MOLECULAR AND EXPERIMENTAL BIOLOGY IN MEDICINE

EPIGENETIC CHANGES IN MALT LYMPHOMA AND THE ACCUMULATION OF FOXP3+ REGULATORY CELLS IN TUMOR MASS

Eva Lovric[1], Tomislav Horvat[2*], Miroslava Katicic[3], Slobodanka Ostojic Kolonic[3, 4], Slavko Gasparov[1, 3], Vlatka Zoldos[2], Petra Korac[2], Mara Dominis[3]*

Abstract: Primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is often induced by a chronic *Helicobacter pylori* infection, while a significant role during its development is ascribed to T lymphocytes, which infiltrate the tumor mass. Even though it is well known that FOXP3+ T regulatory cells can modify clinical outcome of hematological malignancies, it is still unknown whether they can induce epigenetic changes in lymphoma cells. Using gastric biopsies from 11 patients with MALT lymphoma at the time of diagnosis, during follow-up and during progression of the disease, we have analyzed 138 biopsies in total in order to assess the possible association of changes in H3K27me3 production and the presence of cytogenetic changes in small lymphocytes, with the presence of FOXP3+ cells that infiltrate tumor tissue. Our results indicate a putative role of FOXP3+ cells in mechanisms leading to a decreased expression of repressive histone modification H3K27me3 in tumor cells, which could result in transcriptional reactivation of various genes associated with tumor growth and disruption of genomic integrity characteristic of tumor cells.

[1] *Institute of Pathology and Cytology, University Hospital Merkur, Zagreb, Croatia*

[2] *Faculty of Science, Division of Molecular Biology, Department of Biology, University of Zagreb, Zagreb, Croatia*

[3] *Medical School, University of Zagreb, Zagreb, Croatia*

[4] *Department of Medicine, University Hospital Merkur, Zagreb, Croatia*

* equally contributing authors

Corresponding author:
Petra Korac
Faculty of Science, Division of Molecular Biology, Department of Biology, University of Zagreb, Zagreb, Croatia
Tel: +385 1 46 06 278; Fax: + 385 1 46 06 286
e-mail: petra.korac@biol.pmf.hr

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INTRODUCTION

Primary extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) is an indolent extranodal B cell lymphoma. Chronic *Helicobacter pylori* infection is believed to be the main inducer of this neoplasm.[1,2,3] Although different strains of bacteria are present in gastric mucosa, the one expressing the CagA protein is linked with high-grade MALT lymphoma development.[4,5] *H. pylori* in gastric mucosa not only induces the infiltration of lymphocytes that form mucosa associated lymphoid tissue, but also further maintains their proliferation and may cause the development of MALT lymphoma. One of the indirect mechanisms responsible for *H. pylori*-induced lymphoma development includes subpopulations of present T cells.[6] Bacteria translocate their CagA protein directly to tumor B lymphocytes causing their proliferation and resistance to apoptosis.[7] Moreover, bacteria themselves influence tumor B cells through a specific, dependent T cell population and CD40/CD40L costimulatory molecules.[8,9] FOXP3+ T regulatory cells (T regs) were recognized as a subpopulation of T cells that can influence tumor growth. In neoplasms developed from cells of different origin, an increased number of T regs in tumor mass was recognized as a prognostic predictor, but mechanisms of interaction between tumor cells and T regs are still insufficiently understood.[10-16] There are some indications that in B lymphomas T regs can inhibit functions of other cells implicated in the antitumor response, most probably through cell to cell contact. Furthermore, proven effects of interactions between neoplastic B cells and T regs include an increase of T regs in tumor mass

followed by the suppression of the hostôs antitumor response.[17]

