Review Article

Genetic and epigenetic factors involved in B-cell lymphomagenesis

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(Received May 11, 2004/Revised June 23, 2004/Accepted July 5, 2004)

Malignant lymphomas have been classified by the WHO into disease categories based not only on histological features, but also on cell surface markers, cytogenetic and clinical features. It is known that chromosome translocation plays an important role in lymphoma development, but it is not entirely clear yet why a given type of chromosome translocation is associated with a specific type of lymphoma. This review deals with molecular mechanisms of B-cell lymphoma development in association with chromosome translocations. The outcome of chromosome translocations can be categorized into three factors: enhancement of proliferation, inhibition of differentiation and anti-apoptotic activity. It is well known that chromosome translocation by itself cannot cause cells to become malignant because it is only one of the growth advantages leading to malignancy, while additional genetic and epigenetic alterations are required for cells to become fully malignant. Mucosa-associated lymphoid tissue (MALT) lymphomas of the stomach are unique in that a majority can be cured by *Helicobacter pylori* eradication, although 20 to 30% remain resistant. Others as well as we have demonstrated that the presence of the *API2-MALT1* chimeric gene correlates well with resistance to *H. pylori* eradication treatment. These characteristics have led to the speculation that the classification of MALT lymphoma falls somewhere between tumor and inflammation. Although MALT lymphoma seems to have unique features in comparison with other types of B-cell lymphomas, it shares common molecular mechanisms with B-cell lymphoma development. (Cancer Sci 2004; 95: 704–710)

B-cell development and secondary follicles of lymphoid organs

The secondary follicles of lymphoid organs represent one of the most important structures for B-cell development. They consist of at least three layers: the dark, light and mantle zones.[1)] These three layers are essential for B-cell proliferation, differentiation and apoptosis (Fig. 1). B cells originating from bone marrow have their *immunoglobulin heavy* (*IgH*) and *light* (*IgL*) *chain* genes rearranged, and those with productive gene rearrangement reach the mantle zone. The cells that have not been exposed to antigens are known as naïve or virgin B-cells and remain at the mantle zone until they are exposed to antigens. When a naïve B-cell is stimulated with an antigen, its *BCL2* gene is down-regulated by an as-yet unknown mechanism, after which the cell enters the cell cycle and proliferates in the dark zone. These cells undergo somatic mutation of their *Ig* genes and a majority of them dies as a result of apoptosis. Only those that can generate high-affinity Igs survive and exit from the germinal center into the peripheral circulation via the marginal zone.[1)]

Recent WHO classification of malignant lymphomas emphasizes the importance of using all available information (morphology, immunophenotype, genetic features and clinical features) for the diagnosis of lymphomas.[2)] A useful marker for identifying developmental stages of B-cell lymphoma is the variable region sequence of *Ig* genes (Fig. 1). When the nucleotide sequence of the VH (variable heavy chain) region of lymphoma cells is identical to that of the germ line, the lymphoma cells can be assumed to be in the pre-germinal center (GC) stage (e.g., mantle cell lymphoma: MCL). If the mutations vary among lymphoma cells but are clonally related (ongoing mutation), the cells can be assumed to be in the GC stage (e.g., follicular lymphoma: FL). If the mutation is fixed among the lymphoma cells, they can be assumed to be in the post-GC stage (e.g., diffuse large B-cell lymphoma, DLBCL, and extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma).

Translocation junction region (TJR) genes involved in lymphomagenesis

Chromosome translocations are essential for lymphomagenesis, and result in either transcriptional deregulation or production of chimeric protein(s). The former involves translocation of *BCL1, BCL2, BCL6* and *MYC*, whose gene products are not modified by translocation, and the latter that of *API2-MALT1*, whose two genes are fused into one. Most investigators may regard the translocation of transcriptionally deregulated type as an indication that the products are overexpressed. Although this is true for translocation of *BCL1/cyclin D1*, it is not for that of *BCL2* or *BCL6*. The mRNA levels and expression levels of gene products of *BCL2* and *BCL6* in cell line or lymphoma samples without translocation can be as much as those in samples with translocation,[3–7)] which indicates that overexpression of the TJR gene is not essential. In order to gain a full understanding of the effect of transcriptional deregulation by chromosome translocation, it is important first to understand the normal transcriptional regulations of these TJR genes (Fig. 2). Several lines of evidence suggest that *BCL1*, *BCL2* and *BCL6* genes are regulated differently during the course of B-cell development.[3–7)] In the normal developmental stages, the TJR genes are down-regulated at the stage where the related lymphomas arise (Fig. 2). In this respect, it is important to note that the translocation takes place at the pre-B-cell stage for *BCL1* and *BCL2*, whose presence at the translocation breakpoints where JH or DH regions of the *IgH* gene are involved has been demonstrated by sequence analysis.[8, 9)] Once they have been translocated at the pre-B-cell stage, expressions of the TJR genes from the translocated allele are not detected as aberrant, because both genes are expressed at this developmental stage without translocation (Fig. 2). In the case of *BCL1* translocation, the *BCL1* expression from the translocated allele is not down-regulated at the developmental stage of the mantle cell. Thus, the deregulated *BCL1* expression is detected as aberrant

