H. pylori* affects the innate immune system and induces strong cellular and humoral immune responses, it also has developed the ability to induce strong regulatory immune mechanisms to allow its persistence; these include, but are not restricted to, regulatory T cells (Treg cells).

Epidemiological and experimental evidence suggests a protective effect on autoimmune and inflammatory conditions including asthma, inflammatory bowel disease, and multiple sclerosis. The mechanisms of this protective effect are likely to be complex and include Treg cells, other immunoregulatory processes, and other host- and *H. pylori*-associated factors. Some of these have been explored in studies

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in the experimental autoimmune encephalomyelitis models and are currently being investigated in multiple sclerosis.

On the other hand, a positive association has been found between *H. pylori* and neuromyelitis optica.

This chapter reviews and discusses the immune response to *H. pylori*, with emphasis with immunoregulatory mechanisms, its pathogenicity-associated genes, and the evidence for its effects on neuroinflammatory diseases.

Keywords *Helicobacter pylori* • Immunomodulation • T cells • Dendritic cells • Multiple sclerosis

Helicobacter pylori

Helicobacter pylori is a very common Gram-negative bacterial pathogen (Fig. 6.1), which colonizes the gastric mucosa of almost half of all people on the planet [40, 59]. The infection is usually acquired in early childhood and persists lifelong unless antibiotic treatment is given [13]. Chronic colonization with *H. pylori* is the leading cause of peptic ulceration and gastric adenocarcinoma. Over 90 % of those with duodenal ulceration and over 70 % of those with gastric ulceration are infected with *H. pylori* [59]. Despite this very strong causal link, these outcomes only occur in a small proportion of those infected. The lifetime risk of peptic ulceration for those infected is just 10 %, and the risk of developing gastric adenocarcinoma is 2–5 % [12, 105, 135]. Gastric adenocarcinoma is the fifth most common malignancy [36] and the third leading cause of cancer-associated deaths worldwide [40]. *H. pylori* was classified as a human carcinogen over 20 years ago [78] and is the biggest modifiable risk factor for the development of gastric adenocarcinoma. The risk is three to six times higher when the infection

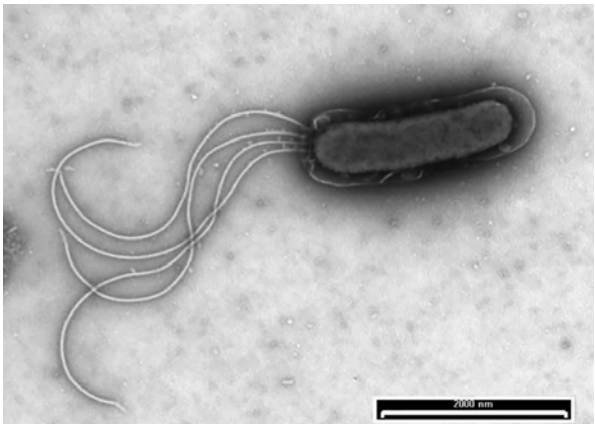

Fig. 6.1 Electron micrograph of a negatively stained preparation of *H. pylori*

is present [36, 40, 59, 130]. Disease is thought to occur due to an interplay of many different factors such as virulence factors expressed by the colonizing strain, host genetics and nature of the immune response, and environmental factors (particularly smoking and diet) [13, 44, 58, 72]. There is also evidence that the infection contributes to increased risk and/or severity of a number of extragastric conditions. These include iron deficiency anaemia, growth retardation in children, and some autoimmune conditions including neuromyelitis optica (NMO) and idiopathic thrombocytopenic purpura (ITP) [147, 171].

The prevalence of *H. pylori* around the world has been declining over the last five decades, and fewer children are now infected [13, 18]. In many developing countries, *H. pylori* remains present in over 80 % of the population, whereas in developed parts of the world, the prevalence is below 20 % overall, and less than 10 % of children are infected. A number of factors are thought to contribute to this, including common antibiotic use in children [105, 135, 186]. Exposure to infectious organisms, particularly during childhood, is thought to be important for the development of a healthy immune system. This was originally referred to as the "hygiene hypothesis" [174], but it has now been renamed the "old friends hypothesis" with realization that modernization diminishes access to many of the necessary immunoregulatory exposures [149]. These include intestinal helminths and gut commensal bacteria, ticks, and soil mycobacteria [8, 106, 117, 149, 150, 183]. *H. pylori* is now emerging as an important member of this group.