Evidence showing the development of a neoplasm caused by bacterial infection in case of MALT lymphoma has led to the recognition of ñthe only tumor that can be cured using antibioticsò.[18] Still, cases of MALT lymphoma independent of *H. pylori* have been described, as well as findings confirming the resistance of a proportion of MALT lymphomas to eradication therapy. *H. pillory*-induced MALT lymphoma cases that harbor t(11:18)(q21;q21) ï *API2(BIRC3)/MALT1* translocation were connected with a failure to respond to bacterial eradication.[19] This translocation was described as a frequent and characteristic cytogenetic aberration in MALT lymphoma that is often present as a sole chromosomal aberration.[20, 21] It forms a chimeric gene that produces a fusion of API2 gene product and C terminal of *MALT1* gene product.[22] An interesting study showing the expression of transgene *API2/MALT1* in human B cell lymphoma BJAB cell line confirmed a possible mechanism that explains how this translocation can influence resistance to *H. pylori*. It was suggested that initial bacterial infection triggers the immune response that results in NF-əB activation in tumor B cells through CD40/CD40L T cell interaction. *API2/MALT1* translocation could produce fusion proteins that could be responsible for constitutive NF-əB activation and therefore cause proliferation independent from the immune response to *H. pylori*.[23]

MALT lymphoma cases marked with *API2/MALT1* translocation are therefore non-responsive to bacteria eradication and are today treated with different protocols including surgical resections, chemo- or radiotherapy or their combination. Although local radiotherapy is the most popular treatment for those patients, there is no consensus on the treatment so far.[3, 24, 25] In order to gain insight into mechanisms that can enhance treatment protocols, in last few decades the development of MALT lymphoma has been explored through genetic changes in tumor cells, and recently based on microenvironmental interactions with cells involved in immune response to a neoplasm. Such approaches have defined different possible mechanisms, but have still left some questions unanswered. Today, we are aware of genetic and epigenetic linkage and the importance of both components for regulation of specific, as well as global transcription regulation.

It has been suggested that epigenetic (re)programming could take part in mechanisms employed by different subsets of cells in order to adapt to the changed environment.[26] Therefore, it is possible that environmental cells in MALT lymphoma could be responsible for the interactions which would induce epigenetic changes in tumor B cells. One of the important epigenetic changes in tumors is the aberration of histone modifications. In this study, we investigated whether the accumulation of T regs would affect the epigenetic status of MALT lymphoma cells. Specifically, we monitored the expression of H3K27me3, a histone modification associated with transcriptional repression and heterochromatin formation.[27, 28] In addition, we observed the correlation between epigenetic and cytogenetic changes in neoplastic cells.

MATERIAL AND METHODS

Formalin-fixed paraffin-embedded gastric biopsies performed prior to and at the time of MALT lymphoma diagnosis and during the disease development, taken from 11 patients, were analyzed (Table 1). 138 gastric biopsy samples were divided into three groups: intact mucosa, inflammatory changes and tumor infiltrates. Independently, three pathologists revised the diagnoses base on histological samples and confirmed the sample group for each biopsy. Clinical data were obtained from a

Table 1. Follow up of 11 patients with MALT lymphoma included in the study

patient	gender	age at first examination	number of examinations	PHD in initial biopsy	*H. pylori*	examination with MALT lymphoma presentation	therapy for MALT lymphoma	examination with transformation to DLBCL	therapy for DLBCL	outcome
1.	Ⅰ	75	10	inflammatory changes	unknown	5th	proton-pump inhibitors	7th	prednisone, chlorambucil, CNOP**	dead
2.	Ⅱ	73	3	MALT lymphoma	+	1st	proton-pump inhibitors	/	/	dead
3.	Ⅰ	71	7	MALT lymphoma	+	1st	unavailable information	/	/	alive
4.	Ⅰ	70	14	MALT lymphoma	-	1st	triple therapy*	/	/	alive
5.	Ⅰ	32	9	MALT lymphoma	+	1st	H_2 receptor antagonists	/	/	alive
6.	Ⅱ	66	2	MALT lymphoma	+	1st	H_2 receptor antagonists	/	/	alive
7.	Ⅰ	53	11	inflammatory changes	+	4th	proton-pump inhibitors	/	/	alive
8.	Ⅰ	85	3	inflammatory changes	unknown	2nd	unavailable information	/	/	unknown
9.	Ⅱ	44	7	MALT lymphoma	-	1st	triple therapy	/	/	alive
10.	♀	74	6	inflammatory changes	+	2nd	triple therapy	/	/	alive
11.	♀	48	4	MALT lymphoma	-	1st	proton-pump inhibitors	4th	proton-pump inhibitors, R-CHOP***	alive

Legend: *triple therapy - proton pump inhibitors and antibiotics, **CNOP-cyclophosphamide, mitoxantrone, vincristine, prednisone, ***R-CHOP - cyclophosphamide, doxorubicin, vincristine, prednisone, rituximab

gastroenterologist as a part of the study approved by the Medical school ethical committee.

