MALT lymphoma: a paradigm of NF-κB dysregulation

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Abstract

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) invariably arises from a background of chronic microbial infection and/or autoimmune disorder at diverse mucosal sites. The prolonged chronic infection and/or autoimmunity generate active immune and inflammatory responses that provide a setting for evolution and development of autoreactive B-cells, their expansion and eventual malignant transformation following acquisition of genetic changes. The immune responses also play a critical role in sustaining the growth and survival of the transformed cells as shown by complete regression of a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin following anti-microbial treatment. B-cell receptor engagement by auto-antigen as well as T-cell help including both cognate interaction and bystander help via soluble ligands such as CD40L and BAFF are thought to underpin the immunological drive in the lymphoma development through activation of the canonical and non-canonical NF-κB pathway respectively. Similarly, the three MALT lymphoma associated chromosome translocations, 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 also capable of activating both canonical and non-canonical NF-κB pathways. Furthermore, *TNFAIP3* (A20) inactivation by deletion and/or mutation abolishes the auto-negative feedback to several signalling including BCR and TLR, which connect to the canonical NF-κB activation pathway. Thus, there is a considerable overlap in the molecular pathways dysregulated by immunological drive and somatic genetic changes, strongly arguing for their oncogenic cooperation in the development of MALT lymphoma.

Nuclear factor (NF)-κB is a family of dimeric transcription factors critical for both innate and adaptive immunities. In response to stimulation of a wide range of surface receptors, NF-κB orchestrates gene expression and governs a variety of biological processes important for the development, maturation and function of immune cells. There are five NF-κB subunits including RelA (p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p105) and NF-κB2 (p52 and its precursor p100). They form various hetero or homodimers, but are kept inactive in the cytoplasm by their inhibitor (IκBα, IκBβ and IκBε) or in its dormant precursor form. In response to surface receptor signalling, the quiescent NF-κB dimer is activated, and permitted for nuclear translocation and transcriptional function. NF-κB activation is mediated via two common signalling pathways, namely canonical and non-canonical NF-κB pathway, and this is a transient and highly regulated process in response to extracellular signals under a physiological condition. Below highlights the key steps relevant to this review and for details on NF-κB signalling please refer to other reviews [1-4].

1. NF-κB activation pathway

Canonical NF-κB pathway. This involves IκB phosphorylation by the IκB kinase (IKK) complex, triggering its K48-linked polyubiquitination and subsequent degradation by proteasome. As a result, NF-κB dimers are released and their nuclear localisation signal exposed, thus enabling their nuclear translocation and transcriptional activities (Figure 1).

Canonical NF-κB pathway is activated by stimulation of several surface receptors such as B-cell receptor (BCR), Toll-like receptor (TLR), interleukin 1 receptor (IL1R) and tumour necrosis factor receptor (TNFR). These receptor stimulations initiate various signalling cascades that involve distinct adaptor molecules, but converge on the canonical NF-κB activation pathway. For example, BCR engagement triggers receptor aggregation, promoting tyrosine phosphorylation of CD79A (Igα) and CD79B (Igβ) ITAM (immunoreceptor tyrosine-based activation motif), and recruitment of spleen tyrosine kinase (SYK). SYK activation then emanates multiple sigalling cascades that connect to the canonical NF-κB, PI3K–AKT and RAS-ERK activation pathways [1,2]. Through the Bruton's tyrosine kinase (BTK) and protein kinase C (PKC) β signalling cascade, the scaffolding adaptor CARD11 (CARMA1) is recruited, undergoes conformational changes and is able to interact with BCL10 and promote its polymerisation and filament formation, subsequent assembly of the CARD11/BCL10/MALT1 (CBM) signalosome complex [5-7]. The CBM complex further recruits TNF receptor associated factor-6 (TRAF6), transforming growth factor β activating kinase-1 (TAK1) and TAK binding protein-2 (TAB 2), which activates the IKK complex and culminates the activation of canonical NF-κB pathway [5,8,9]. Similarly, TLR (or IL1R) engagement triggers its dimerisation and conformational change in its Toll/IL-1R homologous (TIR) domain, which results in recruitment of MYD88, Interleukin-1 receptor-associated kinase-4 (IRAK4) and IRAK1, forming the Myddosome complex (Figure 1). The Myddosome complex then recruits TRAF6, TAK1 and TAB2, subsequently leading to activation of the IKK complex and canonical NF-κB pathway [3,4].

The canonical NF-κB activation pathway is also tightly modulated by several negative regulators including TNFα inducible protein 3 (TNFAIP3, also known as A20), IκBα and CYLD (cylindromatosis) to ensure appropriate level and length of NF-κB activation (Figure 1) [10,11]. IκBα and TNFAIP3 are the transcriptional targets of NF-κB, and their expression following NF-κB activation could serve as an auto-negative feedback. TNFAIP3 can inactivate a number of NF-κB signalling molecules including receptor-interacting protein-1/2 (RIP1/2), ubiquitin-conjugating enzyme 13 (Ubc13) and IKKγ (also known as NF-κB essential modulator, NEMO), thus negatively regulating the signalling of several surface receptors including BCR, TNFR, TLR and IL1βR [12-14].

