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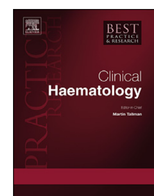

MALT lymphoma: Genetic abnormalities, immunological stimulation and molecular mechanism

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A B S T R A C T

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) occurs at diverse anatomic sites and is closely associated with several distinct chronic inflammatory disorders. Both the acquired genetic abnormalities and active chronic immunological responses play a critical role in the development of MALT lymphoma, interestingly by dysregulating similar molecular mechanisms. The three translocations seen in MALT lymphoma, namely t(14;18)(q32;q21)/*IGH-MALT1*, t(1;14)(p22;q32)/*BCL10-IGH*, and t(11;18)(q21;q21)/*BIRC3* (*API2*)-*MALT1* are capable of activating both canonical and non-canonical NF-κB pathways. *TNFAIP3* (A20) inactivation by deletion and/or mutation abolishes its negative regulation to several signalling including BCR and TLR, which activate the canonical NF-κB pathway. Similarly, the immunological responses also activate the canonical NF-κB pathway via surface antigen receptor and TLR, and the non-canonical NF-κB pathway by T-cell help and BAFFR. There is also emerging evidence indicating oncogenic cooperation between the above genetic changes and immunological stimulation in the pathogenesis of MALT lymphoma.

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Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) originates from the marginal zone B-cells of the acquired MALT. The lymphoma occurs at diverse anatomic sites and has been shown to be associated with several distinct chronic inflammatory disorders, such as chronic infection by *Helicobacter pylori* in the stomach, *Borrelia burgdorferi* in the skin [1–6], *Chlamydia psittaci* in the ocular adnexa [7–10], and *Campylobacter jejuni* in the small intestine [11], as well as autoimmune disorders including lymphoepithelial sialadenitis and Hashimoto thyroiditis [12,13]. The chronic inflammatory and immunological responses generated in these disorders provide a setting sustaining chronic antigenic drive, genotoxic damage and promoting acquisition of genetic abnormalities, malignant transformation and clonal expansion of the transformed neoplastic cells. There is now mounting evidence indicating that both genetic abnormalities and antigenic drive in MALT lymphoma are centred on dysregulation of the molecular pathways that regulate activities of NF-κB, a master transcriptional factor critical for a number of biological processes involved in both innate and acquired immunity.

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NF-κB activation pathways

NF-κB is a family of transcription factors consisting of NF-κB1 (p50 and its precursor p105), NF-κB2 (p52 and its precursor p100), RelA (p65), RelB and c-Rel. They form various homo- or heterodimers through their N-terminal REL homology domains. The NF-κB dimers are kept inactive in the cytoplasm by association with one of the three inhibitors (IκBα, IκBβ and IκBε) or in its dormant precursor forms, but can be activated by a diverse surface receptor signalling, which converge to trigger the canonical or non-canonical NF-κB activation pathway.

Canonical NF-κB pathway

This is characterised by activation of IκB kinase (IKK) complex, consisting of two catalytic subunits IKKα and IKKβ, and one regulatory subunit IKKγ (also known as NEMO). The activated IKK complex phosphorylates IκB, triggering its K48-linked polyubiquitination and subsequent degradation by proteasome (Fig. 1). This releases the NF-κB dimers, exposes their nuclear localisation signal and thus permits their nuclear translocation and transcriptional function.

The signalling from the antigen receptor (BCR or TCR), TLR, IL-1R and TNFR is linked to the canonical NF-κB pathway through various signalling cascades involving distinct adaptor molecules. For example, the proximal BCR signalling triggers the recruitment of the scaffolding adaptor CARMA1 (CARD11), its conformational changes and enables its association with BCL10 and self-oligomerisation, subsequent assembly of the CARMA1/BCL10/MALT1 (CBM) signalosome complex [16,17]. The CBM signalosome then activates the IKK complex through recruitment of TAB2/TAK1/TRAF6 [16,18,19]. Similarly, IL-1R/TLR

