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Molecular pathogenesis of lymphomas of mucosa-associated lymphoid tissue—from (auto)antigen driven selection to the activation of NF-κB signaling

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Lymphomas of mucosa-associated lymphoid tissue (MALT) are typically present at sites such as the stomach, lung or urinary tract, where lymphoid tissues scatter in mucosa lamina propria, intra- or sub-epithelial cells. The infection of certain pathogens, such as *Helicobacter pylori*, *Chlamydophila psittaci, Borrelia burgdorferi*, hepatitis C virus, or certain autoantigens cause these sites to generate a germinal center called the "acquired lymphoid tissue". The molecular pathogenesis of MALT lymphoma is a multi-step process. Receptor signaling, such as the contact stimulation of B cell receptors and CD4 positive T cells mediated by CD40/CD40-ligand and T helper cell type 2 cytokines like interleukin-4, contributes to tumor cell proliferation. A number of genetic alterations have been identified in MALT lymphoma, and among them are important translocations, such as t(11;18)(q21;q21), t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14)(p13;q32). Fusion proteins generated by these translocations share the same NF-κB signaling pathway, which is activated by the caspase activation and recruitment domain containing molecules of the membrane associated guanylate kinase family, B cell lymphoma-10 and MALT1 (CBM) protein complex. They act downstream of cell surface receptors, such as B cell receptors, T cell receptors, B cell activating factors and Toll-like receptors, and participate in the biological process of MALT lymphoma. The discovery of therapeutic drugs that exclusively inhibit the antigen receptor signaling pathway will be beneficial for the treatment of B cell lymphomas in the future.

malt lymphoma, helicobacter pylori, chromosomal translocation, genetic alteration, NF-κB

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Marginal zone lymphomas (MZLs) originate from the marginal zone and are categorized into three subtypes according to the World Health Organization (WHO) classification, including splenic MZL, extranodal MZL of mucosa-associated lymphoid tissue (MALT) type and nodal MZL. Among them, the MALT lymphoma accounts for 8% of the non-Hodgkin's lymphomas.

MALT usually refers to an organized lymphoid tissue with a germinal center, such as the tonsils, intestinal Peyer's patches (or aggregated lymphoid nodules), the appendix. In addition, the gastric, respiratory and urinary tract (lymphoid tissue without capsule, scatter in mucosa lamina propria, intra- or sub-epithelial cells) also account for a proportion of MALT. MALT plays an important role in the resistance of the mucosal immune system to external microbial invasions. However, due to the constant stimulation of certain antigens, the intra-epithelial, lamina propria and sub-epithelial lymphocytes of the extranodal organs generate a germinal center, which is also called "acquired lymphoid tissue" [1]. Consequently, further genetic alterations promote tumor formation.

Infections of certain pathogens are more common in MALT, such as *Helicobacter pylori (Hp)*, *Chlamydophila psittaci (Cp)*, *Borrelia burgdorferi*, hepatitis C virus (HCV),

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or autoimmune responses of autoantigens. Low-grade MALT lymphomas always exhibit an indolent feature and progress slowly, and the use of antibiotics to eliminate certain pathogens, such as *Hp*, leads to the complete or partial regression of low-grade gastric MALT lymphomas in approximately 70% of cases, as determined by echoendoscopy [2]. Currently, some genetic abnormalities, such as chromosomal translocations, were found in MALT lymphomas, and the characteristics of the fusion proteins encoded by these genes, such as apoptosis inhibitor 2 (API2), also called baculoviral inhibitor apoptosis protein repeat containing 3(BIRC-3), forming fusion protein API2/BIRC3-MALT1, were found to be associated with antibiotic refractory (such as *Hp* eradication therapy) and high-grade transformation [3]. Most of the fusion proteins generated by chromosomal translocation participate in the activation of the signaling of nuclear factor κ light chain enhancer of activated B cell (NF-κB) [4], a protein complex that plays an important role in the immune response to infection. Activation of the NF-κB signaling pathway of MALT lymphomas leads to the proliferation of tumor B cells without the help of the B cell receptor (BCR). In this review, we summarize recent advances in the study of the molecular pathogenesis of MALT lymphoma.