Immunohistochemical staining using anti-FOXP3 (Abcam, Cambridge, UK) and anti-H3K27me3 (Abcam, Cambridge, UK) antibodies was performed on all samples. Tissue sections 4 εm thick were used. For immunostaining with anti-FOXP3 antibodies, the samples were pretreated using heat-induced epitope retrieval procedure and stained using Envision FLEX, high pH kit (Dako, Glostrup, Denmark), followed by triple blind reading performed by experienced pathologists. FOXP3-positive cells were counted on whole tissue samples and reported as the number of FOXP3+ cells per 1 mm^2 of section. Immunostaining of H3K27me3 histone modification was performed following dewaxing, dehydrating and pretreatment of slides with a citrate buffer using a pressure cooker (125°C, 3 mins). The staining was performed using the Envision kit (Dako, Glostrup, Denmark) after which slides were counterstained with hematoxylin (Envision FLEX hematoxylin, Dako, Glostrup, Denmark). Finally, the percentage of lymphocytes harboring the H3K27me3 histone modification in the total lymphocyte population per sample was evaluated by three pathologists.

MALT1 (LSI MALT1 dual color break apart probe, Abbott Molecular Inc., Des plaines, IL, USA) and *BCL10* (BCL10 FISH DNA probe, split signal, Dako, Glostrup, Denmark) translocations, as well as possible aneuploidy of chromosome 3 (CEP 3 alpha satellite probe, Abbott Molecular Inc., Des plaines, IL, USA) were analyzed by FISH. Translocations of the *MALT1* gene were further evaluated using dual color dual fusion probes (IGH/MALT1 DF FISH Probe and BIRC3/MALT1 DF FISH Probe, Abbott Molecular Inc., Des plaines, IL, USA) to elucidate the exact *MALT1* translocation partner. Tissue slides were treated in Borg (Borg Decloaker, RTU, Biocare medical, Llc., Concord, CA, USA), in a pressure cooker (125°C, 3 min), followed by incubation with pepsin (37°C, 20 min). Slides were then dehydrated through a series of ethanol solutions and air-dried. FISH probes were applied to whole sections, prior to denaturation for 5 min at 85°C, and overnight hybridization at 37°C. The next day, the slides were washed in preheated detergent solutions and cooled down to room temperature before mounting with Vectashield containing DAPI (Vector Laboratories Inc., Burlingame, CA, USA). Double blind reading was performed.

Laboratory-obtained data were statistically analyzed using non-parametric tests due to the violation of the normality assumption. The correlation between the amount of FOXP3+ cells and the percentage of tumor cells which express H3K27me3 was investigated using Spearman's rank correlation coefficient. The Kruskal-Wallis test was performed to analyze the number of FOXP3-positive cells and the percentage of cells harboring the H3K27me3 histone modification across three groups of samples. Correlations between the amount of FOXP3+ cells and cells expressing H3K27me3 with *H. pylori* infection and different cytogenetic aberrations were tested using the Mann Whitney test.

A Chi-square test for independence was applied to determine the possible correlation of sample groups with *H. pylori* infection or cytogenetic aberrations.

RESULTS

Samples were subdivided into three subgroups: intact mucosa samples (n=22), gastric biopsy samples with inflammatory changes (n=65) and gastric biopsy samples with tumor infiltrates (n=51) (Table 2).