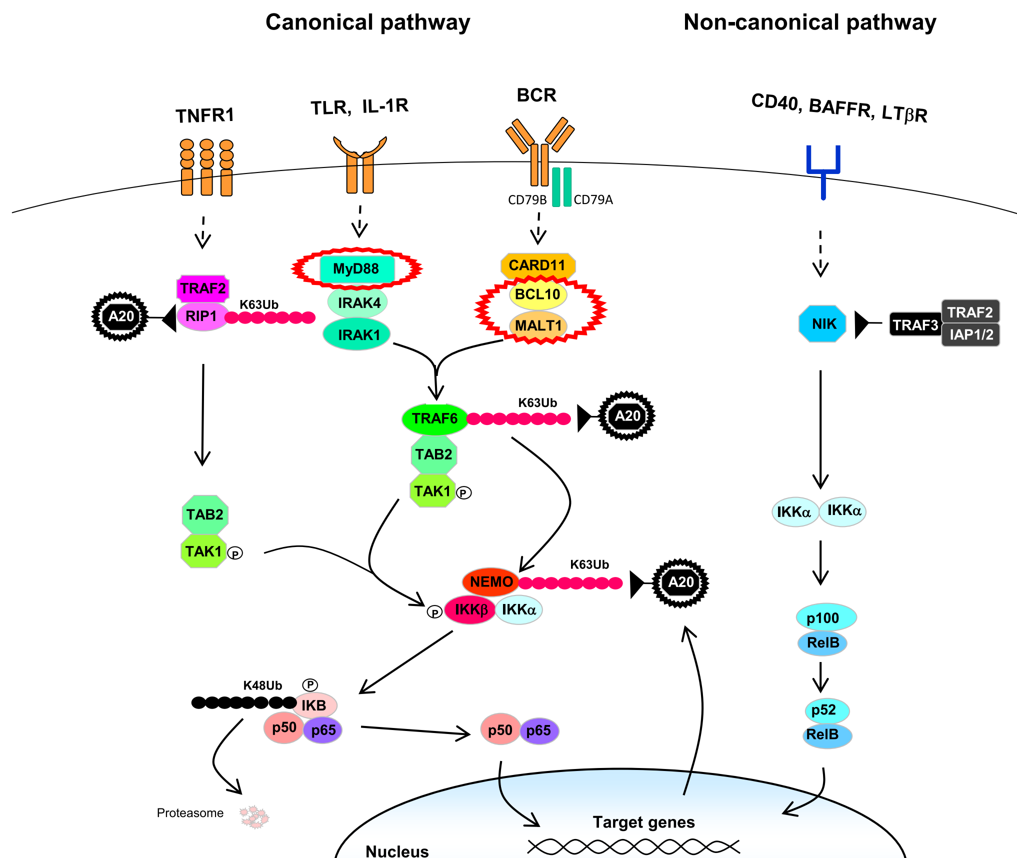

Fig. 1. NF-κB activation pathways and the major players involved in MALT lymphoma. The signalling from the TRAFR, TLR, IL-1R, and antigen receptor activates the canonical NF-κB pathway, which is characterised by activation of the IKK complex, phosphorylation and degradation of IκB. The signalling from CD40, BAFFR and LTβR activates the noncanonical NF-κB pathway, which is featured by activation of NIK, p100 processing and generation of functional active p52. Both canonical and noncanonical pathways are governed by several negative regulators, of which A20 (TNFAIP3) and TRAF3 are typical representatives. Reproduced with permission [14,15]. TNFR: tumour necrosis factor receptor; TLR: toll like receptor; IL-1R: interleukin 1 receptor; BCR: B-cell receptor; TCR: T-cell receptor; TRAF: TNF associated factor; RIP1: receptor interacting protein 1; TAK1: transforming growth factor β activating kinase; TAB: TAK binding protein; IKK: inhibitor of NF-κB kinase; NEMO: NF-κB essential modulator; IκB: inhibitor of NF-κB; BAFFR: B cell activating factor receptor; LTβR: lymphotoxin β receptor; NIK: NF-κB inducing kinase. K63Ub: K63 linked ubiquitin chain; K48Ub: K48 linked ubiquitin chain.

signalling triggers sequential recruitment of MYD88, IRAK and TRAF6 (Fig. 1), and their activation, consequently leading to the activation of IKK complex [20,21]. The canonical NF-κB activation pathway is also governed by several negative regulators such as IκBα, A20 (also known as TNFα inducible protein 3, TNFAIP3), CYLD (Fig. 1) [22,23]. IκBα and A20 are the transcriptional targets of NF-κB, and their expression following NF-κB activation would dampen down NF-κB activities. A20 inactivates several signalling proteins including RIP1/2, TRAF6, Ubc13 and NEMO via its ubiqutin editing activities, and thus potentially restrains the signalling downstream of surface receptors including BCR, TNFR, TLR and IL1βR [24–26].

Non-canonical NF-κB pathway

This is characterised by sequential activation of the NF-κB inducible kinase (NIK) and IKKα (Fig. 1). The activated IKKα phosphorylates NF-κB2 (p100) and triggers its partial proteolysis, generating the functional active form p52. The p52, often in association with RelB, is permitted for nuclear translocation and transcriptional function. The non-canonical NF-κB pathway is activated by signalling from CD40, B-cell activating factor receptor (BAFFR) and lymphotoxin β receptor (LTβR), and negatively regulated by TRAF3, which targets NIK for proteasome degradation. NF-κB transactivates a wide spectrum of genes encoding cell cycle regulators, growth factors, immunoregulatory cytokines, apoptosis inhibitors, negative regulators of the NF-κB pathway etc. In general, activation of NF-κB is normally transient and plays a critical role in lymphocyte development, activation and differentiation. There is now growing evidence that NF-κB is constitutively activated in MALT lymphoma by both genetic changes and chronic antigenic stimulations. Below, I summarise our current understanding of the molecular pathogenesis of MALT lymphoma.