1 Strain-specific or autoantigen-driven selection

1.1 Helicobacter pylori

Currently, a large number of studies ranging from epidemiologic and biological to molecular and genetic studies have supported a causative role of *Hp* in the pathogenesis of gastric MALT lymphoma [5–7]. *Hp*, a spiral microaerophilic bacterium, indirectly induces the proliferation of low-grade B cells in gastric MALT lymphoma, and this effect is site- and strain-specific. Most strains of *Hp* possess the cytotoxin-associated antigen (Cag A), a 120–145 kilodalton protein. Recently, Ye et al. [8] found that Cag A was highly associated with the MALT lymphoma harboring t(11;18)(q21;q21), which exhibits advanced inflammation and the production of certain chemokines in the tumor microenvironment. Other investigators provided evidence that Cag A can reverse the effect of the drug hydroxyurea by inhibiting P53 accumulation, which leads to B cell proliferation without the control of programmed cell death [9,10].

1.2 Other microorganisms

Other microorganisms associated with MALT lymphoma include *Cp*, which is found in ocular adnexa MALT lymphoma (OAMZL) [11,12], and *Borrelia burgdorferi* in cutaneous MALT lymphomas [13–15]. Molecular analysis showed that at an early stage in OAMZL, *Cp* is able to cross-react with self-antigens and promotes inflammation in the tumor microenvironment. With the progression of this disease, autoantigens are presented and eventually promote the proliferation and expansion of self-reactive B cells, which are independent of the support from the tumor microenvironment [16]. The fact that using antiviral therapy for HCV-related B-cell non-Hodgkin's lymphoma (B-NHL) can lead to partial or complete regression, elucidating a cause and effect relationship between HCV infection and the development of lymphoma. Hepatitis C virus infections are documented in half of the patients with gastric MZL [17] and one-third of the patients with non-gastric MALT lymphoma [18]. The continuous stimulation of viral antigens and intracellular replication of the HCV virus could cause permanent B-cell damage and is proposed to be the main determinant of the pathogenesis of HCV-related B-NHL [19].

1.3 Autoantigens

Patients with autoimmune diseases are prone to suffer from MALT lymphomas. Sjögren's Syndrome (SS) patients exhibit a 44-fold increased risk of developing a MALT lymphoma in the parotid gland [20], while patients with Hashimoto's thyroiditis have a 3-fold higher risk of developing lymphoma [21]. The presence of antigen-selective pressure was demonstrated by the analysis of variable part mutations in the immunoglobulin heavy chain (V_H) gene. Preferential use of V_{H1}, V_{H3} and V_{H4} family genes and the ongoing mutations in the *IgH* gene observed in MALT lymphomas imply the production of autoantibodies [22] and the role of certain antigenic stimulations in the clonal expansion of tumor cells [23,24].

2 Receptor signaling leading to monoclonal B lymphocytes proliferation

2.1 Contact stimulation of BCRs and CD4+T cells mediated by CD40/CD40L and T helper cell type 2 cytokines

The molecular pathogenesis of MALT lymphoma is a multistep process, starting with the infection of microorganisms. Accumulating evidence reveals that *Hp* does not directly stimulate the proliferation of B cell lymphomas. Previous studies by Hussell et al. [25] found that removing tumor-infiltrating T cells before the experiment or adding anti-CD40L to the *Hp* strain, which stimulates MALT lymphoma in cell culture, blocks all of the effects of *Hp* on tumor B cells. Therefore, they concluded that the proliferative responses of tumor B cells rely on contact-dependent help from *Hp*-specific T cells via the CD40-CD40L interaction. However, this conclusion is under debate. The study by Craig et al. [26] found that depleting CD40L+ cells from the cultures and blocking the direct interaction between CD40L and its receptor did not abrogate tumor cell proliferation.

Additionally, increased levels of immunoglobulin and interleukin (IL)-2 were shown in response to bacterial stimulation. Tumor B cell proliferation was dramatically enhanced in the presence of tumor-infiltrating CD4+T cells, which produced large quantities of T helper cell type 2 (Th2) cytokines, such as IL-4. All of these observations suggest that interleukins play a role in the proliferation of tumor B cells and that soluble activated T cell-derived signals are more important than direct interactions between the cell types for the induction of tumor B-cell proliferation [26].