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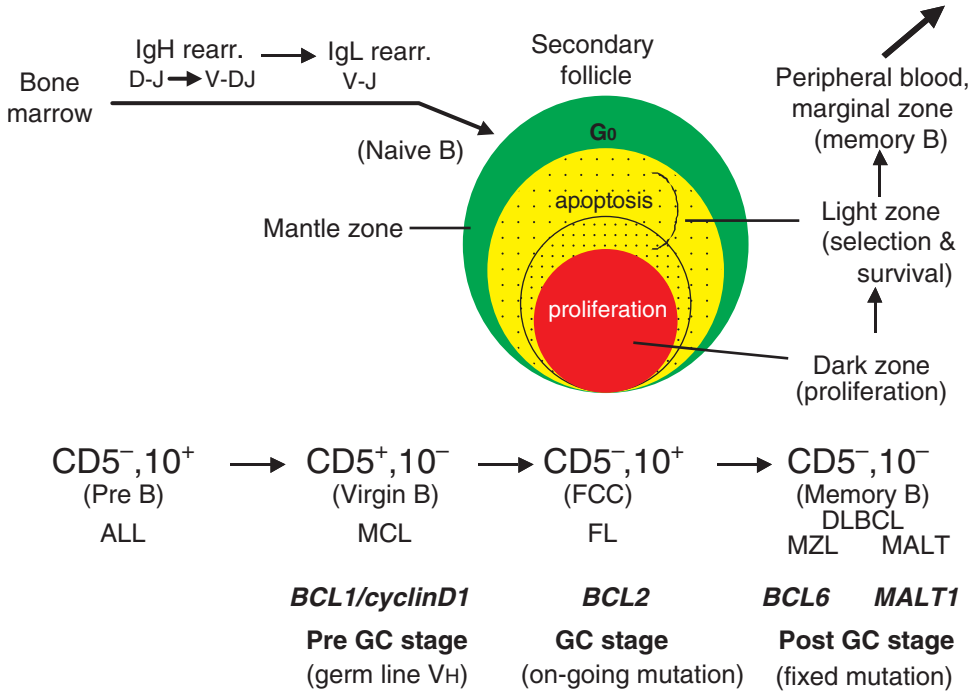

Fig. 1. B-cell differentiation and related B-cell malignancies. Secondary follicles of lymphoid organs are important for B-cell differentiation. The follicle consists of at least three layers: the dark, mantel and light zones. Cells in the mantle zone are positively stained with anti-BCL2 antibody (green area), but not with anti-Ki-67 antibody, suggesting that the cells are at the G0 stage of the cell cycle. The light zone is intermediate between the two layers and B cells in this region are thought to be selected as high-affinity antibody producers. B cells arise from bone marrow, and after successful *immunoglobulin* (*Ig*) gene rearrangements, they become naïve-B cells and remain in the mantle zone until antigens stimulate them. Upon stimulation, B cells proliferate in the dark zone where somatic mutation takes place, resulting in selection of high-affinity antibody producers and death for a majority of the cells that failed to be selected. Once they are selected, *BCL2* expression occurs, and the cells exit from the follicle into the peripheral circulation via the marginal zone. The cells without somatic mutation (germ line sequence) are at the pre-germinal center (GC) stage, those with ongoing mutation are at the GC stage, while those with fixed mutation are at the post-GC stage. CD5 and CD10 markers change during differentiation. Representative lymphomas at each stage are shown with their characteristic translocation junction genes, *BCL1*, *BCL2*, *BCL6* and *MALT1*. MCL, mantle cell lymphoma; FL, follicular lymphoma; DLBCL, diffuse large B-cell lymphoma; MZL, marginal zone lymphoma; MALT, extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma.

at this developmental stage, but not at the pre-B-cell stage. In the case of *BCL2* translocation, the deregulated expression from the translocated *BCL2* gene is detected as aberrant at the follicular center cell stage, but not at the pre-B-cell or mantle cell stage. Thus, the essential effect of the deregulation of *TJR* genes by chromosome translocation is "aberrant expression" in the cells where those genes are normally down-regulated (Fig. 2). In other words, the transcriptional deregulation by chromosome translocation is not at the level of expression, but rather expression at inappropriate developmental stages.