Reduced prevalence of the infection is beneficial, preventing peptic ulceration and gastric cancer; however recent evidence suggests that a lack of exposure to *H. pylori* may have adverse consequences. Over the last 60,000 years, human physiology has developed in concert with *H. pylori* in the stomach [13, 87]. Autoimmunity, allergy, asthma, inflammatory bowel disease, and other chronic conditions have become more common as the infection has declined [77, 163]. There are multiple reports of a correlation between *H. pylori* infection and reduced risk of immune and inflammatory diseases, including autoimmune disorders such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis and coeliac disease [90, 107, 158, 171], allergic asthma [10, 25], and inflammatory bowel disease [30, 151]. The mechanisms behind many of these associations are thought to involve *H. pylori*-mediated immunomodulation [10].

The Immune Response to *H. pylori*

H. pylori stimulates a strong host response in vivo, which in the first instance involves inflammatory cytokine and chemokine expression by gastric epithelial cells. These factors attract the infiltration of neutrophils, macrophages, dendritic cells (DCs), NK cells, and lymphocytes, and a strong antibody is also elicited [133, 146, 175]. The epithelial barrier interacts with both *H. pylori* and the underlying immune cells. The level and type of the immune response vary, depending on factors such as innate recognition of the bacteria and host genetic differences. Genetic

polymorphisms, such as those in cytokine and Toll-like receptor genes, influence the severity of the inflammatory response, which in turn affects the risk of disease development [54, 103].

Innate Immunity and Inflammation

As with the vast majority of infections, initial detection of *H. pylori* occurs via pattern recognition receptors (PRRs). These include Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which bind specific pathogen-associated molecular patterns (PAMPs) such as lipopolysaccharide (LPS), flagellins, and cell wall peptides [169]. *H. pylori* is unusual as it has evolved mechanisms to minimize PRR activation [157], presumably so that it can maintain persistent colonization of the gastric mucosa. For example, its tetra-acetylated LPS is poorly recognized by TLR4 [45, 116], and the *flaA* gene contains a mutation which dramatically reduces flagellin binding to TLR5 [7]. Despite this, *H. pylori* PAMPs do activate PRRs. TLR2 appears to be the main receptor for LPS [121, 170], but TLR2 is also activated by other components including heat shock protein 60 (HSP60) and *H. pylori* neutrophil-activating protein (HP-NAP) [169]. In addition, interactions of the cytotoxin-associated gene pathogenicity island (*cag* PAI)-encoded type IV secretion system (T4SS) with host epithelial cells result in NOD1 activation and increased pro-inflammatory gene expression [180]. This occurs via transfer of soluble peptidoglycan components into the cytoplasm [185]. Such interactions generally result in increased interleukin 8 (IL-8) expression by epithelial cells and increased IL-6 secretion from dendritic cells and macrophages.

Pro-inflammatory chemokines and cytokines, such as IL-8, IL-1β, tumour necrosis factor alpha (TNFα), IL-6, IL-12, CCL2-5, CCL20, and CXCL1-3, are upregulated in the *H. pylori*-infected gastric mucosa, and the expression of homing receptors is also increased [42, 52, 134, 192, 195]. This leads to the recruitment of immune cells, including neutrophils, macrophages, dendritic cells, NK cells, and lymphocytes; however *H. pylori* has multiple immune evasion strategies [13]. Neutrophils and macrophages attempt to control the infection by phagocytosis; however *H. pylori* prevents the oxidative burst and can survive intracellularly [4, 162]. *H. pylori*-derived arginase also inhibits nitric oxide production [67]. Both M1 and M2 macrophages are present in the infected gastric mucosa [88, 141], and macrophage-derived cytokines have an important influence on the development and balance of damaging and immunomodulatory T helper subset responses [119].

There is a paucity of data on invariant lymphocytic cells (ILCs) and NK cells during *H. pylori* infection; however NKT cells are more abundant in the gastric mucosa [125], and increased numbers of NK cells have also been detected in the peripheral blood [153]. The inflammatory cytokine response of NK cells may be modulated by exposure to *H. pylori* [154].

There are also increased numbers of dendritic cells (DCs) in *H. pylori*-infected gastric tissue from humans [24, 129] and mice [3, 50]. These are $CD11c^+$, indicating

that they are of a myeloid type (mDC) [24, 83, 129]. Oertli et al. [129] showed that mucosal DCs tend to be DC-SIGN$^+$, HLA-DR^{hi}, CD80^{lo}, and CD86^{lo} and have a semi-mature and tolerogenic phenotype. Reduced numbers of pDCs have been found in the peripheral blood of *H. pylori*-infected adults with ITP, a disorder caused by autoreactive antibodies against platelets, but mDC populations were unaffected [156].