2.2 Regulatory T cells—highly suppressive to effector T cells and essential for tumor B-cell proliferation

Increasing evidence shows that the regulatory T cells (Tregs) play a role in MALT lymphoma [27,28]. Immunohistochemical staining of FoxP3 in human low-grade gastric MALT lymphoma showed that FoxP3+ Tregs heavily infiltrated tumor tissue [26]. Patients with a higher number of tumor cells with infiltrating Foxp3+ showed a favorable prognosis due to better responses to antibiotics [29]. Craig et al. [26] conducted a transwell migration assay to observe the migration of Tregs toward supernatants of cultures that had been induced to proliferate by adding *Helicobacter* extract. This chemo-attraction process of Tregs was maintained, at least partially, in pure B cell cultures and is approximately proportional to their level of proliferation. However, the depletion of total $CD4^+$, $CD40L^+$ or $CD25^+$ T cells prevented tumor cells from proliferation [26].

2.3 Toll-like and B-cell activating factor receptors

Bacterial ligands and some autoantigens recognized by Toll-like receptors (TLRs) activate the release of proinflammatory cytokines and chemokines that trigger the proliferation of B cells. A study by Adam et al. [30] showed that gastric MALT lymphoma exclusively express TLR4, which enables the tumor to interact with *Hp* and autoantigens. B-cell activating factor (BAFF), is part of the tumor necrosis factor ligand family and plays an important role in the proliferation and differentiation of B cells [31]. In the case of SS, the overexpression of BAFF causes excessive immunoglobulin production and exerts a sustained stimulation of B cell proliferation, leading to the production of autoantibody-producing plasma cells [32].

3 The microenvironment of "acquired lymphoid tissue"

In addition to the contact stimulation of BCRs and $CD4^+$ T cells mediated by CD40/CD40L and Th2 cytokines induced by certain pathogens or autoantigens, another important component of the "acquired lymphoid tissue" are the neutrophils [33]. Certain pathogens, such as *Hp*, recruits neutrophils and promotes reactive oxygen species (ROS) [34]. The presence of excessive ROS can cause fatal cellular lesions by damaging cellular proteins, lipids and DNA [35]. ROS are associated with various transcription factors, such as NF-κB[36], activator protein-1 (AP-1) [37], hypoxia-inducible factor-1α [38] and signal transducer and activator of transcription 3 (STAT3) [39], which are involved in inflammation, cellular transformation and tumor biology. Furthermore, ROS also control the expression of various tumor suppressor genes, such as phosphatase and tensin homolog (PTEN) [40]. Other studies showed that nicotinamide adenine dinucleotide phosphate oxide 2 (NOX2), a product of ROS, is overexpressed in gastric MALT compared to patients with gastritis [41]. This implies that ROS participate in the formation of the "acquired lymphoid tissue". Another component of the "acquired lymphoid tissue" is the lymphoma-associated macrophages that release a proliferation inducing ligand (APRIL), which promotes the progression of *Hp*-associated MALT lymphoma [42,43]. With the help of *Hp*-specific T-cells, this phenomenon could be further amplified and prolonged [43]. Finally, the up-regulation of certain chemokines, such as C-C chemokine receptor type 7 (CCR7), CXC chemokine receptor (CXCR)3, CXCR7 and Chemokine C-X-C motif ligand 12 (CXCL12), as well the down-regulation of CXCR4, are found in gastric MALT lymphoma, which indicates that chemokines also play an important role in disease progression (Figure 1) [44,45].

4 Genetic abnormalities in MALT lymphomas

4.1 Chromosomal translocation and its fusion protein

A number of genetic alterations have been identified in MALT lymphomas. These abnormalities include aneuploidy, such as trisomy 3,7,12 and 18, and a number of chromosomal translocations, such as t(11;18)(q21;q21),t(1;14)(p22;q32), t(14;18)(q32;q21) and t(3;14)(p13;q32). Other abnormalities include point mutations in the c-Myc oncogene [46], loss of heterozygosity in the *P53* gene [47], somatic mutation of Fas/CD95 [48], and CpG island hyper-methylation [49].