Lymphoma development by TJR genes

Mantle cells are at the G0 stage in the cell cycle.[1)] When the *BCL1* gene is aberrantly expressed as a result of chromosome translocation, the expression of *BCL1*/cyclin D1 is apt to drive cells into the cell cycle, resulting in a growth advantage for mantle cells that are otherwise in the resting stage (Fig. 2). This impetus towards cell cycling is thought to lead to MCL development.

Follicular center cells undergo somatic mutation, and the cells producing antibodies with high affinity are selected and survive. During this process, *BCL2* expression at follicular center cells under normal conditions is down-regulated, and most cells die as a result of apoptosis (Fig. 1). When the *BCL2* gene is deregulated by chromosome translocation however, its expression is not down-regulated. The *BCL2* down-regulation of normal alleles in follicular lymphoma has been clearly demonstrated.[4)] This expression, resulting from chromosome translo-

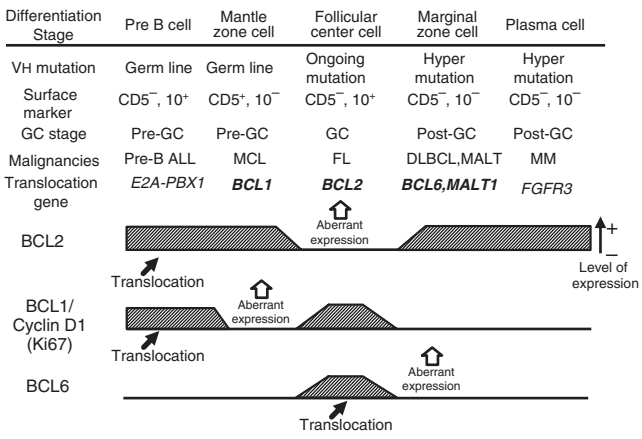

Fig. 2. Transcriptional regulation of translocation junction genes during B-cell development and their deregulation by chromosome translocation. Black arrows indicate when the translocation takes place and white arrows indicate aberrant expression through deregulation of the translocation junction region (TJR) gene by chromosome translocation. Bold letters represent TJR genes associated with respective malignant lymphomas. The stages at which translocation takes place can be recognized from the translocation breakpoint sequences.[8, 9, 37)] The level of BCL1/cyclin D1 expression is estimated from the Ki-67 staining pattern because cyclin D1 is not immunostained under ordinary conditions.

cation, is detected as aberrant at the follicular center cell stage, but not at either the pre-B-cell or mantle cell stage. The aberrant *BCL2* expression provides cells with an anti-apoptotic signal, resulting in a growth advantage for these cells at the follicular center cell stage, a majority of which would otherwise die because of apoptosis.

In the case of DLBCLs it is somewhat difficult to evaluate the role of *BCL6* translocation because DLBCLs comprise a number of disease entities.[2, 10–12] The *BCL6* gene is expressed at the follicular center cell stage during normal development, but not in mantle or marginal zone cells.[5] It is therefore conceivable that the expression caused by chromosome translocation becomes aberrant at the post-GC stage where the *BCL6* gene is down-regulated in normal B-cell development. For these reasons, the effect of *BCL6* translocation on DLBCL appears to be similar to the effect of *BCL1* translocation on MCL and that of *BCL2* translocation on FL.

Functional categories of chromosome translocation for lymphomagenesis

Chromosome translocations found in B-cell lymphomas are classified into three functional categories, enhancement of proliferation, inhibition of differentiation and anti-apoptotic activity, as shown in Fig. 3. These three categories are important for understanding the common mechanisms of lymphomagenesis. First, this discussion will focus on *BCL2* translocation for follicular lymphoma.

BCL2 is known to have an anti-apoptotic function against various death signals.[13] The aberrant expression caused by chromosome translocation will provide cells at the follicular center cell stage with an anti-apoptotic signal. This represents a growth advantage for cells at this stage, because most of them would die without *BCL2* expression. However, *BCL2* does not provide a growth-promoting signal, so that there must be other signals that make the cells proliferate. For a full understanding of the mechanism of FL development, the unique growth pattern of FL, which is characterized by the formation of many follicles where lymphoma cells proliferate, must be taken into account. Kagami *et al*. have provided important evidence that follicular dendritic cells (FDCs) can support follicular lymphoma cells, and they also established a follicular lymphoma cell line whose growth depends on the presence of FDCs.[14] Although soluble factors could support its growth for a short time, it was shown that direct contact of lymphoma cells with FDCs is required for longer-lasting growth. Dogan *et al*. also showed that FL cells proliferated in the follicles but not outside of them.[15] Both of these reports strongly indicate that FDCs are essential for the growth of FL cells. Thus, aberrant *BCL2* expression caused by chromosome translocation prevents cell death of FL cells originating from follicular center cells, while at the same time FDCs provide them with growth signals.