Genetic abnormalities

Although the spectrum of genetic abnormalities in MALT lymphoma remains to be investigated by whole genome or whole exome sequencing, various recurrent genetic abnormalities identified to date, including chromosome translocations, somatic mutations and copy number changes, have been shown to commonly affect the signalling pathways that regulate NF-κB activities.

t(1;14)(p22;q32)/BCL10-IGH

This translocation is recurrently seen in MALT lymphoma of the lung (~9%) and stomach (~4%), but not or rarely in those of other anatomic sites, nor other lymphoma subtypes (Fig. 2) [27–29]. The translocation juxtaposes the *BCL10* gene under the regulatory control of the IG gene enhancer, and causes BCL10 over-expression (Fig. 3) [30,31]. As aforementioned, BCL10 is an essential component of the CBM complex that connects the BCR signalling to the canonical NF-κB activation pathway. Over-expression of BCL10 results in its constitutive activation through its auto-oligomerisation via its N-terminal CARD/CARD interaction, thus causing constitutive NF-κB activities [17,32].

There is also evidence for a role of BCL10 in the regulation of non-canonical NF-κB pathway from mouse studies. B-cells with Bcl10 over-expression showed constitutive activation of both canonical and non-canonical NF-κB signalling pathways, and the activation of non-canonical pathway was thought to be indirect, due to enhanced BAFF expression [38]. Similarly, Bcl10 deficiency B-cells exhibited reduced expression of NF-κB2 (p100), as well as a reduced level of nuclear p52/RelB complex following BAFF stimulation [39]. In keeping with these findings, BAFF has been shown to be over-expressed in MALT lymphoma [40,41].

In line with the role of BCL10 in linking BCR to the canonical NF-κB pathway, the protein is expressed in the cytoplasm of reactive B-cells [42]. However, BCL10 is aberrantly expressed in the nuclei of lymphoma cells with t(1;14)(p22;q32)/*BCL10-IGH* or t(11;18)(q21;q21)/*BIRC3* (*API2*)-*MALT1*, and also in the marginal zone B-cells of Eu-BCL10 mice [27,38,42–44],

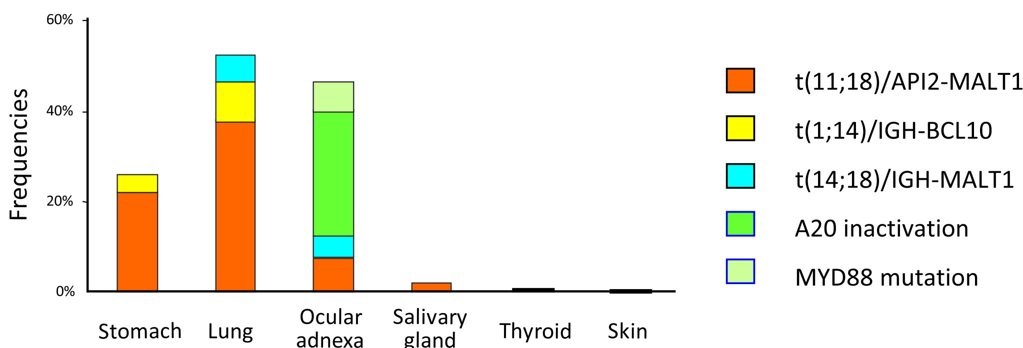

Fig. 2. Frequencies of genetic abnormalities in MALT lymphoma of different sites. The data are based on our previous studies [27,29,33–37]. Reproduced with permission [15].