4.1.1 t(11;18)(q21;q21)—API2(BIRC3)-MALT1

t(11;18)(q21;q21) is mostly seen in gastric MALT lymphoma. The *API2* gene is located at 11q21, and the *MALT1* gene is located at 18q21. The full-length protein product of API2, also called BIRC3, belongs to the inhibitor apoptosis protein (IAP) family and inhibits the biological activity of caspases 3, 7 and 9 [50,51]. API2-MALT1 is comprised of the N-terminal API2 region with three intact baculovirus inhibitors of apoptosis protein repeat domains (BIR) and an intact caspase-like domain in the C-terminal MALT1 region (Figure 2). API2-MALT1 is significantly associated with infections of the Cag A-positive strains of *Hp* and induces

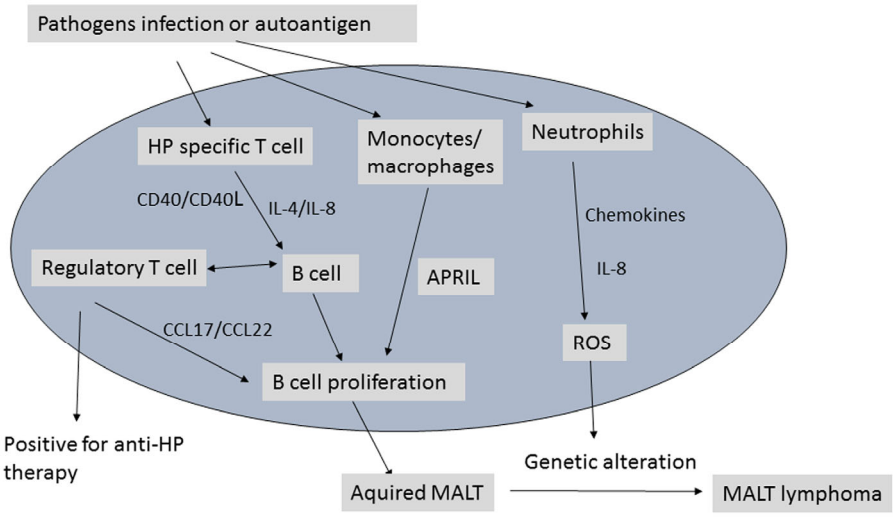

Figure 1 (color online) Microenvironment of the "acquired lymphoid tissue". The infection of certain pathogens or autoantigens induce chronic inflammation by attracting T-cells, B-cells, regulatory T-cells, neutrophils, macrophages, cytokines and chemokines.