A similar scenario can be drawn up for MCL development. MCLs originating from the developmental stage of mantle cells proliferate in response to the growth signal from the aberrant expression of the *BCL1* gene. At the same time, the anti-apoptotic function is provided by *BCL2*. Examination of the developmental stage of MCLs shows that they are naïve-B cells in which *BCL2* is expressed and that reside in the mantle zone (Figs. 1 and 2). The *BCL2* expression at this stage is not caused by chromosome translocation; *BCL2* is one of the genes that are normally expressed at this stage of development. The *BCL2* expression at this stage is reasonable because naïve-B cells need to remain alive at the G0 stage for an as-yet unknown period of time before they are exposed to antigens.

In the case of DLBCLs with *BCL6* translocation, *BCL6* expression is aberrant for cells at the post-GC stage, but it is not known exactly what kind of signal is provided. However, it is clear that the anti-apoptotic function must be provided by *BCL2*, which is expressed at the post-GC stage (Fig. 2). Some evidence indicates that BCL6 may function to protect cells against terminal differentiation.[16, 17] It is indeed true that differentiation block can be oncogenic, as demonstrated for PML-RARα in acute promyelocytic leukemia (FAB classification, M3). It remains to be explored, however, what kind of proliferation signals are provided for DLBCLs.

Translocation alone cannot make cells malignant

BCL2 translocation has been proven to exist in the peripheral blood mononuclear cells (PBMNC) of 16–45% of normal individuals when analyzed with 1×10^6 cells.[18, 19] Since the lymphoid organs of all normal individuals contain FDCs, if *BCL2* translocation alone is the single genetic alteration required for

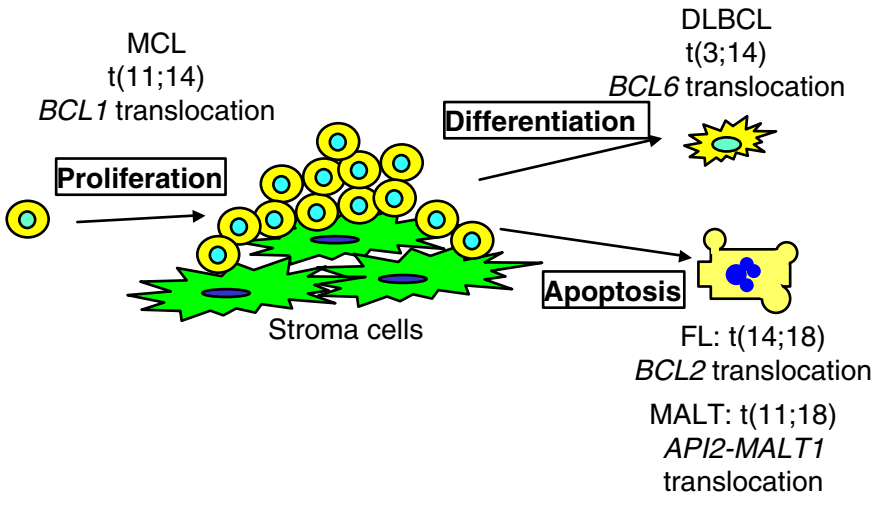

Fig. 3. Proliferation, differentiation and apoptosis associated with various types of lymphomas and chromosome translocations. Each lymphoma has a specific proliferation site, as is most clearly represented by the follicular lymphoma that proliferates in the follicles.[15] Specific chromosome translocations associated with each type of lymphoma are shown. *BCL1* translocation results in deregulation of the cell cycle. *BCL6* translocation is not yet clearly understood, but it is well known that the *BCL6* knock-out mouse fails to generate secondary follicles, suggesting that *BCL6* translocation is associated with deregulation of differentiation. *BCL2* and *API2-MALT1* are known to have anti-apoptotic function.[13, 34] Stroma cells are depicted because their importance for lymphomagenesis has been shown.[14, 15]

FL development, 16 to 45% of all normal individuals should develop FLs. However, this is not the case. Statistical data suggest that only one in 1,000,000 Japanese develop follicular lymphoma.[20] Then, what is the reason why people with *BCL2* translocation do not develop FLs? The fact that FL development occurs less frequently than *BCL2* translocation itself indicates that *BCL2* translocation alone is not enough for cells to become malignant, and that multi-genetic (also epigenetic) alterations are likely to be required for FL development. The exploration of these genetic and/or epigenetic alterations leading to lymphoma development is one of the most important directions for future exploration.