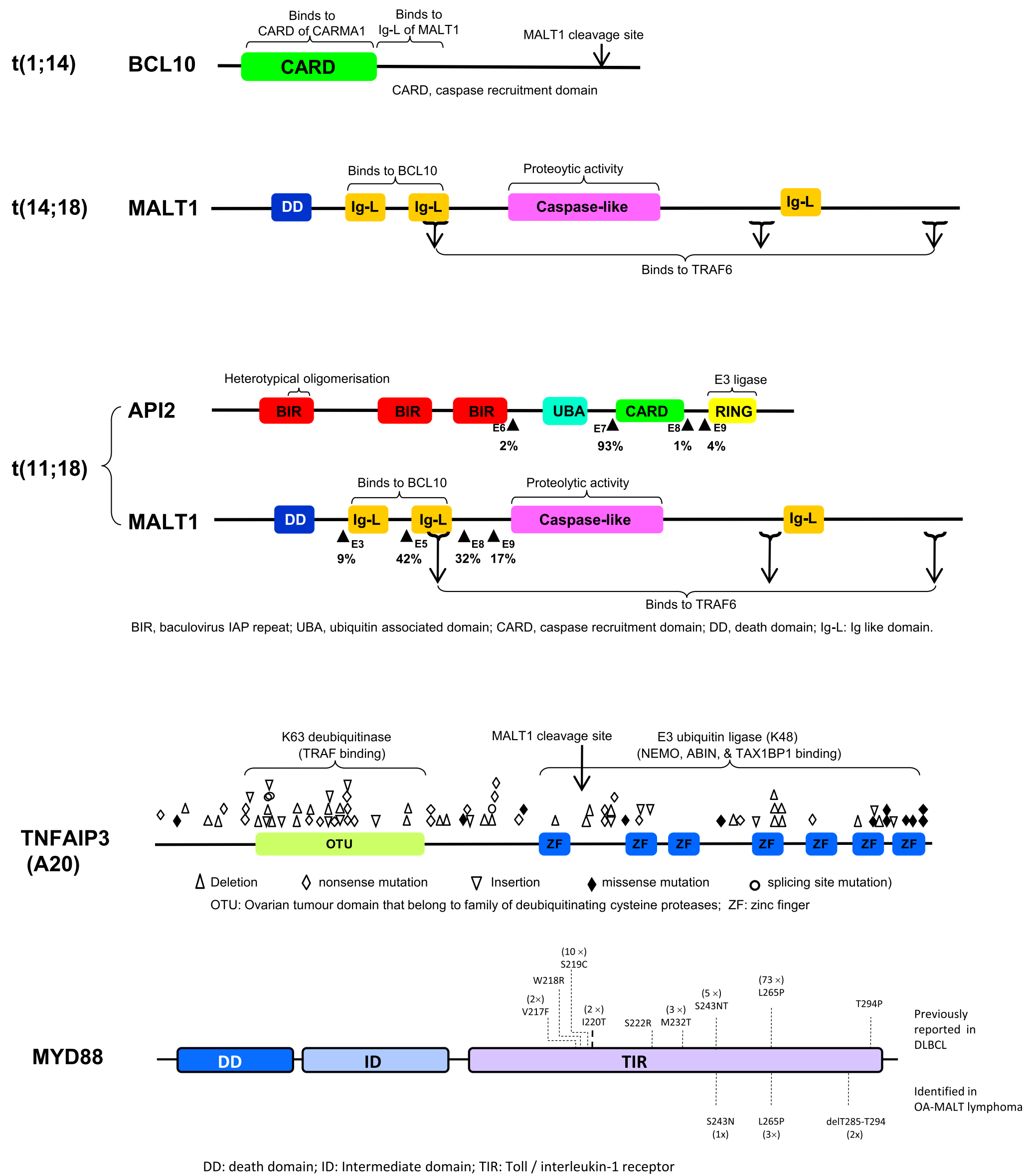

Fig. 3. Key features of MALT lymphoma associated oncogenes or tumour suppresser genes. T(1;14)(p22;q32)/*BCL10-IGH* and t(14;18)(q32;a21)/*IGH-MALT1* cause over-expression of BCL10 and MALT1 respectively, while t(11;18)(q21;q21)/*BIRC3* (*API2*)-*MALT1* fuses the N-terminal API2 to the C-terminal MALT1 and generates a chimeric fusion product. Various breakpoints in API2 and MALT1 and their frequencies are indicated. *TNFAIP3* (*A20*) is commonly inactivated by deleterious mutations and deletion. Reproduced with permission [14].

suggesting a yet unappreciated function of nuclear BCL10 in the pathogenesis of MALT lymphoma. The clinical utility of t(1;14)(p22;q32) is not yet fully investigated due to its relatively low frequency. A preliminary retrospective study suggests that gastric MALT lymphomas with strong BCL10 nuclear expression or t(1;14)(p22;q32) do not respond to *H. pylori* eradication [45].

t(14;18)(q32;q21)/IGH-MALT1

This translocation occurs mainly in MALT lymphoma of the ocular adnexa (7%) and lung (6%), but not or rarely in those of other anatomic sites (Fig. 2) [28,29]. Like the BCL10 translocation, it brings the *MALT1* gene under the regulatory control of the IG gene enhancer, and causes MALT1 over-expression [46]. MALT1 possesses several functional domains including an N-terminal death domain, three immunoglobulin-like domains and a proteolytically active caspase-like domain (Fig. 3). Unlike BCL10, MALT1 lacks a structural domain mediating its self-oligomerisation, and its activation depends on its interaction with BCL10 via its N-terminal Ig-like domains (Fig. 3) [47,48]. In line with this, the lymphoma cells carrying

t(14;18)(q32;q21)/*IGH-MALT1* show not only over-expression of MALT1, but also BCL10 accumulation in cytoplasm, suggesting that MALT1 may immobilise BCL10 in cytoplasm through their interaction [29]. MALT1 also regulates the activation of the canonical NF-κB pathway through its protease activities by cleavage and inactivation of several NF-κB regulators including A20, CYLD, RelB and BCL10 [49–52]. Among these, A20, CYLD and RelB are NF-κB negative regulators [49–53], and constitutive activation of MALT1 by chromosome translocation may eliminate these negative regulators and cause relentless activation of the canonical NF-κB pathway. Furthermore, MALT1 has a role in regulation of the non-canonical NF-κB activation pathway although not yet fully characterised. MALT1 deficiency B-cells show impairments in BAFF-induced phosphorylation and degradation of NF-κB2 (p100), thus a reduced level of the functional active form p52 [54]. As a result, MALT1 deficiency significantly impairs BAFF-induced cell survival of marginal zone B-cell [54]. These findings suggest that over-expression MALT1 by translocation may potentially dysregulate the non-canonical NF-κB activation pathway.