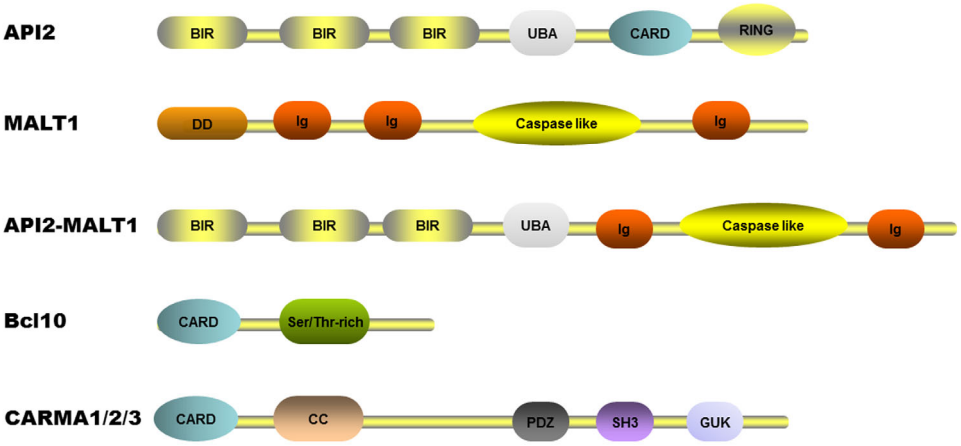

Figure 2 (color online) Structure of the API2, MALT1, Bcl-10 and CARMA. *API2* gene comprises three BIR, a CARD motif and a C-terminal zinc-binding RING-finger domain; *MALT1* gene comprises an N-terminal death domain (DD), two immunoglobulin-like domains (Ig-I) and a caspase-like domain; Bcl-10 encodes a CARD motif and a Ser/Thr-rich carboxylterminus; CARMA1/2/3 comprises the PSD-95/Dig/Z0-1 homologous (PDZ) domain, the Src-homology (SH3) domain, the guanylate kinase (GUK)-like domain, the coiled coil (CC) domain and an N-terminal CARD.

the release of IL-8 to activate neutrophils and ROS [8]. And this translocation exhibits more resistance to antibiotic treatments than other translocation types [3,52]. API2-MALT1 deregulates MALT1 ubiquitin ligase activity, causing the constitutive activation of NF-κB and promoting tumorigenesis [53]. It is thought that the presence of this translocation is not related to the transformation of MALT lymphoma into gastric diffuse large B-cell lymphoma (DLBCL) because no frequency difference was found between these two diseases [54].

4.1.2 t(1;14)(p22;q32)—IGH-Bcl-10

MALT lymphomas that harbor t(1;14)(p22;q32) tend to be associated with advanced stages of the disease [55]. Translocation to chromosome 14 brings Bcl-10 under the control of *IGH*-gene enhancer, which results in the nuclear overexpression of Bcl-10 [56]. Wild-type Bcl-10 is believed to promote proliferation rather than apoptosis [57]. It encodes an intracellular protein of 233 amino acids, characterized by an amino-terminal caspase activation and recruitment domain (CARD) motif and a Ser/Thr-rich carboxyl terminus of unknown function (Figure 2).

4.1.3 t(14;18)(q32;q21)—IGH-MALT1

Translocation of t(14;18)(q32;q21) always occurs outside the gastrointestinal or pulmonary tract, in the ocular adnexa, skin, liver or salivary glands [58–60]. This type of translocation is mainly associated with autoantigens rather than infectious agents. Similar to t(1;14)(q22;q32), the *MALT1* gene is controlled by IGH, which leads to the overexpres-

sion of MALT1. *In vitro* and *in vivo* experiments have shown that MALT1 is associated with Bcl-10 in the enhancement of NF-κB activation in both B and T cells, suggesting that these proteins might function together in the same signaling pathway [61].

4.1.4 t(3;14)(p13;q32)—IGH-FoxP1

The *FoxP1* gene is located at 3p13 and codes for a member of the forkhead box (FOX) family of transcription factors. It contains a common DNA-binding winged helix or forkhead-domain and N-terminal zinc-finger and leucine-zipper domains [62]. Spontaneous mutations in these regions are related to various congenital disorders; additionally, FOX transcription factors play a role in carcinogenesis via retroviral integration, transcriptional regulation, chromosomal translocation and gene amplification [63]. Recently, FoxP1 was found to be expressed in lymphoid tissue. Similar to t(1;14)(q22;q32), t(3;14)(p13;q32) leads to the overexpression of MALT1. However, the significance of FoxP1 overexpression in lymphomas is controversial. One study found nuclear FoxP1-positive cells to be confined to MALT lymphomas with poor clinical outcome [64].

4.1.5 t(X;14)(p11;q32)—IGH-GPR34

Recently, studies found that loss-of-function mutations in certain gene cause X linked lymphoproliferative disease [65,66]. By using interphase fluorescence *in situ* hybridization (FISH), Ansell and his colleagues found a novel translocation involving the IGH locus and an unknown partner in a primary MALT lymphoma patient with SS [67]. This unknown partner is now confirmed to be the X chromosome, resulting in the deregulation of the expression of the G-protein-coupled receptor, GPR34. Increased levels of GPR34 were detected in MZL tumor cells and normal immune cells. The overexpression of GPR34 results in the phosphorylation of extracellular signal regulated kinase (ERK) and protein kinase C (PKC) and induces NF-κB-related gene transcription, thus leading to increased cell proliferation [67].

