

Helicobacter pylori inflammation and gastric MALT lymphoma

Brigitte Dragosics

Clinical Department IV, Subdivision of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria

Keywords: autoimmunity, gastric MALT lymphoma, genetic aberrations, *Helicobacter pylori*, oncogenetic pathways, virulence factors

Abstract

Half a century ago, Denis Burkitt's report of a lymphoma of the jawbone in an African boy has been the first one about an infection-associated human tumour in the history of medicine. Some decades later primary gastric lymphoma of the mucosa associated lymphoid tissue has been found to be closely associated to *Helicobacter pylori* (Hp) infection of the gastric mucosa. Moreover, early stages of lymphoma have been shown to completely regress after antibiotic eradication of the bacterium, thus providing strong evidence for a causal role of Hp in lymphomagenesis. The oncogenetic pathways, first, from infectious gastritis to "early" lymphoma and, second, from Hp dependency of lymphomatous pro-

liferation to autonomous tumour growth are poorly understood. However, some more examples of infection-associated lymphomas are presented suggesting mechanisms like (i) tissue transformation to "altered self" creating new epitops for immunoreponse, (ii) enhancement of autoimmunoreactivity, (iii) production of idiotypic immunoglobulins, and (iv) T-cell directed specific B-cell proliferation with consecutive selection of a tumour clone. In contrast to Hp-associated gastric carcinogenesis, the main pathways to Hp-associated gastric MALT lymphoma may be determined by the immunoreponse with features of autoimmunoreactivity of the host combined with the Hp strain-induced release of highly genotoxic oxygen reactive species from neutrophilic leukocytes in the gastritic inflammatory infiltration.

Prof. Brigitte Dragosics, M.D., Ph.D.
Medical University of Vienna
Clinical Department IV, Subdivision of Gastroenterology and Hepatology
Fasangartengasse 40/5, AT-1130 Vienna, Austria
Phone: +43 676 602 8595
E-mail: b.dragosics@gmx.at

In the year 1958, surgeon Denis Burkitt observed highly malignant jawbone tumours in young African children and took them for sarcomas (1). Few years later, Epstein identified the lymphomatous nature of these tumours and successfully derived viral particles from the tumour cell culture (2). The first human infection associated tumour model was established. In fact, the prevalence of these specific tumours is restricted to the tropical climate zone of equatorial Africa and most likely dependent on vectors simultaneously transmitting Epstein Barr Virus (EBV) and malaria-plasmodia. Such co-infection, however, may substantially influence and, probably, alter the immunologic milieu in a host. This tumour model is classically addressing the question about the major players among the three actors – infectious agent, human being, and environment, respectively.

In 1983, a new infectious agent appeared on the medical stage (3). It was discovered in Australia, identified as *Helicobacter pylori* (Hp), and later on accepted as pathogenic for the gastric mucosa. In the very same year but on the opposite side of the globe, in England, a “distinctive lymphoma derived from the gastric MALT” was described (4). Ten years later, mucosal lymphoid follicles – acquired on occasion of Hp infection and switching the gastric mucosa secondarily into a lymphatic organ – revealed to be the “crucial link” between Hp infection and MALT lymphoma (5). In 1991, J. Parsonnet published very similar odds ratios for carcinoma and lymphoma, respectively, of persons with Hp infection as compared with persons without such infection (6). As a consequence, Hp was put into class I of carcinogens by the WHO. Since then, plenty of questions have arisen upon the pathways along which MALT lymphoma develops and why its incidence is low, whereas worldwide prevalence of Hp infection is high. Which factors select the type of disease associated with chronic Hp gastritis? The answer is very likely resulting from the dialogue between the Hp strain and the host. In fact, Hp is sending toxins into the gastric mucosa provoking specific T-cell response, cytokine production, and B-cell stimulation of the host. Extensive studies did not

show a clear cut association of Hp virulence factors and lymphoma (7–9). Interestingly, for unknown reasons, an *H. heilmannii* infection is ten times more prone to be associated with MALT lymphoma than Hp, as demonstrated by the data from the Institute of Pathology in Bayreuth, BRD (10).