Finally, MALT1 is capable of interacting with caspase-8 in a protease independent manner, and converts its function to activate NF-κB rather than apoptosis pathway upon antigen receptor stimulation in T-cells [55,56]. It remains to be investigated whether MALT1 functions similarly in B-cells and if yes, has any potential role in lymphoma pathogenesis. The clinical impact of t(14;18)(q32;q21) is unclear due to its relatively low frequency.

t(11;18)(q21;q21)/BIRC3 (API2)-MALT1

This translocation occurs predominantly in MALT lymphoma of the stomach (24%), lung (38%), but rare or not in those of other anatomic sites (Fig. 2) [28,29]. The translocation generates a chimeric functional fusion product between the N-terminal *API2* and the C-terminal *MALT1* (Fig. 3) [57–59], and the resulting API2-MALT1 fusion product gains novel abilities to activate both the canonical and non-canonical NF-κB pathways (Fig. 4).

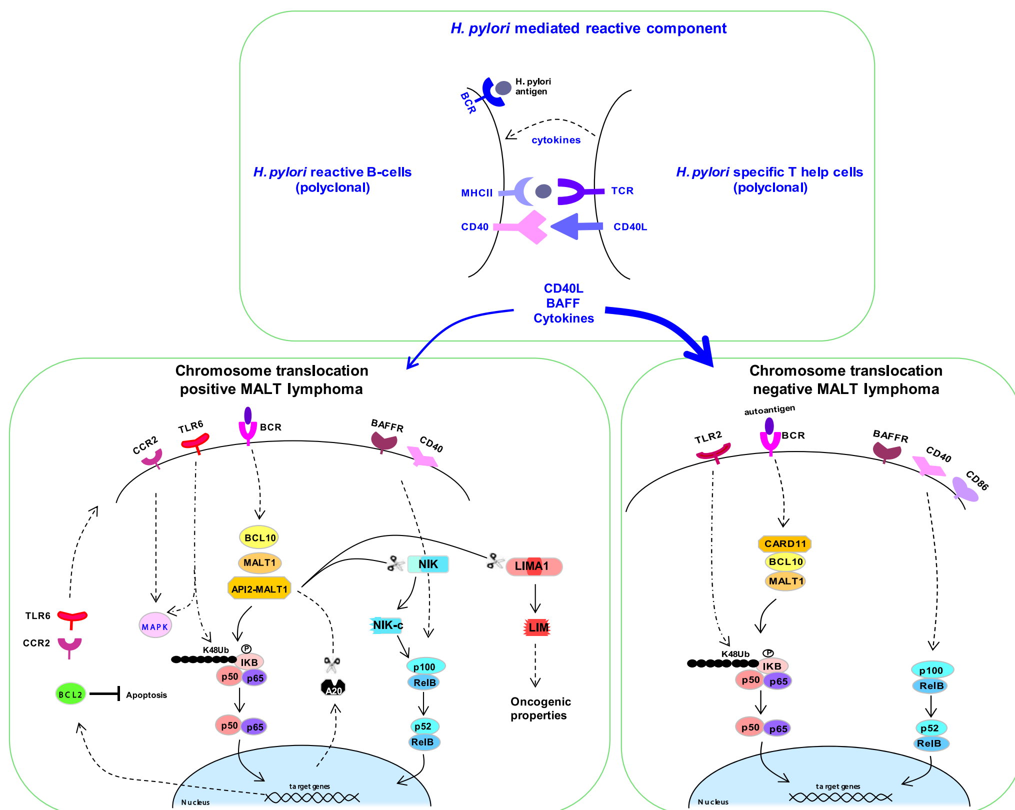

Fig. 4. The proposed model of molecular pathogenesis of gastric MALT lymphoma with and without chromosome translocation. The oncogentic products of t(1;14)(p22;q32)/*BCL10-IGH*, t(14;18)(q32;21)/*IGH-MALT1* and t(11;18)(q21;q21)/*API2-MALT1* are potent activators of the canonical NF-κB activation pathway. They may further augment their mediated NF-κB activation by enhancing expression of surface receptors TLR6 and CCR2, as well as proteolytic cleavage of the negative inhibitor A20. These oncogenic products may also potentially cooperate with the signalling from BCR, BAFFR and CD40, via helps of bystander T-cells generated in the *H. pylori* mediated reactive component. In addition, the API2-MALT1 fusion product gains ability to cleave NIK and generate a stable NIK C-terminal fragment, capable of activating the non-canonical NF-κB pathway, and also to cleave LIMA1 and generate a LIM domain-only (LMO) fragment, conferring oncogenic properties. The growth of translocation negative MALT lymphoma is largely driven by *H. pylori* generated immune responses including signalling from CD40 and CD86 through bystander T cell helps, and direct triggering of TLR and BCR by *H. pylori* associated lipopolysaccharides and autoantigen respectively. This underscores that most of translocation negative gastric MALT lymphomas can be cured by *H. pylori* eradication. Modified and reproduced with permission [14,15]. TLR: toll like receptor; BCR: B-cell receptor; MAPK: MAP kinase; IκB: inhibitor of NF-κB; BAFFR: B cell activating factor receptor; K48Ub: K48 linked ubiquitin chain. NIK: NF-κB inducible kinase; LIMA1: LIM domain and actin-binding protein 1.

Like BCL10 and MALT1, the API2-MALT1 fusion product activates the canonical NF-κB pathway through self-oligomerisation, but this is mediated by interaction between the BIR1 of the API2 moiety and the C-terminal region of MALT1 [60,61]. All the fusion products contain the intact caspase-like domain of MALT1, and can also cleave A20 and CYLD and thus eliminate their negative feedback regulation (Fig. 4) [49,62]. The API2-MALT1 induced NF-κB activation may also enhance its own expression since the genomic fusion is under the transcriptional control of API2, which itself is a transcriptional target of NF-κB [63]. In support of the above experimental findings, high levels of polyubiquitination of NEMO, evidence of IKK complex activation, are seen in MALT lymphomas with t(11;18)(q21;q21)/*API2-MALT1* and