Out of all samples, 15 were *H. pylori*-positive, 28 harbored trisomy 3 and 24 had *MALT1* translocation (in

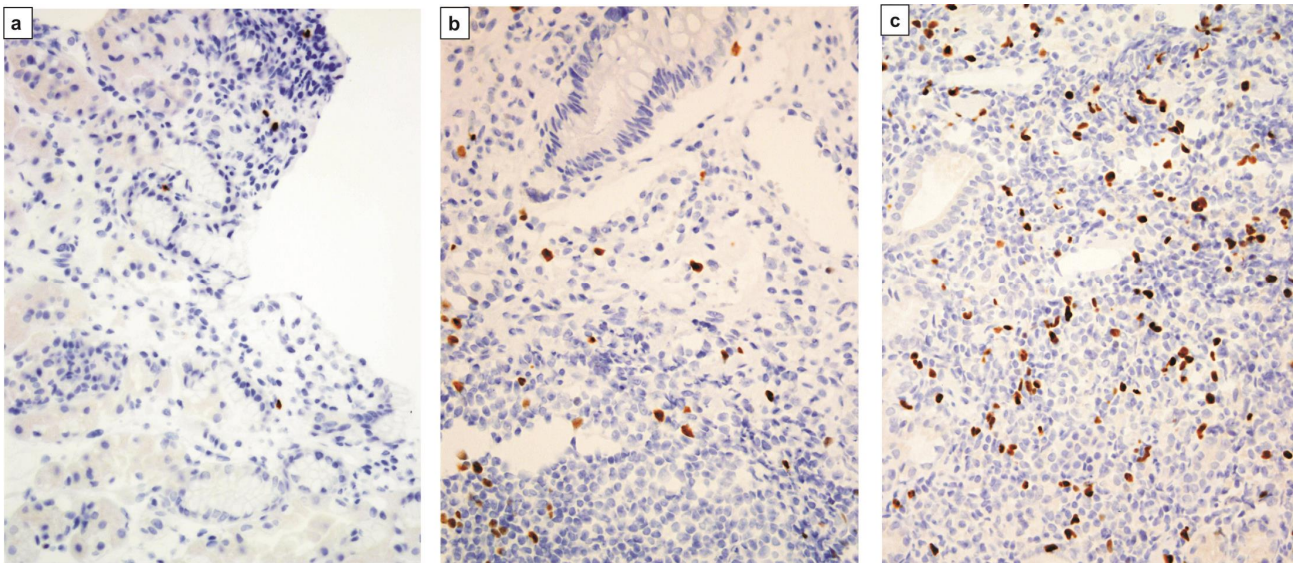

Figure 1. FOXP3-positive cells in a) intact mucosa tissue, b) mucosa tissue with chronic inflammatory changes, and c) MALT lymphoma infiltrate. The blue stain, (hematoxylin counterstain) represents FOXP3- cells, while the brown stain (diaminobenzidine precipitate) represents FOXP3+ cells.

Table 2. Amount of FOXP3+ cells and H3K27me3+ lymphocytes in all sample types

sample type	number of samples	median number of FOXP3+ cells per 1 mm^2	median percentage of H3K27me3+ lymphocytes
intact mucosa	22	1.11	65%
inflammatory changes	65	10.03	80%
tumor infiltrate	51	74.54	40%

all cases with *MALT1* translocation, the translocation partner was *API2* gene). There were no samples with *IGH/MALT1* translocation or rearrangement of *BCL10*.
The median number of FOXP3+ cells per 1 mm^2 was 1.11 in intact mucosa samples, 10.03 in samples with chronic inflammatory changes, and 74.54 in samples with tumor infiltrates (Figure 1a-c, Table 2).
The median percentage of lymphocytes harboring H3K27me3 histone modification was 65% in total lymphocyte population of intact mucosa samples, 80% in samples with chronic inflammatory changes and 40% in samples with tumor infiltrates (Figure 2a-c, Table 2).
Statistical analysis of immunohistochemically-detected FOXP3+ cells revealed a significant increase in their number in tumor infiltrates when compared to intact mucosa samples or samples with inflammatory changes (χ^2=54.568, p<0.001) (Figure 3). This increase was linked to the *H. pylori* infection as well as to the presence of *MALT1* translocation and/or trisomy 3 in neoplastic cells (p=0.048; p<0.001; p=0.001; respectively). Interestingly, we observed a negative correlation between the number of FOXP3+ cells infiltrating tumor mass and the percentage of tumor cells harboring the histone modification H3K27me3 (Spearman's rank correlation coefficient; r=-0.195; n=131, p=0.025) (Figure 3). Accordingly, the percentage of cells harboring H3K27me3 in tumor tissue was significantly lower in comparison to intact mucosa or inflammation samples (χ^2=13.348 and p=0.001) (Figure 3). In addition, the percentage of lymphocytes harboring H3K27me3 was significantly lower in tumor tissue samples with the presence of *API2/MALT1* translocation (p=0.026) when compared to samples of tumor tissue without this translocation. *API2/MALT1* translocation, as well as chromosome 3 gain, were predominantly detected in tumor infiltrates when compared to intact mucosa or inflammatory samples (p=0.006 and p<0.001).