MALT lymphoma

The development of malignant lymphomas with deregulated types of translocation has been discussed. Can this concept also be applied to malignant lymphomas with fusion gene type translocation, and perhaps even to lymphomas without translocation?

MALT lymphoma is unique in various respects. This low-grade B-cell lymphoma originates from an extranodal lymphoid organ, known as mucosa-associated lymphoid tissue (MALT), which is different from lymphoid organs such as lymph node or spleen. MALT lymphomas are thought to originate from cells in the marginal zone of secondary follicles that are generated in response to various types of chronic inflammation.[2, 21] These

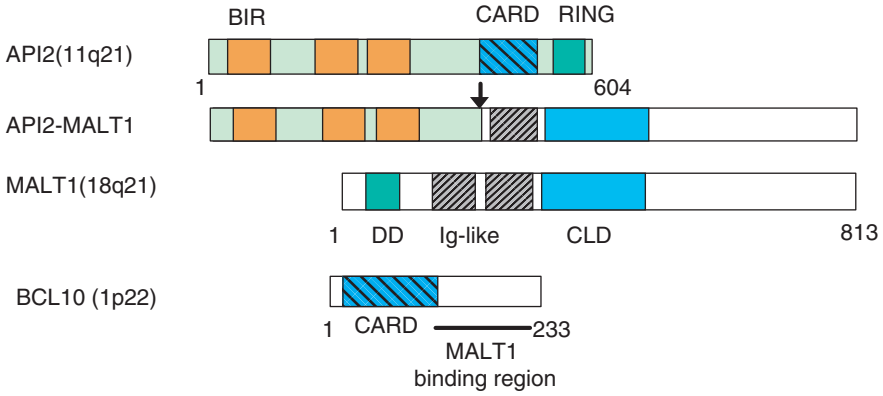

Fig. 4. Gene products involved in MALT lymphoma. *API2* (APoptosis Inhibitor protein 2) gene was originally identified as a TNFR2-associated protein and found to have an anti-apoptotic function.[27] API2-MALT1 chimeric products were identified as a result of the analysis of t(11;18)(q21;q21).[28–30] MALT1 is a novel protein with unknown function.[28, 29] *BCL10* was isolated from the chromosome translocation junction region at 1p22 that is activated by juxtaposition of the *IgH* gene in t(1;14)(p22;q34).[22] It was recently found that MALT1 and BCL10 play an important role in signal transduction of cell-surface antigen receptors on B and T lymphocytes. It was also shown that MALT1 binds BCL10 through two Ig-like domains.[31] BIR, Baculovirus Inhibitor of apoptosis Repeat; CARD, CAspase Recruitment Domain; RING, RING finger domain; DD, Death Domain; Ig-like, Immunoglobulin-like domain; CLD, Caspase Like Domain.

