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Bacteria associated with marginal zone lymphomas

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A B S T R A C T

In the last decades some bacteria have been associated with a various extent with marginal zone (extra nodal, nodal and splenic types) lymphomas are frequently associated with chronic infections, with important clinical, molecular, biological, and therapeutic implications. The well-known correlation between *Helicobacter pylori* and gastric MALT-lymphoma, the recently reported links between *Chlamydia psittaci* and ocular adnexal MALT-lymphoma and *Borrelia burgdorferi* and cutaneous MALT lymphoma constitute the most studied examples; in addition, *Campylobacter jejuni* and some more recent associations encompassing *Achromobacter xylosoxidans* and *Haemophilus influenzae* will be further reported. Biological and clinical features, therapeutic implications and future perspectives of these lymphoma–microbial associations are discussed in this review.

Introduction

Marginal zone lymphomas (MZL) may represent the ideal model for better understand the development of antigen-driven malignancy, where a major role in its pathogenesis is played by environmental factors, including host immune response. The revised updated 2016 WHO classification of hematological malignancies [1] recognizes under the term MZL three entities: the extra nodal MZL (EMZL) of Mucosa-Associated Lymphoid Tissue (MALT)-type, the nodal MZL (NMZL) and the splenic MZL (SMZL). The heterogeneous group of MALT-type lymphomas arises in a number of organs and cumulatively accounts for 7–8% lymphomas.

Among EMZLs, the stomach is the commonest site of involvement (50% of cases), followed by the ocular adnexa, lung, skin, salivary glands, thyroid, and breast in a variable proportion of cases [2]. Thymus and meninges may be involved as well, but with a much lesser frequency. MALT lymphomas usually occur in the context of chronic inflammation, in particular related to infectious disease, such as *Helicobacter pylori* (*Hp*)-associated chronic gastritis, or autoimmune disorders such as Sjögren syndrome or Hashimoto thyroiditis [3]. Since the seminal discovery of the pathogenic association between *Hp* and gastric MALT lymphoma [4], other microorganisms have been linked to EMZL, including *Chlamydia psittaci* (*Cp*) in ocular adnexal MALT lymphomas (OAML) [5] and *Borrelia burgdorferi* in cutaneous MALT lymphomas [6]. These microorganisms have been accomplished by other putative associations that show lower levels of evidence, like those involving *Campylobacter jejuni* in immunoproliferative small intestinal disease, *Achromobacter xylosoxidans* in MALT lymphoma of the lung, and *Haemophilus influenzae* in pediatric nodal marginal zone hyperplasia/lymphoma. This review will discuss the various levels of evidences

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(epidemiological, morphological, clinical, and molecular) linking the above-mentioned bacteria to individual MZL types, with few mentions also on of the available results obtained by the treatment of these malignancies.

Histopathological features

MALT-type lymphoma lesions are mostly characterized by a diffuse infiltrate of neoplastic lymphocytes cells showing a variable amount of centrocytic-like, small or monocytoid-looking cells. Neoplastic cells are usually intermingled with scattered blasts (usually not exceeding 20% of neoplastic population) and display a B-cell immunophenotype characterized by immunoreactivity for CD20, CD79a, Bcl2, IgM, in a variable proportion of cases for CD21, CD35, MDNA, IRTA1, CD23, CD43 and negative for Cyclin D1, CD5, CD10, and IgD [3]. The demonstration of immunoglobulin light chain restriction is helpful to differentiate this lymphoma from a reactive lymphoid infiltrate. Importantly, CD5 and Cyclin D1 (or nuclear SOX-11, when these two markers are not conclusive) immunostaining are essential to exclude mantle cell lymphoma, although it should be taken into account that a small proportion of CD5-positive EMZL do exist [7]. Lymphoepithelial lesions and reactive lymphoid follicles, together with intermingled small sized T-lymphocytes, complete the typical morphological features of microenvironment in these malignancies.

Helicobacter pylori

Hp is a member of Gram-negative Epsilonproteobacteria and are considered type I carcinogen by the International Agency of Research against Cancer [8]. Gastric infection by *Hp* is reported in 80% of inhabitants of developing countries and half of those living in industrialized countries. This bacterium causes chronic active gastritis, whose persistence has been associated with the possible development peptic ulcer disease and gastric adenocarcinoma or lymphoma. The malignant transformation, however, is a rare occurrence, involving only 1–2% of infected individuals.