DISCUSSION

Data obtained in this study demonstrate an accumulation of FOXP3+ cells during MALT lymphoma development and their increased number in samples infected by *H. pylori*. It is known that *H.pylori* infection of gastric mucosa not only induces infiltration of lymphocytes that form mucosa associated lymphoid tissue, but also stimulates their proliferation and potentially causes the development of MALT lymphoma. Bacteria translocate their CagA protein directly into tumor B lymphocytes inducing their proliferation and resistance to apoptosis.[7] They further affect tumor B cells through an indirect mechanism, using dependent specific T cell population which communicates with neoplastic cells by CD40/CD40L costimulatory molecules.[7, 8, 29] FOXP3+ (T regs) cells have already been considered as prognostic predictors in many tumor types.[10-16] Even though interactions

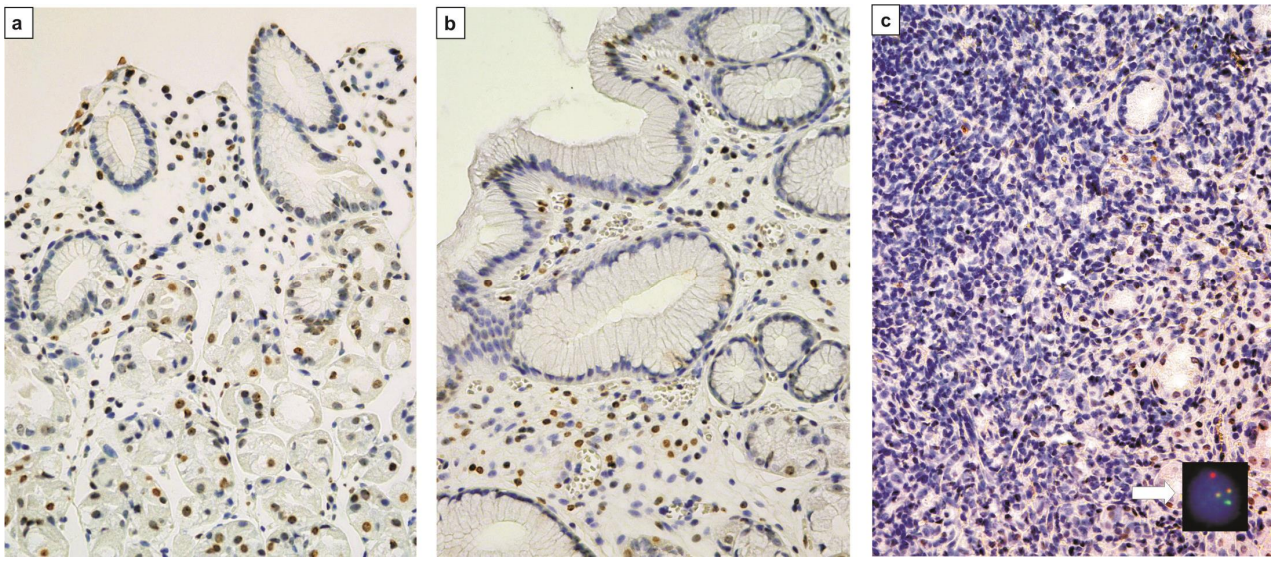

Figure 2. Lymphocytes harboring the H3K27me3 mark in a) intact mucosa tissue, b) mucosa tissue with chronic inflammatory changes and c) MALT lymphoma infiltrates (tumor cells with *API2/MALT1* translocation). The blue stain, (hematoxylin counterstain) represents H3K27me3- cells, while the brown stain (diaminobenzidine precipitate) represents H3K27me3+ cells.