Fundamental insights into lymphomagenesis are given by the studies of human MALT lymphoma cell cultures (11). Tumour cells derived from three gastric resection specimens were proliferating in culture, exclusively, when transfected with the very same Hp strain isolated from the individual gastric mucosa before resection. Different strains, even associated with MALT lymphoma in other patients, did not raise the lymphoma cell culture, at all. In addition, removing of T-cells from the culture was followed by its decline, whereas leaving them within further promoted its growing. Furthermore, a tumour specific immunoglobulin could be gained from the supernatant of the cell culture, which was identified – by murine antibody testing – as idiotypic immunoglobulin known to be produced, exclusively, by B-cell clones of autoreactive type. These results strengthen the causal role of a distinctive Hp strain stimulating strain-specific T-cells and clonal B-cell proliferation in the host. The production of an idiotypic immunoglobulin is presuming the presence of a local epitop, probably strain-induced created in the culture environment. The coincidence of an Hp strain capable of inducing lymphoma, on one side, and a host inclining to immunologic autoreactivity, on the other, is very likely to be a rare event and might thus explain the rarity of these tumours. In literature, examples of infection-associated MALT lymphoma in patients with already established autoimmune disease have been reported (12–15).

In summary, several pathways of lymphomagenesis may exist, either persistent antigen presentation by an infectious agent, or an autoantigen per se might exert chronic immunostimulation. Moreover, it is likely that infection may induce structural tissue damage followed by “altered self” epitops, which are acting as autoantigens. Cause-specific T-cells and

cytokines in the host select a B-cell clone, which in an “autoimmune” reacting host within an appropriate microenvironmental setting – rich with inflammatory neutrophilic leukocytes derived genotoxic oxygen reactive species – may transform to lymphoma.

As to the issue of control of inflammation-associated diseases, in the case of MALT lymphoma, the complete remission of early tumour stages may be regarded the most spectacular argument for the causal role of Hp infection in lymphomagenesis. Reported in 6 cases already in 1993 (16), it holds true in more than 80% of cases till to date (17). Meanwhile, molecular biologic findings support the Hp-associated pathogenesis of MALT lymphoma (18, 19). Especially the t(11;18) has proven a valuable marker of predicting response to antibiotic therapy.

In conclusion, there is strong evidence for a causal role of Hp in the oncogenesis of a major subgroup of gastric MALT lymphomas. Pathogenesis might start with Hp infection in childhood or youth, persistently presenting bacterial antigens over decades and activating strain-specific T-cells in the host. Starting the cascade of immunoresponse resulting in lymphoma, however, might be dependent on an intimate crosstalk between the individual germ and its suitable host. Only in an appropriate setting the bacterial cytotoxins induce cytokines in the gastric mucosa, probably altering tissue structures consecutively provoking idiotypic monoclonal immunoglobulins with autoreactive effect. After transformation to “aberrant tumour clone”, the proliferation might start to become autonomous and to be directed by the host, exclusively – according to Shakespeare’s Othello – “...the germ has done its obligation, the germ may go...”.