Many lines of evidence link gastric EMZL to *Hp* infection. First, it has been observed that *Hp*-induced gastritis reproduces at histopathological level the features of acquired MALT. Second, it has been found a high prevalence of *Hp* infection in 92% of patients with in gastric lymphoma, a figure that mostly occurs in endemic regions [4,9]. On these grounds, a B-cell clone that eventually gave rise to MZL has been detected in cases of *Hp*-related gastritis, thus confirming that this malignancy might results from a multi-step process initiated by *Hp* infection [10]. Third, an important pathogenic clue derives from the observation of 75% tumor regression rate registered in patients with gastric MALT lymphoma exclusively treated with *Hp*-eradicating antibiotics as antitumor therapy [11].

Some genotypes, mostly depending upon geographical variability, have been reported as associated with an increased risk of lymphoma development and therefore must be interpreted with caution. For instance, *IL-1 RN 2/2* genotype and the *GST T1 null* genotype have been significantly associated with an increasing risk of developing gastric EMZL in Northern England [12], in comparison to what observed in other countries [13,14]. In addition, the TNF-α-857T genotype shows a 3-fold decreased risk of developing a gastric EMZL in Taiwan (Wu YY 2004) and a 1.8 fold increased risk in a Caucasian population [14].

Clearly enough, either innate and adaptive immune responses against pathogens are involved in the pathogenesis of gastric EMZL. In fact, *Hp* infection *per se* drives a Th1-type immune response, which is mediated by several pro-inflammatory cytokines. In addition, signals released by *Hp*-specific CD4+ T helper cells provide a strong signal for B-cell activation and proliferation through CD40-mediated signaling and Th2 cytokines [15]. Moreover, cytotoxic T lymphocytes of gastric EMZL display a defect in their cytotoxicity activity mediated by perforin and a reduced capability to induce apoptosis mediated by Fas-Fas ligand system; taken together, these mechanisms thus allow B-cell growth and facilitate the development of the lymphoma [16]. It is likely that such impairment in T-cell response may be direct consequence of microenvironmental stimuli as in the case of cytotoxic lymphocytes [17], or the result of gene polymorphisms, as occurs for the cytotoxic T-lymphocyte antigen-4 (CTLA4) molecule. Intriguingly, CTLA4 is considered as a negative regulator of T-cell activation [18] and any mechanism leading to defective action of this molecule might be responsible for impaired activity of this T-cell subset. It should be noted also that *Hp* infection induces neutrophils to produce DNA-damaging reactive oxygen species (ROS). The production of ROS activates cellular defense mechanisms including glutathione S-transferase (GST) enzymes that act as strong antioxidants.

Along with molecular mechanisms, MZ lymphoma-associated chromosomal translocations play an important role in MALT lymphomagenesis as well. In fact, API2-MALT1 protein, the chimeric product of t (11; 18) (q21; q21), exerts anti-apoptotic effects and activates NF-κB pathway. These anti-apoptotic effects are mediated by inhibition of *SMAC*, *TRAF2* and *HtrA2*, ubiquitination of *Bcl10* and *NEMO*, up regulation of *TRAF6*, and self-activation [19]. Of note, *Bcl10* positively regulates proliferation of lymphocytes proliferation and links T- and B-cell antigen receptor signaling to NF-κB activation. Bcl-10 up-regulation could escape the upstream antigen-receptor signaling and constitutively activates NF-kB pathway in an *Hp*-independent manner. In addition to activating *per se* NF-κB pathway as well, MALT1 protein is important also in the proteolytic activity of bcl10 and A20 proteins [20]; the latter is an important molecule in keeping constitutively activated the pathway (see below on '*Chlamydia psittaci*' section). Finally, also the cytotoxin-associated antigen A (*cagA*) carried by *Hp* seems to play an important pathogenic role by virtue of its particular link with t (11; 18)+ gastric EMZL [21]; in fact, *CagA*+ is carried by 70% of *Hp* strains and is also linked to duodenal ulcer and gastric adenocarcinoma.

The current standard treatment of *Hp*-associated gastric EMZL is eradication of the bacterium with a combination of antibiotics, in particular clarithromycin-based triple therapy with either amoxicillin or metronidazole, and plus proton-pomp