***Non-canonical NF-κB pathway*:** This involves successive activation of the NF-κB inducible kinase (NIK) and IKKα (Figure 1). The activated IKKα phosphorylates NF-κB2 (p100) and triggers its partial proteolysis, and this generates a functional active form p52, which is permitted, together with RelB, for nuclear translocation

and transcriptional function. The signalling from CD40, B cell activating factor receptor (BAFFR), TNFRSF13B (also known as TACI) and lymphotoxin β receptor (LTβR) primarily activates the non-canonical NF-κB pathway. The non-canonical NF-κB pathway is negatively regulated by TRAF3, apoptosis inhibitor-1/2 (API1/2) and TRAF2, which control the turnover of NIK by targeting it for ubiquitin mediated degradation by proteasome [15].

In view of the diverse signalling that trigger NF-κB activation and its multiple functional roles in both innate and adaptive immunities, it is not surprising that NF-κB dysregulation is implicated in a wide range of lymphomas including extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), activated B-cell like diffuse large B-cell lymphoma, primary mediastinal B-cell lymphoma, Hodgkin's lymphoma and multiple myeloma [16,17]. Among these, MALT lymphoma provides a unique model to appreciate the role of various immunological stimulations and genetic changes, and their oncogenic cooperation in lymphoma pathogenesis.

2. MALT lymphoma is causatively linked to chronic inflammation

MALT lymphoma may occur at diverse anatomic sites, but always at those that are devoid of any native organised lymphoid tissue. However, such organised lymphoid tissue can be acquired following a prolonged chronic microbial infection or autoimmune disorder, and it has been proposed that MALT lymphoma originates from the marginal zone B-cells of the acquired MALT as suggested by their immunophenotype and preferential marginal zone localization [18]. Although not yet fully characterised, MALT lymphoma at several sites is associated with distinct aetiological factors. For example, the vast majority of gastric MALT lymphomas develop from a background of chronic gastric *Helicobacter pylori* infection, while those from the skin and ocular adnexa, and immunoproliferative small intestine disease are variably associated with chronic infection of *Borrelia burgdorferi* [19-24], *Chlamydia psittaci* [25-28], and *Campylobacter jejuni* [29] respectively. Furthermore, MALT lymphoma of the salivary gland and thyroid are commonly derived from a background of lymphoepithelial sialadenitis and Hashimoto thyroiditis respectively [30,31]. For detailed association between etiological factors and MALT lymphoma, please refer to excellent recent review [32].

Despite association with different aetiological factors, the development of MALT lymphoma may follow a similar multistep process (Figure 2). The prolonged chronic microbial infection or autoimmunity generates immune and inflammatory responses that maintain a population of dynamic B-cells in a microenvironment at an increased risk of genomic damage. B-cells attaining certain immunological properties and/or genetic changes may gain growth advantage and undergo clonal expansion, eventually emerge as a transformed clone on rare occasions. Presence of minor clonal B-cells in reactive conditions such as *H. pylori* associated gastritis, lymphoepithelial sialadenitis and Hashimoto thyroiditis, and their subsequent clonal progression to an overt MALT lymphoma have been well described in literature [33-37].

Apart from malignant transformation, the immune and inflammatory responses are also critical for sustaining the growth and survival of the transformed cells. This is best illustrated by the findings that a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin can be successfully treated by eradication of the associated microbial organisms using antibiotics [38-41]. The potential factors that sustain malignant B-cells are numerous. The immune responses generate a network of B-cell helper signals, such as those from T-cells, dendritic cells and innate lymphoid cells, which are also potentially important for malignant B-cells. In addition, the inflammatory responses likely produce further growth factors and cytokines, which may support malignant B-cells. Despite numerous potential helper signals from the immune and inflammatory responses, the occurrence of MALT lymphoma is rather a rare event, indicating a highly selective process for B-cell clones that acquire certain immunological properties, such as aberrant responses to their microenvironment. Although not yet fully investigated, there is evidence to suggest that several surface receptor signalling may underpin the immunological drive in development of MALT lymphoma.