Adaptive Immunity

Strong IgG and IgA antibody responses are detected in *H. pylori*-infected individuals [191], and this may contribute to pathogenesis by triggering autoimmunity. The molecular mimicry of host antigens by *H. pylori* elicits an antibody response which reacts with human antigens such as the parietal cell H^+, K^+-ATPase in the gastric mucosa [46]. These autoreactive antibodies are commonly found in the serum of infected patients and may be responsible for increasing local inflammation and tissue damage in the stomach or contribute to extra-gastric autoimmune conditions.

The T-cell response to *H. pylori* infection includes both CD4$^+$ T helper (Th) and CD8$^+$ cytotoxic T cells, but most research has focussed on the Th response. Increased numbers of CD8$^+$ cells are present in the gastric mucosa and peripheral blood of infected humans and the stomachs of *H. pylori*-infected mice [63]. These contribute to *H. pylori* inflammation and disease, possibly by expressing cytokines such as IL-17 [32, 178].

The main Th subsets induced by *H. pylori* infection are pro-inflammatory Th17 and Th1 and anti-inflammatory regulatory T-cell (Treg) populations [5, 56, 140, 148, 165]. Increased numbers of these cell types have been found in the gastric mucosa and peripheral blood of infected donors [42, 172, 187]. Th cells orchestrate the nature of the host response, are thought to be an important contributing factor in determining *H. pylori*-associated disease risk, and have an important impact on *H. pylori*-mediated protection from immune and inflammatory diseases.

Th1 cells primarily secrete interferon-gamma (IFNγ) and TNFα and induce macrophages to secrete further pro-inflammatory mediators and have more bactericidal activity [76, 139]. Th17 cells secrete IL-17A, IL-17 F, IL-21, and IL-22, and these also exert important antibacterial and inflammatory effects including the expression of antimicrobial peptides, stimulation of reactive oxygen and nitrogen species, and augmented chemokine expression, leading to neutrophil recruitment (reviewed by [118, 190]). In *H. pylori*-infected mice, the induction of a Th17 response occurs in conjunction with a Th1 response, leading to more severe gastritis [133, 168]. Release of the cytokine B-cell activating factor of TNF family (BAFF) from macrophages exposed to *H. pylori* plays an important role in the differentiation of Th17 cells [119]. *H. pylori* may be adapted to direct the immune system away from a pro-inflammatory Th1/Th17 response and towards a predominant anti-inflammatory Treg response in order to allow persistence [82]. Peptic ulceration is more frequently found in those with a reduced Treg response [148, 166]. Tregs may act in a bystander

manner by secreting immunosuppressive cytokines such as IL-10 and transforming growth factor beta (TGFβ) to modulate inflammation, or they may act in an antigen-specific manner via a myriad of mechanisms (reviewed in [2]).

H. pylori-Induced Immunomodulation

Immunomodulatory Mechanisms

H. pylori infections are usually established in early childhood [51], when the immune system is developing and there is a bias in favour of immunomodulatory responsiveness. The main *H. pylori*-mediated mechanism being investigated in the research field is the stimulation of Tregs. Increased numbers of Tregs are present in the gastric mucosa and peripheral blood of *H. pylori*-infected patients [42, 101, 143, 148, 187]. The infection is well known to protect against allergic asthma in a mouse model [9]. Infected animals had significantly reduced airway hyperresponsiveness, with lower levels of allergen-specific serum IgE, and pulmonary infiltration of Th2 cells, Th17 cells, and eosinophils. The protective effects were strongest in mice that had been infected as neonates and were conferred by Treg cells. *H. pylori* induces DC differentiation into a tolerogenic type, which promotes the differentiation of naive T cells into Tregs [57, 128, 129].

In addition, expression of the co-stimulatory molecule B7-H1 is upregulated in gastric epithelial cells during *H. pylori* infection. Interaction of T cells with this molecule suppresses T-cell activity [48]. *H. pylori* engagement of dendritic cell-specific intercellular adhesion molecule 3-grabbing non-integrin (DC-SIGN) also caused reduced pro-inflammatory gene expression [71] and modulation of damaging T helper 1 (Th1) subset responses [22]. It has been shown that oral doses of *H. pylori* DNA could substantially reduce the severity of murine colitis models [75, 102]. This was accompanied by increased expression of IL-10 and reduced expression of IL-17 in the draining lymph nodes and mucosal tissues of these mice. These protective effects were also proposed to be mediated through dendritic cells.