also in marginal zone B-cells of Eμ-API2-MALT1 mice [61,64]. The API2-MALT1 fusion product is also capable of activating the non-canonical NF-κB pathway through concerted actions of both the API2 and MALT1 moieties (Fig. 4). The API2 moiety of the fusion product recruits NIK and places it in close proximity with the MALT1 protease domain [65]. This causes cleavage of NIK at arginine 325, generating a C-terminal NIK fragment that retains kinase activity but resists to TRAF3 dependent proteasomal degradation [65]. As a result, the API2-MALT1 fusion product causes constitutive activation of the non-canonical NF-κB pathway [65].

In a similar manner, the API2-MALT1 fusion product also cleaves the tumour suppresser protein LIMA1 (LIM domain and actin-binding protein-1) via concerted actions of the API2 moiety and MALT1 caspase-like domain, generating a novel oncogenic LIM domain-only (LMO) fragment (Fig. 4) [66]. Expression of the LMO fragment promotes survival and proliferation of primary B-cells *in vitro* and tumour formation in xenograft model [66]. Nonetheless, the molecular mechanism underlying LMO mediated oncogenesis remains to be investigated. T(11;18)(q21;q21) is a strong predictor of the response of gastric MALT lymphoma to *H. pylori* eradication. The translocation is seen in 47% and 68% of gastric MALT lymphomas at stage I_E and stage II_E or above respectively, which do not respond to *H. pylori* eradication, but only in 3% of those that respond to *H. pylori* eradication and additionally these translocation positive cases often show residual disease or lymphoma relapse [33,67–73]. The translocation was also associated with treatment failure of single oral alkylating agents (chlorambucil or cyclophosphamide) [74]. For these reasons, testing for t(11;18)(q21;q21) at diagnosis is highly recommended to guide treatment choice [75].

TNFAIP3 (A20) inactivation

TNFAIP3 was identified as the target of 6q23 deletion in ocular adnexal MALT lymphoma, and subsequently found to be also inactivated by mutation in a range of B-cell lymphomas including diffuse large B-cell lymphoma, primary mediastinal large B-cell lymphoma and Hodgkin's lymphoma [35,36,76–82]. In MALT lymphoma, *TNFAIP3* deletion and mutation are mainly seen in those of the ocular adnexa, salivary gland and thyroid, which show infrequent or a lack of the above chromosome translocations (Fig. 2) [35,36,76–78].

TNFAIP3 contains an N-terminal OTU domain that possesses deubiquitinating activity, and 7 zinc finger domains in its C-terminus, which confers the E3 ubiquitin ligase activity (Fig. 3) [22,83]. TNFAIP3 can inactivate a number of NF-κB positive regulators including RIP1/2, TRAF6, Ubc13 and NEMO through removing the K63-linked ubiquitin chain, catalysing the K48-linked polyubiquitination, or direct binding to the linear polyubiquitin chain of its targets [24–26]. The vast majority of TNFAIP3 mutations seen in lymphoma are deleterious changes such as frameshift indels and nonsense mutations, and would result in a truncated protein product. As expected, various TNFAIP3 truncation mutants show a substantial impairment in repression of NF-κB activation triggered by BCR, TLR and TNFR signalling [84]. Thus, TNFAIP3 inactivation can potentially augment NF-κB activation triggered by these receptor signalling, and its oncogenic activities depend on corporation with these antigenic and inflammatory stimulations.