4.2 MicroRNA is related to MALT lymphoma

MicroRNAs represent important regulators of gene expression, ranging from B-cell maturation to the generation of various differential stages of B cells [68]. They also participate in the regulation of important signaling pathways, such as NF-κB [69], phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/ protein kinase B (also known as AKt) [70], tumor growth factor-β (TGF-β)[71], and BCR signaling [72], and regulate pro-apoptotic proteins, such as Bcl-2 [73], p53 [74] and transcription factors, such as Myc, FoxP1 [75] and Bcl-6 [76]. MALT lymphomas may transform into gastric diffuse large B-cell lymphoma (gDLBCL); however, the mechanisms of this transformation have not been elucidated. Craig et al. [75] used a microarray approach to compare the microRNA expression profiles of gastric MALT lymphoma and gDLBCL. They found that microRNAs, which were deregulated in high-grade but not low-grade cases, were transcriptionally repressed by Myc. By knocking down Myc, the proliferation of DLBCL cell lines was blocked. Furthermore, they found tumor-suppressive effects of miR-34a on the deregulation of its target, FoxP1. Similarly, using microarrays, Craig et al. [75] revealed a strong down-regulation of the tumor suppressor miR-203 in human MALT lymphoma samples as a result of the hypermethylation of the promoter of this locus. Demethylating agents led to increased miR-203 expression and down-regulation of the target of miR-203, leukemia viral oncogene homolog1 (ABL1). Conversely, re-expression of miR-203 was sufficient to prevent tumor cell proliferation *in vitro*.

5 Activation of the NF-κB pathway in MALT lymphomas

NF-κB signaling is a well-known pathway that controls DNA transcription ranging from the production of inflammatory mediators to cell survival and proliferation [53]. It can be activated by a number of cell-surface receptors, including tumor necrosis factor (TNF), IL-1, TLR, lymphotoxin (LT)- β, and BAFF receptors [77], and plays a pivotal role in regulating the immune response to infection. Three independently existing fusion proteins mentioned before, IGH-BCL10, IGH-MALT1 and API2-MALT1, are the result of translocations and share a common cell survival pathway—that of NF-κB signaling. The NF-κB family comprises homodimers or heterodimers of five members (p50, p52, RelA, RelB or c-Rel) and is classified into two distinct pathways: the canonical and noncanonical pathways (Figure 2).

In the canonical pathway, in an unstimulated state, RelA/p50 dimers are kept in the cytoplasm and inhibited by inhibitors of κB kinase (IκB) protein. The IκB family consists of IκBα, IκBβ, IκBε, and Bcl-3, and the best-studied and major IκB protein is IκBα. The upstream activation signal of the IκB kinase (IKK) complex, which mainly comprises heterodimers of the catalytic IKKα, IKKβ subunits and NF-κB essential modulator (NEMO), also called IKKγ, induces the degradation of IκBα proteins. IKKβ phosphorylates two serine residues located in IκB regulatory domains, which leads to their degradation [78]. After the degradation of IκB, the NF-κB complex is then released and enters the nucleus to "turn on" the expression of specific genes.

Members of the TNF receptor superfamily, including BAFF, CD40 and LT-β, activate the non-canonical NF-κB pathway by inducing NF-κB (RelB/p52) dimer translocation