IL-10 and TGFβ are known to be upregulated in the serum and gastric mucosa of infected patients, and low levels correlate with increased disease risk. The cellular source of these suppressive factors is not restricted to T cells, but also includes gastric epithelial cells, B cells, monocytic cells, and DCs [23, 61, 82, 95, 188].

H. pylori *Virulence Factors and Immunomodulatory Molecules*

A number of pro-inflammatory molecules, toxins, and adhesins expressed by *H. pylori* are known to increase the risk of developing gastroduodenal disease via effects on both gastric epithelial cells and immune cells. In addition to their disease-contributing effects, some of these factors are also reported to have potent

immunomodulatory activity. They could therefore play a role in *H. pylori*-mediated protection against autoimmune and inflammatory diseases.

Vacuolating Cytotoxin A (VacA) VacA has multiple effects on epithelial immune cells [43]. This pore-forming toxin permits the passage of anions and small molecules through epithelial cell membranes and generates a great number of vacuoles in cultured epithelial cells [92]. The *vacA* gene is present in almost all *H. pylori* strains, but is polymorphic with three areas of biologically important variation [147]. The signal region and intermediate region determine cytotoxic activity and may be of types s1 or s2 and i1 or i2, respectively. The mid-region determines binding to host cells and may be either m1 or m2. s1/i1/m1 forms of VacA are the most active. Many reports from around the world show strong associations between infection with strains expressing more active VacA types and incidence of peptic ulcer disease or gastric adenocarcinoma [14, 15, 62, 84, 110, 111, 121, 144, 152].

VacA also interacts directly with immune cells, and this is thought to have immunomodulatory consequences. Binding to activated human T cells occurs via the β2 (CD18) integrin receptor subunit [167]. VacA inhibits the activation and proliferation of human B and T lymphocytes [182]. In Jurkat T cells, VacA inhibits IL-2 production and downregulates the expression of IL-2 receptor-α, via inhibition of the nuclear factor of activated T cells (NFAT), and blockade of calcium influx and calcineurin activation of the IL-2 promoter [27, 66, 160]. However, VacA inhibition of proliferation in primary human $CD4^+$ T cells was achieved in an NFAT- and IL-2-independent manner, and acid activation of VacA markedly increased its suppressive potency. This suggests that VacA interferes with T-cell proliferation via multiple mechanisms [176].

VacA may also exert immunosuppressive effects via antigen-presenting cells. Exposure to VacA results in downregulation of MHC class II, inhibition of DC maturation, and a reduced capacity for antigen presentation [86, 114]. Experiments in mice have shown that VacA reprogrammes DCs to a more tolerogenic phenotype, which induces the differentiation of naive T cells into Tregs. This has been implicated as a mechanism for *H. pylori*-mediated protection against asthma and other allergic diseases [10, 128, 157]. Recent data has shown that these effects may be induced via infection or through the administration of purified VacA [57].

Gamma-Glutamyl Transpeptidase (GGT) GGT is a potent virulence factor that causes damage to the gastric epithelium. It stimulates inflammatory responses in gastric epithelial cells, with activation of the nuclear factor kappa B (NF-κB) transcription factor, and the generation of reactive oxygen species. This is thought to lead to DNA damage in the gastric mucosa and thus contribute to carcinogenesis [31, 49, 68]. GGT is an essential factor for *H. pylori* colonization in mice [34], most likely by enabling the bacteria to use extracellular glutamine and glutathione as a source of glutamate [145]. In addition to its contribution to virulence, GGT also has potent immunomodulatory activity [161]. It suppresses T-cell activation, proliferation, and cytokine expression during infection, and, in addition to VacA, it plays a key role in *H. pylori*-mediated protection against allergic asthma in mice [128]. The mechanism behind these effects has recently been shown to involve glutamate deprivation of T cells in the gastric mucosa [193].