MYD88 mutation

The mutation is recurrent in ocular adnexal MALT lymphoma (~5%), but appears to be infrequent in those of other anatomic sites albeit not yet fully investigated (Fig. 2) [85–89]. In addition to the hotspot mutations such as L265P in the TIR domain, which are frequently seen in several other B-cell lymphomas, novel inframe deletions were also identified in MALT lymphoma (Fig. 3) [85–89]. Regardless the nature of these mutations, they all are gain-of-function changes as shown by *in vitro* functional assays [85,87]. MYD88 mutants are constitutively active and can spontaneously assemble a protein complex comprising IRAK1 and IRAK4, to activate NF-κB, STAT3 and AP1 transcription factors [85].

Somatic mutations in other NF-κB regulators

Apart from *TNFAIP3* and *MYD88* mutation as discussed above, MALT lymphoma shows rare or no mutations in other NF-κB regulators including CD79A, CD79B, CARD11, BIRC3, TRAF3 and TNFRSF11A, which are frequently seen in several B-cell lymphomas characterised by constitutive NF-κB activation [86–88,90–92]. However, the spectrum of somatic mutations in MALT lymphoma is not yet fully characterised, and the extent of unique and common genetic changes between MALT and other B-cell lymphomas awaited to be investigated.

Other chromosome translocations

Conventional cytogenetic studies have also identified several novel chromosome translocations in isolated cases of MALT lymphoma, and their involved genes have been depicted by cloning and sequencing analysis of the breakpoint. They include t(3;14)(p13;q32)/*FOXP1-IGH* [93–95], t(1;14)(p21;q32)/*CNN3-IGH*, t(5;14)(q34;q32)/*ODZ2-IGH*, t(9;14)(p24;q32)/*JMJD2C-IGH* [96] and t(X;14)(p11.4;q32)/*GPR34-IGH* [97,98]. These translocations typically juxtapose the oncogene involved to the IGH gene locus, thus most likely cause their over-expression. FOXP1 has been shown to repress expression of several proapoptotic genes as well as transcriptional factors including PRDM1, IRF4, and XBP1 that are critical for plasma cell differentiation [99,100]. Though inhibition of apoptosis and plasma cell differentiation, FOXP1 over-expression may contribute to the pathogenesis of MATL lymphoma. The molecular mechanism underlying the oncogenic activities of other aforementioned translocation remains to be investigated.

Immunological drive

Histologically, MALT lymphoma commonly shows blast transformation, plasma cell differentiation and sometimes follicular colonisation where the neoplastic cells enter B-cell follicle and undergo active proliferation and similar phenotypic changes, reminiscing the reactive B-cells that undergo the T-cell dependent germinal centre reaction [101,102]. These histological features clearly indicate that MALT lymphoma cells possess a range of biological properties of reactive B-cells and are responsive to their microenvironment milieu, most likely through their surface receptor signalling. There is growing evidence showing that both BCR and CD40 signalling play a critical role in the pathogenesis of MALT lymphoma.

B-cell receptor (BCR) signalling

MALT lymphoma cells almost always express surface IgM and crosslinking their surface IgM is capable of stimulating their proliferation or enhancing their proliferative responses to mitogens [103], indicating that the BCR signalling is operational. Sequencing analysis of IG gene rearrangements shows a biased usage of certain IG genes in MALT lymphoma of the stomach, ocular adnexa and salivary gland. IGHV4-34 and IGHV1-69 are significantly biasedly used in MALT lymphoma of the ocular adnexa and salivary glands respectively [14,104–109,119,120], while IGHV3-7 and IGHV1-69 appear to be over-represented in those of the stomach [110–114]. In addition, the usage of IGHV4-34 and IGHV1-69 in MALT lymphoma is often associated with a biased usage of IG light chain genes (IGKV3-20) [111,115], arguing for recognition of certain antigenic determinants.

Characterisation of antigenic determinants by MALT lymphoma associated BCR is not yet extensively investigated. Nonetheless, studies to date show that recombinant antibodies from various MALT lymphoma associated IG gene rearrangements are auto-reactive. For example, the recombinant antibodies from MALT lymphoma associated IGHV1-69 or IGHV3-7 rearrangements are reactive to the Fc portion of human IgG, a characteristic feature of rheumatoid factor [111]. Similarly, the immunoglobulin encoded by the IGHV4-34 rearrangement seen in both malignant and reactive B-cells binds to *N*-acetyl-lactosamine residues via its unique and conserved FR1 hydrophobic patch (Q^6W^7 and $A^{24}V^{25}Y^{26}$) [116,117]. Furthermore, MALT lymphoma immunoglobulin encoded by IGHV3-23 and IGHV3-30 gene are self-polyreactive, albeit their antigenic determinants remain to be defined [115,118]. The BCR engagement by autoantigen is likely to cause chronic BCR signalling, triggering activation of the canonical NF-κB pathway and consequently enhancing cell proliferation and survival together with signalling from other surface receptors such as TLR and CD40.