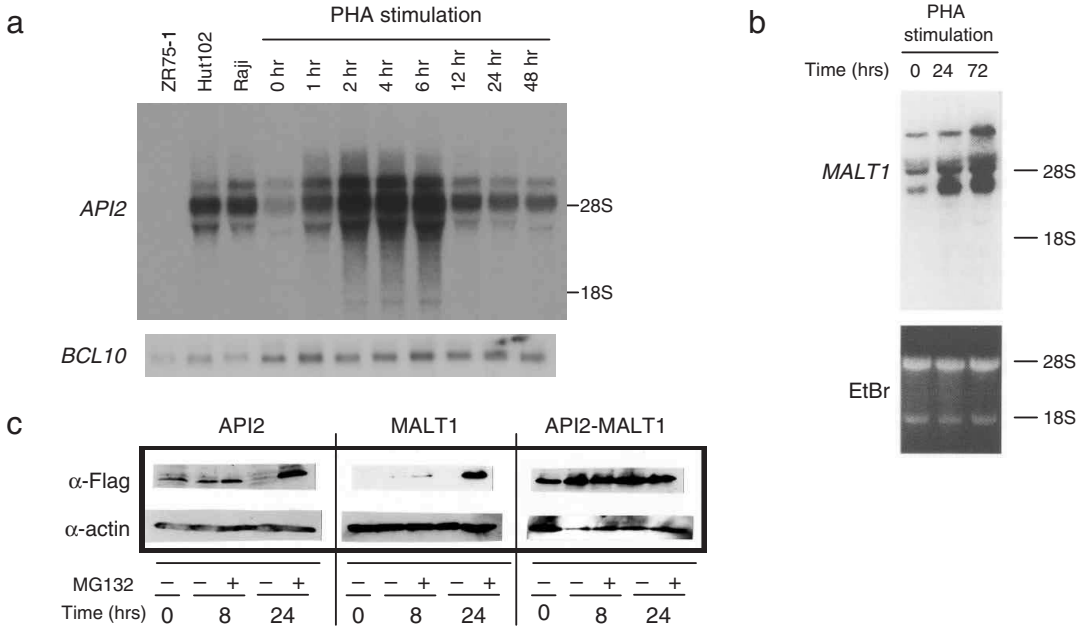

Fig. 5. a) API2, MALT1 and BCL10 kinetics upon PHA stimulation and protein stability. PBMNCs are stimulated with PHA (10 ml of 1.0×10^6 cells/ml with 30 μg/ml of PHA), after which cells are harvested at the indicated time points. After harvesting, total RNA was prepared and 5 μg/lane was applied. The *API2* signal rapidly increased within 1 h and stayed at that level for 6 h. The signal then slowly decreased, but even at 48 h, the signal was stronger than at 0 h. *BCL10* expression, however, did not change during the PHA stimulation. b) *MALT1* expression was also activated upon PHA stimulation although the activation is slower than that of API2. ZR75-1, a breast cancer cell line; Hut102, a T-cell line; Raji, a B-cell line. EtBr, ethidium bromide staining. c) Western blot analysis of *API2*, *MALT1* and *API2-MALT1* with or without MG132. Cos cells (2×10^4 cells) in a 6-cm dish were transiently transfected with the indicated expression vectors and after 24 h, MG132 (10 μ*M*), a proteasome inhibitor, was added. After 8 and 24 h, cells were harvested and subjected to western blot analysis. *API2* and *MALT1* were not detected in the absence of MG132, while API2-MALT1 chimeric protein did not show any significant difference between lanes in the presence or absence of MG132, indicating that API2 and MALT1 are unstable but that API2-MALT1 chimeric protein is stable in the proteasome-mediated degradation pathway.

include chronic gastritis due to *Helicobacter pylori* and chronic inflammation induced by autoimmune diseases such as Hashimoto's disease (chronic thyroiditis) and Sjögren's syndrome (chronic inflammation of the salivary and lacrimal glands). Finally, the lesion of MALT lymphoma tends to reside within the original organ until the late stage of the disease. All these features are unique to MALT lymphoma. Characteristic chromosome aberrations are t(1;14)(p22;q32)[22] and t(11;18)(q21;q21). The former is the *IgH-BCL10* translocation found in about 3% of MALT lymphomas and the latter, that of *API2-MALT1* found in about 30% of the cases.

MALT lymphoma: marginal zone between tumor and inflammation

The most distinct feature of MALT lymphoma is seen in gastric MALT lymphoma, with 70–80% of cases known to regress in response to *H. pylori* eradication therapy with antibiotics. However, it is also true that 20–30% do not regress in spite of successful *H. pylori* eradication.[23–25] This leads to the possibility that gastric MALT lymphoma may not be a true tumor but rather a reactive hyperplasia or inflammation. MALT lymphomas are diagnosed by grading from 0 to 5 (grade 0, normal; grade 1, chronic active gastritis; grade 2, chronic active gastritis with florid lymphoid follicle formation; grade 3, suspicious lymphoid infiltrate, probably reactive; grade 4, suspicious lymphoid infiltrate, probably lymphoma; grade 5, MALT lymphoma). Most of the cases of grade 4 or beyond (4 and 5) have been found to show a clonal proliferation, indicating that there are cases with monoclonal proliferation that regress in response to *H. pylori* eradication.[24] These features seem to beg the question whether MALT lymphoma is a tumor or an inflammation, but in fact indicate that MALT lymphoma should be classified somewhere between tumors and inflammations. Others as well as we have demonstrated that a majority of gastric MALT lymphomas resistant to *H. pylori* eradication therapy contain the *API2-MALT1* chimeric gene.[23, 25] This means that, while it can be agreed that MALT lymphoma with *API2-MALT1* is a tumor, the question remains whether MALT lymphoma with monoclonal proliferation responding to *H. pylori* eradication therapy is a tumor or inflammation.