Cytotoxin-Associated Pathogenicity Island The best known virulence determinant of *H. pylori* is encoded by the cytotoxin-associated gene pathogenicity island (*cag* PAI) [180]. *cag* PAI-positive strains are more commonly associated with peptic ulceration and gastric adenocarcinoma [137]. It encodes components of a type IV secretion system (T4SS) which delivers CagA into gastric epithelial cells. Upon entry to the cytoplasm, CagA is phosphorylated by Src kinases and activates MAP kinase signalling and NF-κB to induce multiple cellular effects [127]. Cellular interactions with the T4SS pilus by itself also result in activation of NOD1, MAP kinase pathways, and the NF-κB and AP-1 transcription factors [29, 69, 89]. These cascades stimulate disruption of the cell cycle, increased apoptosis, and inflammatory cytokine and chemokine expression, leading to a greater risk of peptic ulcer disease and gastric malignancy [16, 26, 122, 123, 134, 180]. Although the *cag* PAI is linked to increased inflammation and disease risk, there are some reports of CagA and $CagA^+$ strains having immunomodulatory activity. Stronger IL-10 and Treg responses are present in those infected with *cagA*+ strains [74, 148], and these infections also provide stronger protective associations with asthma [33]. CagA-dependent T-cell priming in infected mice is also thought to be important for inducing Treg differentiation [85]. Additionally, it has been shown that CagA can inhibit the mitogen-induced proliferation of human T cells [132].

Outer Inflammatory Protein A (OipA) OipA is also thought to be an important driver of disease, acting by enhancing mucosal inflammation [194, 196, 197]. A recent paper reported that recombinant OipA has a suppressive effect on the maturation of mouse spleen DCs in vitro [181].

***H. pylori* Neutrophil-Activating Protein (HP-NAP)** HP-NAP induces the secretion of IL-12 and IL-23 by neutrophils and monocytes, creating an environment which drives differentiation of T cells down the Th1 and Th17 pathways. It has been shown to modulate Th2 responses in humans and mice [5, 6, 35, 47]. For example, when HP-NAP was administered to mice undergoing allergen sensitization, lung eosinophils and serum IgE levels were reduced, and there were lower concentrations of Th2 cytokines in the lung [35].

Multiple Sclerosis and Its Animal Model, Experimental Autoimmune Encephalomyelitis

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory and neurodegenerative disease of the central nervous system (CNS), which predominantly affects young adults and represents a leading cause of neurological disability in this age group. Other age groups are also affected, from childhood to advanced age [38]. There are two main clinical courses of MS, on the basis of whether disease onset is characterized by an acute attack of neurological dysfunction or not. The most common form at presentation is relapsing-remitting (RR) MS, manifesting as recurrent attacks (relapses) of neurological dysfunction followed by periods of remission. After a variable period of time (typically 10–20 years), this is followed, in about 50 % of patients,

by a gradual progression, with or without superimposed relapses, called secondary progressive (SP) MS. The other main type of clinical course, observed in approximately 15 % of patients, is characterized by progressive neurological dysfunction from the onset and is called primary progressive (PP) MS [100].

Neuroinflammation in MS can involve any part of the CNS, and the most common manifestations are sensory, motor, and visual disturbances, bladder and bowel dysfunction, and balance problems [38]. Neuropathic pain and cognitive disturbances are also quite common and increasingly recognized. Mild to moderate fatigue is also extremely common in MS, and when it is severe, it can be one of the most disabling symptoms. Its mechanisms are poorly understood [79].

The pathogenesis of MS is multifactorial. On the basis of a genetic susceptibility to autoimmunity in general and CNS damage more specifically, environmental factors are thought to trigger damage directed towards CNS myelin [80, 124]. Amongst infectious environmental factors, exposure to herpes viruses during adolescence appears to play an important role. The strongest epidemiological links are with post-childhood exposure to Epstein-Barr virus (EBV; human herpesvirus 4, HHV4) [11]. Importantly, other infections, including early exposure to *H. pylori* may exert a protective effect not only against MS but also other immune-mediated diseases [41, 149, 179]. Noninfectious environmental factors thought to be involved as MS triggers include smoking and low vitamin D [19].

The target of the autoimmune response in MS is CNS myelin, which is produced by oligodendrocytes. Therefore, much study has gone into the identification of specific myelin protein targets. The most abundant protein components of CNS myelin, myelin basic protein (MBP) and proteolipid protein (PLP), are also expressed in the peripheral nervous system (PNS), which is not affected by MS, and are therefore unlikely to be primary targets of the autoimmune response. Myelin oligodendrocyte glycoprotein (MOG), on the other hand, is only expressed in the CNS and could be a more important target of immune-mediated damage. It is possible that once autoreactivity starts against one protein, it can then spread to other antigenic epitopes of the same protein or indeed to other myelin proteins [124, 142]. Every cell type of the immune system, serving the cellular and humoral, the innate and adaptive immune responses, is involved in the orchestration of the inflammatory demyelinating damage. Although the myelin sheath and the oligodendrocyte are considered the main targets of the pathological process, other neural cells are affected by MS. For example, it is the secondary damage to the demyelinated neuronal axons that correlates most closely with chronic loss of brain and spinal cord volume and with the accumulation of irreversible disability in MS [173, 184]. Microglia and astrocytes are also affected, displaying both protective and pathogenic features, as reviewed elsewhere [104, 109]. Experimental autoimmune encephalomyelitis (EAE), a useful albeit imperfect model of MS [39], has provided evidence for the involvement of adaptive and innate immunity in the induction of CNS inflammatory demyelination [138], as well as for the importance of the blood-brain barrier (BBB) in controlling the influx of inflammatory molecules (and consequently cells) from the peripheral circulation to the CNS. EAE has been criticized for the low rate of translational success of treatment from rodent models to human disease. Nevertheless, it has been the source of significant success in the development of some of the most effective treatments available for MS. It is discussed more extensively in recent reviews [17, 177].