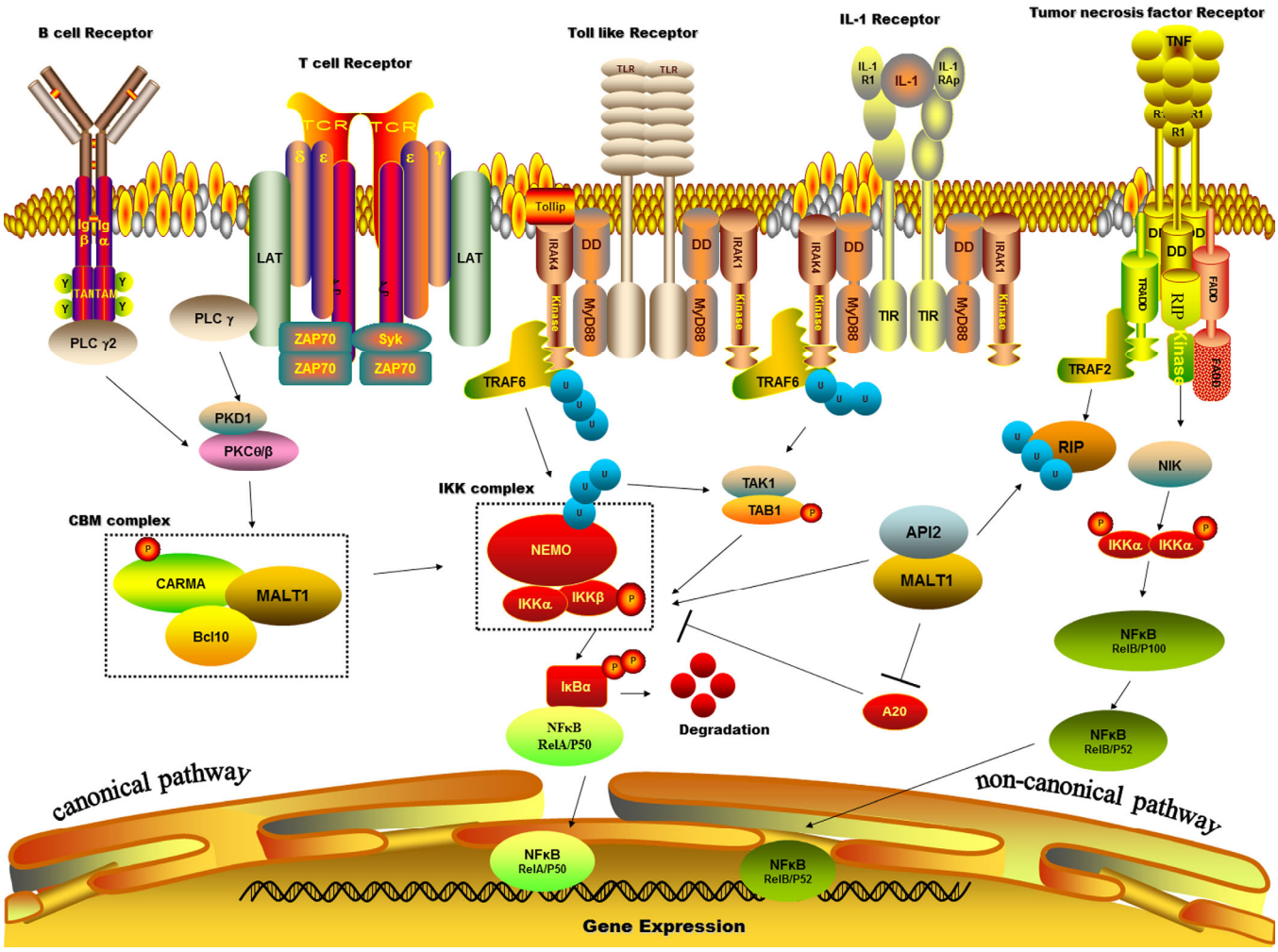

Figure 3 (color online) The canonical and non-canonical pathway of NF-κB signaling. The CBM signalosome and the fusion oncoprotein API2-MALT1 activate canonical NF-κB signaling. For the non-canonical pathway, activated NIK phosphorylates and activates IKKα kinase subunit, leading to the phosphorylation of the precursor p100, which degradate partially to p52, allowing RelB/p52 heterodimers to translocate to the nucleus and drive gene transcription.

into the nucleus. This process is independent of the classical IKK complex. TNF receptors activates NF-κB-inducing kinase (NIK), which consequentlyphosphorylates and activates the IKKα kinase subunit, leading to the phosphorylation of the precursor p100, which partially degrades to p52, setting the RelB/p52 heterodimers free; ultimately, RelB/p52 translocates to the nucleus and drives gene transcription. Recent analyses showed that the synthesis of RelB and p52 is controlled by IKK-IκBα-RelA/p50 signaling. The impairment of the canonical pathway will lead to the aberrant activation of the non-canonical pathway [79]. This evidence reveals that the canonical and non-canonical pathways are not separated, and an interaction exists between them.