Proliferation, differentiation and apoptosis in MALT lymphoma

The genes known to be involved in MALT lymphomas are *BCL10, API2, MALT1* and *API2-MALT1* (Fig. 4).[22, 27–30] *H. pylori* gastritis inflammation also plays a major role in gastric MALT lymphomagenesis. Although the kinetics differ, both *API2* and *MALT1* in lymphoid cells are transcriptionally activated upon PHA stimulation, suggesting that both genes are up-regulated under inflammatory conditions (Fig. 5, a and b). *BCL10*, on the other hand, is consistently expressed under conditions of PHA stimulation (Fig 5a). MALT1 was recently found to bind to BCL10 (Fig. 4) and to enhance NF-κB transcription.[31] It is also important to note that *API2-MALT1* alone can activate NF-κB.[31] Based on these findings, a possible schema of gastric MALT lymphomagenesis is shown in Fig. 6. First, *H. pylori* infection induces inflammation that is the result of the interaction of T cells, B cells and antigen-presenting cells (APC). This interaction provides a growth-promoting effect for lymphoid cells, partly involving cytokines. The inflammatory stimuli, at the same time, result in the up-regulation of *MALT1* and *API2* genes. The up-regulation of *MALT1* results in an increase in the amount of BCL10-MALT1 complex that activates NF-κB, while *API2* activation by itself provides anti-apoptotic activity. Both of these functions most likely provide the cells

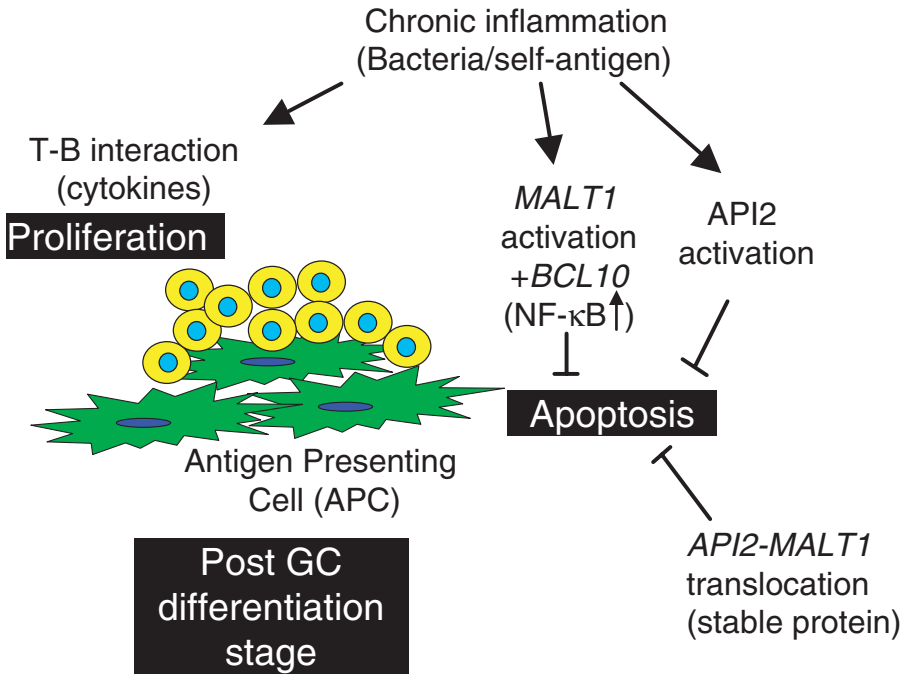

Fig. 6. Chronic inflammation and MALT lymphoma. When inflammation is induced by either bacteria such as *H. pylori* or immunoreaction against autoantigens, T-B-APC (antigen presenting cells) interactions are induced and lymphoid cells will proliferate. The inflammation then activates *MALT1* and *API2* transcription in the stimulated cells. Activation of *MALT1* will cause an increase in the BCL10-MALT1 complex, that in turn will activate NF-κB. *API2* is also activated and the increase in API2 protein will inhibit apoptosis. During these reactions, monoclonal B-cells seem to be selected by an as-yet unknown mechanism. The clone can grow as long as the inflammation is present. In the case of gastric MALT lymphoma, when the inflammation is removed by *H. pylori* eradication, T-B-APC interactions as well as *MALT1* and *API2* activations will disappear, resulting in lymphoma cell death. However, if the *API2-MALT1* chimeric gene is present in lymphoma cells, the stable API2-MALT1 chimeric protein will be maintained even after the inflammation has been eliminated, preventing apoptosis of lymphoma cells and maintaining NF-κB activity, thus resulting in resistance to *H. pylori* eradication treatment.

with anti-apoptotic activity, and cytokines produced as a result of T-B-APC interaction can be expected to stimulate cell growth. This schema is very similar to that for follicular lymphomas growth, although the genes, molecules, and differentiation stages involved are different (Fig. 3)