Links Between *H. pylori* and Neuromyelitis Optica

Neuromyelitis optica (NMO) is an immune-mediated disorder of the central nervous system (CNS) preferentially affecting the optic nerves and the spinal cord. NMO patients tend to have serum IgG antibodies against the astrocyte water channel aquaporin-4 (AQP4), and this is a useful marker for distinguishing NMO from multiple sclerosis (MS) [20, 131]. Interestingly, AQP4 is also expressed by gastric acid-secreting parietal cells, and a recent study has shown that its expression in the gastric mucosa of mice is influenced by *H. pylori* infection [64, 108]. Patients with positive AQP4 serology and NMO also tend to have antibodies that react with gastric parietal cells [81].

Several papers have indicated a positive association between *H. pylori* infection and NMO. Li et al. [93] reported that rates of *H. pylori* serology were higher amongst AQP4 antibody-positive NMO patients. A second study also determined that *H. pylori* was significantly more common amongst NMO patients compared with healthy controls [98]. A further study of 116 Japanese NMO patients and 367 healthy controls reported that *H. pylori* was significantly more common amongst the AQP4 antibody-positive NMO group than the healthy controls. There was no difference between the controls and the AQP4 seronegative NMO group, however, and it was concluded that *H. pylori* infection is a risk factor for AQP4 antibody-positive NMO [200]. There has recently been a published case report of a patient presenting simultaneously with AQP4 seropositive NMO and ITP (an autoimmune platelet disorder associated with *H. pylori* infection) [112]. After eradication of *H. pylori*, the titre of AQP4 IgG was reduced, platelet counts returned to normal levels, and the symptoms resolved almost completely. In a further paper, it was shown that the *H. pylori* virulence factor HP-NAP may be associated with pathology and neural damage in AQP4 antibody-positive NMO, as there was a significant positive correlation between anti-HP-NAP serology, concentrations of the inflammatory marker myeloperoxidase in serum, and disability scale scores [93]. These papers all indicate a role for *H. pylori* in NMO. It therefore seems likely this association could be driven via induction of an autoreactive antibody response in the gastric mucosa.

Links Between *H. pylori* and Multiple Sclerosis

Epidemiology

Several epidemiological studies (Table 6.1) have reported a significantly lower prevalence of *H. pylori* infection amongst MS patients [41, 60, 94, 113, 189, 199]. Two case-control studies found that amongst MS patients, those with *H. pylori* had reduced levels of neurological disability [94, 113]. Others have failed to find any association between *H. pylori* infection and MS, however, and perhaps this is because of differences in the classifications of MS and NMO between studies, the methods used to determine *H. pylori* status, or small group sizes [65].

Factors such as gender, age, and social class have a strong influence on *H. pylori* infection rates, and it is more common in older people, in males, and in those of

Table 6.1 Summary of epidemiological studies on *H. pylori* and multiple sclerosis