References

1. Burkitt D. A sarcoma involving the jaws in African children. *Brit J Surg* 1958; 46 (197): 218–23.
2. Epstein MA, Achong BG, Barr YM. Virus particles in cultured lymphoblasts from Burkitt’s lymphoma. *Lancet* 1964; 15: 702–3.
3. Warren JR. Unidentified curved bacilli on gastric epithelium in active chronic gastritis. *Lancet* 1983; 1 (8336): 1273–5.
4. Isaacson P, Wright DH. Extranodal malignant lymphoma arising from mucosa-associated lymphoid tissue. *Cancer* 1984; 53 (11): 2515–24.
5. Stolte M, Eidt S. Lymphoid follicles in antral mucosa: immune response to *Campylobacter pylori*? *J Clin Pathol* 1989; 42 (12): 1269–71.
6. Parsonnet J, Friedman GD, Vandersteen DP, Chang Y, Vogelman JH, Orentreich N, et al. *Helicobacter pylori* infection and the risk of gastric carcinoma. *N Engl J Med* 1991; 325 (16): 1127–31.
7. Yamaoka Y, Kita M, Kodama T, Sawai N, Imanishi J. *Helicobacter pylori* cagA gene and expression of cytokine messenger RNA in gastric mucosa. *Gastroenterology* 1996; 110 (6): 1744–52.
8. Höcker M, Hohenberger P. *Helicobacter pylori* virulence factors – one part of a big picture. *Lancet* 2003; 362 (9391): 1231–3.
9. Lehours P, Menard A, Dupouy S, Bergey B, Richey F, Zerbib F, et al. Evaluation of the association of nine *Helicobacter pylori* virulence factors with strains involved in low-grade gastric mucosa-associated lymphoid tissue lymphoma. *Infect Immun* 2004; 72 (2): 880–8.
10. Morgner A, Lehn N, Andersen LP, Thiede C, Bennedsen M, Trebesius K, et al. *Helicobacter heilmannii*-associated primary gastric low-grade MALT lymphoma: complete remission after curing the infection. *Gastroenterology* 2000; 118 (5): 821–8.
11. Hussell T, Isaacson PG, Crabtree JE, Spencer J. The response of cells from low-grade B-cell gastric lymphomas of mucosa-associated lymphoid tissue to *Helicobacter pylori*. *Lancet* 1993; 342 (8871): 571–4.
12. Green JE, Hinrichs SH, Vogel J, Jay G. Exocrinopathy resembling Sjogren’s syndrome in HTLV-1 tax transgenic mice. *Nature* 1989; 341 (6237): 72–4.
13. Ferreri AJ, Guidoboni M, Ponzoni M, De Conciliis C, Dell’Oro S, Fleischhauer K, et al. Evidence for an association between *Chlamydia psittaci* and ocular adnexal lymphomas. *J Natl Cancer Inst* 2004; 96 (8): 586–94.
14. Lecuit M, Abachin E, Martin A, Poyart C, Pochart P, Suarez F, et al. Immunoproliferative small intestinal disease associated with *Campylobacter jejuni*. *N Engl J Med* 2004; 350 (3): 239–48. Lecuit M, et al. *NEJM* 2004; 350: 239.
15. Ye MQ, Suriawinata A, Black C, Min AD, Strauchen J, Thung SN. Primary hepatic marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type in a patient with primary biliary cirrhosis. *Arch Pathol Lab Med* 2000; 124 (4): 604–8.
16. Wotherspoon AC, Doglioni C, Diss TC, Pan L, Moschini A, de Boni M, et al. Regression of primary low-grade B-cell gastric lymphoma of mucosa-associated lymphoid tissue

- type after eradication of *Helicobacter pylori*. *Lancet* 1993; 342 (8871): 575-7.
17. Morgner A, Bayerdorffer E, Neubauer A, Stolte M. *Helicobacter pylori* associated gastric B cell MALT lymphoma: predictive factors for regression. *Gut* 2001; 48 (3): 290-2.
 18. Liu H, Ruskon-Formestaux A, Lavergne-Slove A, Ye H, Molina T, Bouhnik Y, et al. Resistance of t(11;18) positive gastric mucosa-associated lymphoid tissue lymphoma to *Helicobacter pylori* eradication therapy. *Lancet* 2001; 357 (9249): 39-40.
 19. Schreuder MI, Hoeve MA, Hebeda KM, Verdijk MA, Ligtenberg MJ, Bot FJ, et al. Mutual exclusion of t(11;18)(q21;q21) and numerical chromosomal aberrations in the development of different types of primary gastric lymphomas. *Brit J Haematol* 2003; 123 (4): 590-9.