It remains enigmatic why in MALT lymphomagenesis B cells, but not T-cells, are selected for the lymphoma even though it has been demonstrated that T cells are essential for the growth of MALT lymphoma cells.[32] When *API2-MALT1* translocation takes place, the chimeric *API2-MALT1* protein is produced (Fig. 4), which, interestingly, becomes very stable although each of the gene products is unstable (Fig. 5c).[33] We have recently shown that *API2-MALT1* exerts an anti-apoptotic activity,[34] so that the production of *API2-MALT1* alone can replace NF-κB activation caused by the *BCL10-MALT1* complex under inflammatory circumstances.[31] The effect of this chimeric protein can also replace the anti-apoptotic activity of *API2* (Fig. 6).[34] Thus, one can speculate that the clinicopathologic difference between MALT lymphomas with *API2-MALT1* and those without it is the result of the difference in stability between *API2-MALT1* fusion protein and the respective gene products. When antibiotics remove all of the inflammatory circumstances, T-B-APC interactions as well as *MALT1* and *API2* activations would be eliminated. This is indeed the case for MALT lymphoma without *API2-MALT1*. In the presence of the stable *API2-MALT1* chimeric protein, however, its stable expression helps cells to remain resistant to cell death signals through removal of the inflammation. This concept provides a clear explanation of the difference between MALT lymphoma with and without *API2-MALT1*. Regarding the mechanism of MALT lymphomagenesis, a question remains, however, about the role for lymphomagenesis of BCL2 expression at the marginal zone stage (Fig. 2), which should give anti-apoptotic function to the cells at this stage. One possibility is that the genes involved in lymphomagenesis may require a specific developmental stage at which to exert oncogenic activity. Alternatively, BCL2 expression at this stage is not strong enough to prevent apoptosis, so that anti-apoptotic function of API2-MALT1 is required.

Perspective

Whether MALT lymphomas with monoclonal proliferation that regress in response to *H. pylori* eradication can be completely cured remains to be explored. If the regressed monoclonal lymphoma does not recur, it may be assumed that MALT lymphoma showing regression in response to *H. pylori* eradication is a reactive inflammation. However, it can also be speculated that monoclonal MALT lymphoma which has regressed as result of *H. pylori* eradication, would recur upon re-infection with *H. pylori*. The normal counterparts of MALT lymphoma cells are marginal zone cells that are likely to be memory B-cells, which would be difficult to completely eradicate without cytotoxic agents. Memory B-cells can survive for quite a long time, which suggests that eradication of *H. pylori* can reduce the number of cells but would fail to eliminate the clone. This is very similar to the situation encountered in autoimmune diseases, where elimination of the auto-reactive clone is extremely difficult once autoimmunity has been established. This is also likely to be the case for MALT lymphoma, because it is a lymphoma originating from memory B-cells. In a clinical setting, however, eradication of *H. pylori* would be the first priority because it is not toxic, and also because the prognosis for MALT lymphoma is very good in comparison to that for other types of lymphoma. Careful observation and clinical management are warranted, however, to gain insight into the molecular nature of lymphomagenesis not only of MALT lymphoma, but also of other types of malignant lymphomas. Further analyses for multigenetic and epigenetic alterations in malignant lymphoma by various means, including array CGH, are also important to explore new insights into molecular mechanisms of lymphomagenesis,[35, 36] which should lead to new therapeutic strategies.

Conclusion

Development of malignant lymphoma can be understood in terms of three factors, i.e. proliferation, differentiation and apoptosis. These factors are manifested by chromosome translocations that are closely associated with a specific disease entity. However, such chromosome translocations alone are not enough for the cells to become malignant. FL and MCL in association with *BCL2* and *BCL1* translocation, respectively, were examined as factors other than chromosome translocation that may play an important role in lymphomagenesis. The findings presented and discussed here make it clear that the controversy over whether MALT lymphoma is a tumor or an inflammation can now be resolved. That is, if monoclonal expansion is observed, it is likely to be a tumor. Thus, the concept of three factors in lymphomagenesis can be applied to not only MCL, FL and DLBCL, but also to MALT lymphoma.

The author is especially grateful to Dr. Shigeo Nakamura at Aichi Cancer Hospital for continuous guidance on malignant lymphoma research and to Dr. Yasuo Morishima for suggestions from a clinical viewpoint. The author was first guided by Dr. Stanley J. Korsmeyer at National Cancer Institute, Bethesda (now at Dana-Faber Cancer Institute) on the basic ideas of molecular mechanisms of lymphomagenesis. His continuous support and encouragement are greatly appreciated. The work reviewed here was supported in part by a Grant-in-Aid from the Ministry of Health, Labour and Welfare, a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology, a Grant-in-Aid (B2) from the Japan Society for the Promotion of Science, a Grant-in-Aid from the Foundation of Promotion of Cancer Research, a Grant-in-Aid for Cancer Research from the Princess Takamatsu Cancer Research Fund, and a Grant-in-Aid from the China Japan Medical Association.

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