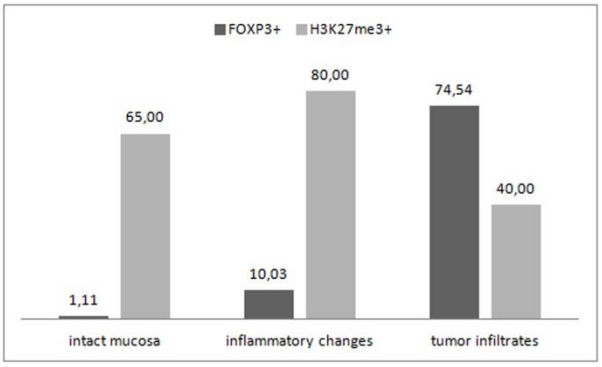

Figure 3. Comparison of FOXP3+ and H3K27me3+ cell amounts in all tissue types. Amount of FOXP3+ cells is given as a median of the total number of immunohistochemically positive cells per 1 mm^2 of tissue sections; the amount of H3K27me3+ cells is given as a median percentage of positive lymphocytes in tissue sections.

between tumor cells and T regs are still insufficiently understood, we believe that the observed correlation between FOXP3+ T regs and B tumor progression of MALT lymphoma might be triggered by *H. pylori* infection. Interestingly, we also observed a lower expression of repressive histone mark H3K27me3 in tumor cells as the disease progresses. The significant decrease of tumor cells harboring H3K27me3 also coincides with the accumulation of FOXP3+ cells in tumor tissue. Trimethylation of H3K27 in lymphocytes is the result of EZH2 activity. EZH2 is methytransferase which is marked by gain-of-function mutation in more than 25% cases of diffuse large B cell lymphoma and follicular lymphoma.[26, 27] This enzyme is also known to act in a context-specific manner.[28] In our samples, the accumulation of FOXP3+ cells could be the change in microenvironment that induces the adaptation of neoplastic cells, and, through EZH2 activity, a decrease of H3K27me3 can be a part of epigenetic (re)programming they undergo.[29]

The decreased number of tumor cells with H3K27me3 also correlated with the presence of *H. pylori* infection as well as with the presence of *API2/MALT1* translocation and/or trisomy 3 in neoplastic cells. As mentioned above, *H. pilory*-induced cases of MALT lymphoma harboring t(11:18)(q21;q21) ï *API2(BIRC3)/MALT1* translocation failed to respond to bacterial eradication.[19] We believe that the genomic instability, potentially leading to chromosome rearrangements such as *API2/MALT1* translocation, could be related to lower production of H3K27me3 histone modification. Since this modification is associated with proper heterochromatin formation which ensures genome stability, its decreased expression could be tightly related to instable mitosis resulting in chromosome aberrations characteristically found in MALT lymphoma.[30, 31]

Taken together, the results obtained in this work suggest an important role of T regs in mechanisms leading to a decrease in expression of H3K27me3 within the tumor mass. Since the analyzed epigenetic mark is associated with transcriptional repression of many developmentally regulated genes, stem cell maintenance and differentiation, a considerable decrease in its expression, possibly caused by FOXP3+ T regs, could result in gene reactivation and thus stimulation of tumor growth.

Presented data should be tested in monitored follow-up studies on a bigger cohort, and eventually these results might be used as the basis for new therapeutic protocols aiming to interfere with the so far unrevealed interaction between T regs and tumor cells.

Additionally, H3K27me3 and possibly some other histone modifications in MALT lymphoma should be considered and evaluated as simple immunohistochemical prognostic markers for the identification of patient groups which might undergo more aggressive course of disease and potentially transform to diffuse large B-cell lymphoma.

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