Evidence for a negative association		Reference
Study of 90 Polish MS patients	18.9 % *H. pylori* seropositivity, much lower than the general prevalence rate in Poland	[189]
105 Japanese MS patients (divided into 52 with optico-spinal MS (OSMS) and 53 with conventional MS (CMS)) and 85 healthy controls	*H. pylori* seropositivity was lower in CMS patients compared with OSMS ($p=0.0019$) and healthy controls ($p=0.018$). Patients with CMS had a significantly lower disability score if *H. pylori* positive ($p=0.03$)	[94]
Case-control study of 163 Iranian MS patients and 150 age- and sex-matched healthy controls	*H. pylori* positive serology in 54 % of MS patients compared with 73 % of controls ($p<0.001$). Significantly reduced scores amongst the *H. pylori*-infected patients on the Expanded Disability Status Scale ($p=0.017$)	[113]
Study of 90 Japanese MS patients (none with NMO) and 177 healthy controls	Significantly reduced number of *H. pylori* seropositive patients amongst the MS group ($p=0.045$)	[199]
71 MS patients from the UK (48 with relapsing-remitting MS, 19 with secondary progressive MS, and 4 with primary progressive MS) and 42 age- and gender-matched healthy controls	21 % of MS patients were *H. pylori* seropositive, compared with 42.9 % of healthy controls ($p=0.018$)	[41]
550 Australian MS patients and 299 age- and gender-matched healthy controls	*H. pylori* seropositivity lower amongst MS patients compared to controls, but only statistically significant amongst females ($p=0.027$). *H. pylori*-infected females had lower disability scores than the uninfected females ($p=0.049$); however the reverse was true amongst the males ($p=0.025$). No association between *H. pylori* status and relapse rate	[60]
No evidence of an association		
145 Japanese MS patients and 367 healthy controls	No differences in anti-*H. pylori* antibody positivity between the groups	[201]
135 AQP4 antibody-negative Japanese MS patients (52 with OSMS and 85 with CMS) and 85 healthy controls	No significant difference in *H. pylori* seropositivity between the groups	[93]
Evidence for a positive association		
29 MS patients and 25 anaemic controls	Significantly increased proportion of *H. pylori*-infected patients amongst the MS group ($p=0.007$)	[65]

lower socioeconomic status [105]. In contrast, MS is more common in females of a higher socioeconomic status [115]. The recently published study by Fabis Pedrini et al. [60] was based on large groups of MS patients and age- and gender-matched healthy controls. They found that *H. pylori* seropositivity was lower amongst the MS patients; however this was only statistically significant amongst the females. *H. pylori*-infected female MS patients had lower disability scores than the uninfected female MS patients, but surprisingly the reverse was true amongst the males. Differences in the type of MS also have an impact on studies aiming to identify associations with *H. pylori* status. Li et al. [94] found that *H. pylori* seropositivity was lower amongst conventional MS (CMS) patients compared to those with opticospinal MS (OSMS), which is a variant of MS with similar clinical features to NMO and common in Asian populations. This illustrates the need for studies to be carefully controlled for confounding influences and bias.

To date, there is little mechanistic evidence of *H. pylori*-mediated protection against MS, and it is possible that presence of the infection could merely be a marker for other co-exposures which actually drive the protective effects. Unfortunately as yet there have been no published case studies on the effects of *H. pylori* eradication therapy in MS patients; however such combinations of antibiotics would also have an impact on the entire bacterial microflora. This would make it difficult to assess the role of *H. pylori* in particular. It would be helpful if it could be shown, as in asthma research, that associations are stronger in people infected with a particular subset of *H. pylori* strain types [33]. The best way to prove whether *H. pylori* is protective against MS would be to administer the infection or its components to patients. It has only recently become possible to deliberately infect healthy volunteers with *H. pylori*, and adverse effects were observed [1, 70]. This makes it an unlikely strategy to inhibit the development of MS or reduce disease progression. One article has called for the development of *H. pylori* nanoparticles as a treatment for MS [136]. This could be a useful alternative, especially if the protective bacterial components can be identified. Many of the protective effects attributed to *H. pylori* could require infection from an early age or even throughout life. This also complicates strategies to understand the mechanisms and harness them for therapies.

Experiments with Animal Models

Only one animal study on *H. pylori* and its impact on a model of MS has been reported so far. Our group showed that prior *H. pylori* infection of mice inhibited the severity of experimental autoimmune encephalomyelitis (EAE) [41]. This is the most commonly used model for human MS [39]. EAE was induced by immunization with the myelin oligodendrocyte glycoprotein (MOG) peptide $MOG_{35–55}$ in a strong adjuvant formulation, leading to an autoimmune response that mimics MS [39, 177]. It has been shown that injection of mice with heat killed *H. pylori* bacteria, and Freund's incomplete adjuvant, however, was not sufficient to trigger EAE [28]. Over three independent EAE experiments, we found that there were

significantly reduced clinical scores in mice previously infected with *H. pylori,* compared to groups that were administered placebo doses. The average maximal scores were also lower; however there was no delay in the onset of EAE [41]. Effects of the infection on the severity of EAE were therefore only moderate, especially when this is compared to other bacterial treatments such as daily administration of the *Bacteroides fragilis* PSA (polysaccharide) which protected against the development of EAE [126]. The impact of *H. pylori* on the T-cell responses in EAE mice, however, was very marked.