T-cell help and CD40 signalling

This is primarily based on studies of gastric MALT lymphoma. Despite that the development of gastric MALT lymphoma is causatively linked to chronic *H. pylori* infection, *H. pylori* antigens do not directly stimulate the lymphoma B-cells. The growth of the lymphoma cells critically depends on tumour infiltrating *H. pylori* specific T-cells [118,119]. This may involve cognate interaction between the malignant B and *H. pylori* specific T-cells [120–122], as well as bystander T-cell help via soluble ligands and cytokines, such as CD40L and BAFF, thus activating the non-canonical NF-κB pathway (Fig. 4) [123].

There are several strands of evidence supporting the above notion. First, reactive B-cell follicles are invariably present in gastric MALT lymphoma, and these reactive components would enable classical immunological responses that generate *H. pylori* specific T-cells and bystander T-cell helps. Second, gene expression profiling study shows an enriched expression of proinflammatory cytokines such as IL8 and IL1β, and the molecules involved in B and T-cell interaction such as CD86, CD28 and ICOS in gastric MALT lymphoma, particularly those without chromosome translocation [124]. Nonetheless, mouse model of *Helicobacter* induced gastric MALT lymphoma appear to suggest that Th2 cytokines such as IL-4, rather than CD40 signalling, are critical for the proliferation of lymphoma cells [125].

Oncogenic cooperation among genetic changes and immunological stimulation

There is growing evidence indicating that the development of MALT lymphoma is the result of oncogenic cooperation among acquired genetic changes and immunological stimulation. It has been well established that none of the genetic abnormalities in MALT lymphoma alone is sufficient for malignant transformation. For example, over-expression of BCL10 or

API2-MALT1 in mice results in development of splenic marginal zone hyperplasia but not lymphoma [38,64]. However, stimulation of API2-MALT1 expressing mice with Freund's complete adjuvant leads to development of splenic marginal zone lymphoma-like lesion [126], indicating oncogenic cooperation between genetic abnormalities and immunological stimulations.

As discussed above, both the acquired genetic changes and immunological stimulations implicated in MALT lymphoma are centred on dysregulation of the NF-κB activation pathways (Fig. 4), which are known to be critical for the development and function of marginal zone B-cells [127,128]. For example, the receptor signalling connecting to the canonical NF-κB pathway, such as BCR and TLR, and those linking to the non-canonical NF-κB pathway such as BAFFR and CD40, are affected by both genetic changes and immunological stimulations. The activation of canonical and non-canonical NF-κB pathways by chromosome translocation could be enhanced by chronic stimulation of surface BCR, TLR, BAFFR and CD40 respectively [124]. Similarly, the BCR and TLR signalling stimulated by microenvironment milieu, which link to the canonical NF-κB pathway, could be enhanced by inactivation of the negative regulator *TNFAIP3* (A20) via genetic changes. It is most likely that such oncogenic cooperation among different receptor signalling is operational in MALT lymphoma cells, and together cause constitutive NF-κB activation. Furthermore, the extent of potential oncogenic cooperation among immunological responses and genetic abnormalities is underestimated due to incomplete characterisation of both microenvironment milieu and the genetics of MALT lymphoma at various anatomic sites.

Conclusions

MALT lymphoma is a fascinating model for investigation of oncogenic cooperation between genetic abnormalities and immunological drive in lymphoma genesis. Although not yet fully characterised, there are remarkable differences in the aetiology, IG gene usage and genetic abnormalities in MALT lymphoma of different anatomic sites. These differences will provide various models of oncogenic cooperation between genetic abnormalities and immunological stimulations in MALT lymphoma of different sites, with the underlying molecular mechanisms probably being similar. A comprehensive investigation on genetic changes, IG gene usage and immunological properties of tumour cells will provide rich information and insights into the biology and molecular mechanisms of MALT lymphoma.

Conflicts of interest

The author declares that there are no conflicts of interest.

Practice points

- T(1;14)/*BCL10-IGH*, t(14;18)/*MALT1-IGH* and t(11;18)/*API2-MALT1* are specific to MALT lymphoma, but only t(11;18) is frequent, mainly seen in those of the stomach (~25%) and lung (~40%);
- Gastric MALT lymphoma with t(11;18)/API2-MALT1 does not normally respond to *H. pylori* eradication therapy. Investigation of the translocation by interphase FISH at diagnosis is highly recommended to guide treatment choice.

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