The three key molecules, Bcl10, MALT1 and CARMA (CARD-containing molecules of the membrane associated guanylate kinase family), work upstream of the IKK complex and downstream of the antigen receptor. CARMA1/CARD11, CARMA2/CARD14 and CARMA3/CARD10 are highly conserved across species, sharing a similar structure but expressed in a tissue-specific pattern [80–82]. Upon the activation of T cell receptor (TCR), protein kinase C-θ (PKCθ) is recruited by CARMA1, and the activated PKCθ subsequently phosphorylates CARMA1 to recruit Bcl-10 and MALT1, thus promoting TCR-induced NF-κB signaling [83]. Another molecule, 3-phosphoinstitide-dependent kinase (PDK)-1 can also activate PKCθ and recruits the IKK complex as well as interacts with CARMA1 to recruit Bcl-10 and MALT1 [84]. Once BCR is activated, the CARMA/Bcl- 10/MALT1 (CBM) and IKK complexes are recruited, and PKCβ phosphorylates CARMA1, thus promoting NF-κB signaling [85]. TNF receptor-associated factor 6 (TRAF6), belongs to the TRAF family (TRAF1~7), which mediates interactions with other signaling components such as the transmembrane TNF receptors and CD40 [86]. TRAF6 ubiquitin itself, and IKKγ recruits the

TAB/TAK1 kinase complex. Finally, with the phosphorylation of the β subunit, the IKK complex is activated, and eventually, IκB is phosphorylated and degraded. This process ultimately leads to signaling cascades of NF-κB [87].

CARMA deficiencies, as well as BCL10- or MALT1-deficient lymphocytes, showed defective proliferation. In the CARMA1-deficient mouse model, primary B and T lymphocytes were defective in mitogen-induced NF-κB activation and failed to proliferate [88]. By overexpressing Bcl-10 alone, NF-κB was weakly activated. However, this effect can be increased in the presence of MALT1, while MALT1 alone is insufficient to induce NF-κB activation [61]. This evidence suggest that the CBM complex cooperates with and integrates signals from the upstream regulator to the IKK complex in classical NF-κB signaling.

Unlike wild-type MALT1, which requires Bcl-10 to assist in its oligomerization, API2-MALT1 is capable of auto-oligomerization via its BIR domain (Figure 2). API2-MALT1 alone can stimulate the IKK complex activation and induce NF-κB [53,89]. The moiety of API2-MALT1 interacts with multiple upstream mediators of NF-κB activation, including TRAF2 [90] and NIK [91]. Recent discoveries showed that the receptor-interacting protein-1 (RIP1) is a novel API2-MALT1-associated protein. It is ubiquitinated by API2-MALT1 with the help of TRAF2, leading to the activation of the canonical NF-κB signaling pathway [92]. Other studies discovered that after a positively-charged Arg residue, MALT1 not only cleaves its signaling partner Bcl-10 but also the NF-κB inhibitor A20 [81]. Upon TCR stimulation, A20 is recruited to and cleaved by MALT1. Thereby, the NF-κB-inhibitory function of A20 is prohibited and the induction of NF-κB signaling is maximized.

6 Perspectives

Until recently, dozens of researchers have made efforts to better understand the molecular mechanisms of MALT lymphomas. It is publicly known that the strain-specific and autoantigen-driven stimulation of tumor cell surface receptor signaling leads to the activation of NF-κB via a canonical or non-canonical pathway. The identification of the role of the CBM signalosome in disease progression led to the discovery of the drugs that target the CBM complex in the treatment of some B-cell lymphomas [93,94]. As a result, further studies will be able to shed light on the use of therapeutic drugs that exclusively inhibit the antigen receptor signaling pathway. Additionally, recent studies indicated that specific inhibitors of the API2-MALT1 ubiquitin ligase would also be beneficial [95]. Currently, the combination use of anti-HCV therapies with monoclonal antibodies or IFN regimens to treat HCV-related lymphomas needs to be verified with more randomized controlled trials. Future studies in this field should focus on identifying the mechanisms of lymphomagenesis and the relationship between lymphomas, microorganisms and the host.

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