Firstly, MOG peptide-specific proliferation of splenic T cell from infected EAE mice was significantly reduced by threefold in comparison with cells from uninfected EAE mice [41]. Similar findings were shown in the response of spleen cells to polyclonal T-cell activation. Since EAE is characterized by infiltration of $CD4^+$ and $CD8^+$ cells into the CNS [120], at the peak in EAE severity, we also investigated whether there were differences in the size of these populations in the spinal cords of *H. pylori*-infected and *H. pylori*-uninfected mice [41]. The populations were indeed reduced, by 4.5-fold and 2.5-fold, respectively, and we consider that this is probably responsible for the difference in EAE clinical scores. Both $CD4^+$ and $CD8^+$ cells play an important role in EAE and MS. $CD8^+$ cells cause inflammatory lesions in the optic nerve, brain, and spinal cord, with focal loss of oligodendrocytes and axonal damage [159].

We then went on to investigate differences in the frequencies of Th1 and Th17 cells in the CNS, hypothesizing that these would also be reduced since they play a major role in EAE pathogenesis [99]. The proportion of Th1 cells (identified as T-bet$^+$ and IFNγ^+) amongst the $CD4^+$ population in the infected EAE mice was half that of the uninfected EAE group. There were similar reductions in Th17 cells (RORγt$^+$ and IL-17$^+$). Differences in Th1 and Th17 populations in the spleen were much larger, however. Th1 cells were reduced by 31-fold in infected EAE mice and Th17 cells by 11-fold.

The balance between Th1/Th17 and Treg subsets is important in MS development and progression [53, 164]. Because of this and the wealth of data on *H. pylori*-mediated immunomodulation (see section "*H. pylori*-Induced Immunomodulation" above), we therefore hypothesized that there would be increased frequencies of $Foxp3^+$ $CD4^+$ cells in infected EAE mice. Surprisingly no differences were observed, either in the spinal cord or the spleen. Unfortunately because we limited our quantification of Tregs to $Foxp3^+$ cells, we must now begin to examine other Treg and immunomodulatory cell populations. The most likely mechanism of protection is via IL-10, since *H. pylori*-induced Tregs tend to act by secretion of this suppressive factor [10, 148]. It has recently been shown that a subset of FoxA1$^+$, Foxp3$^-$ Tregs are protective against EAE. This IFNβ-responsive cell type is present in MS patients and has an impact on the effectiveness of IFNβ therapy [97]. It is as yet unknown whether these cells are influenced by *H. pylori* infection status.

Another possibility is that the infection may inhibit EAE by altering the expression of chemokine receptors and integrins by T effector or regulatory T cells, leading to reduced numbers of T cells entering the CNS. We have previously reported that *H. pylori* infection results in increased numbers of human peripheral blood

Tregs expressing the chemokine receptor CCR6 and that there are high concentrations of CCL20 (the ligand for CCR6) in the infected gastric mucosa [42]. CCR6 is also thought to play an important role in moderating the balance between Tregs and Th17 cells [37], and it has an impact on EAE [55, 96]. It is therefore possible that the trafficking of $CCR6^+$ cells is diverted to the inflamed stomach. The peak of EAE severity correlates with DC recruitment to the CNS [155]. Since *H. pylori* infection reduced the peak EAE clinical scores, the involvement of DCs in protection should also be investigated in the future.

H. pylori may merely be acting as a marker for other protective co-exposures and infections. Evidence using the Mongolian gerbil infection model has shown that *H. pylori* infection alters the microbiota of the gastrointestinal tract [73, 198]. Since the gut microbiota is known to have an impact on EAE [21, 91], it is possible that the protective effects of *H. pylori* are not mediated directly.

Conclusions

Epidemiological and serological evidence points to an inverse association between *H. pylori* infection and MS. This is supported by studies in the experimental model, EAE, in which exposure to *H. pylori* reduces the severity of the autoimmune T cell-mediated central nervous system inflammation, with a reduction in the production of pro-inflammatory cytokines. The exact mechanisms of this protection are unclear and are currently being investigated, but, based on evidence from previous studies, immunoregulatory networks activated by the infection with *H. pylori* are likely to play an important role. On the other hand, *H. pylori* may show a positive association with another neuroinflammatory disease, NMO. This reflects the distinct underlying immunopathological mechanisms of MS and NMO. The further elucidation of the role of *H. pylori* in the pathogenesis of neuroinflammatory diseases is likely to improve our insight both into the potential for immunomodulatory strategies of these diseases and into the complex effects of *H. pylori* on the immune system.

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