3. Immunological drive

3.1. BCR signalling

i) Biased IG gene usage in MALT lymphoma

Sequence analysis of the rearranged IG genes in MALT lymphoma shows evidence of positive or negative selection of replacement mutations, indicating antigen mediated affinity maturation. There is increasing evidence showing that there is a biased usage of certain IG genes in MALT lymphoma, particularly in those of the stomach, ocular adnexa and salivary gland where a relatively reasonable number of cases has been investigated. In the vast majority of the related studies, particularly those of earlier investigations, the focus is largely on the analysis of the rearranged IG heavy chain genes. In general, MALT lymphoma of the ocular adnexa and salivary glands clearly show a significantly biased usage of IGHV4-34 and IGHV1-69 respectively, while those of the stomach appear to show over-representation of IGHV3-7 and IGHV1-69 usage (Table 1). Although not yet fully characterised, the biased usage of IGHV4-34 and IGHV1-69 in MALT lymphoma are also in association with a biased usage of IG light chain genes (IGKV3-20) [42,43], further arguing for their recognition of defined antigenic determinants. Interestingly, the biased usage of IGHV4-34 in ocular adnexal MALT lymphoma is far more prevalent in those negative for *Chlamydia psittaci* [44].

ii) Properties of immunoglobulin expressed by MALT lymphoma.

Despite the causative relationship between microbial infection and MALT lymphoma at several anatomic sites, there is no evidence yet showing that the lymphoma derived immunoglobulin recognises microbial antigens [42,43,62]. Instead, there is mounting evidence indicating that at least a high proportion of immunoglobulins expressed by MALT lymphoma of various sites are auto-reactive as shown by analysis of their recombinant antibodies and/or demonstration of their high homology to a stereotypic complementarity determining region 3 (CDR3) sequence, such as those of rheumatoid factors (RF) (Table 2).

In a large survey of lymphoma derived IG gene sequences for homology to RF associated stereotypic CDR3 sequences, Bende and colleagues have demonstrated that a high proportion of MALT lymphoma of the salivary gland (41%) and stomach (18%), but not those from the lung, harbour significant homology to the CDR3 sequences of canonical RFs (IGHV1-69-RF, IGHV3-7-RF and WOL-RF) [42]. *In vitro* binding analysis of the recombinant antibodies from the representative MALT lymphoma associated IGHV1-69 or IGHV3-7 rearrangements confirms their activities to the Fc portion of human IgG [42]. Moreover, strong RF activities are also demonstrated for recombinant antibodies from two MALT lymphomas that harbour classic RF IGHV1-69/IGHJ4 rearrangement, but not yet meet the criteria for a high homology to a RF CDR3 sequence, and additionally from a HCV-associated MALT lymphoma that harbours a novel IGHV4-59/IGHJ5 stereotypic rearrangement [42,63]. These findings indicate that the true frequency of MALT lymphomas that express BCR bearing RF activities is underestimated.

The IGHV4-34 rearrangement frequently seen in ocular adnexal MALT lymphoma is also most likely autoreactive. Autoantibodies encoded by IGHV4-34 rearrangement in reactive B-cells are known for their dependence on the unique and conserved germline FR1 hydrophobic patch ($Q^{6}W^{7}$ and $A^{24}V^{25}Y^{26}$), which is critical for binding to *N*-acetyl-lactosamine residues, present in a wide range of surface glycoproteins [64]. Importantly, the germline FR1 hydrophobic patch is commonly spared by somatic mutations in lymphomas including ocular adnexal MALT lymphoma (personal communication with Dr Richard Bende, July 2016) [65]. Furthermore, analysis of recombinant antibodies from MALT lymphomas that harbour IGHV4-34 rearrangement confirms their polyreactivity [43].

Apart from the above well-characterised IG gene rearrangements that encode autoantibodies, there is further evidence of polyreactivity of MALT lymphoma associated-BCRs encoded by other IG gene

rearrangements such as those involving IGHV3-23 and IGHV3-30, IGHV3-33 and IGHV3-66, as shown by several recombinant antibody studies [42,43,48,62]. As the number of cases investigated to date is small, the extent of autoreactive BCR expressed by MALT lymphoma is likely not yet fully appreciated.

iii) Evidence of BCR signalling is operational in MALT lymphoma

There are several strands of evidence indicating that the BCR expressed by MALT lymphoma cells is operational. The lymphoma cells almost always express surface IgM, and possess a range of biological properties of reactive B-cells including ability to undergo blast transformation, plasma cell differentiation and even further "germinal centre reaction", known as follicular colonisation [66,67]. While in the colonised follicles, MALT lymphoma cells show active proliferation and similar phenotypic changes like reactive B-cells. Genetically, MALT lymphoma cells frequently exhibit intraclonal variations or ongoing mutations in their rearranged IG genes, which are probably the result of their follicular colonisation of reactive B-cell follicles [45,53,68-70]. Like normal B-cells, these phenotypic and genetic changes in MALT lymphoma cells are most likely the result of their responses to microenvironment milieu including stimulation through surface BCR, co-stimulating receptors and cytokine receptors. It is highly likely that BCR engagement by autoantigen triggers a chronic and active BCR signalling, thus causes NF-κB activation, consequently enhancing the lymphoma cell survival and proliferation. In line with this, crosslinking surface IgM on MALT lymphoma cells is capable of stimulating their proliferation or enhancing their proliferative responses to mitogens [71]. Nonetheless, BCR engagement alone is unlikely sufficient to maintain the growth and survival of MALT lymphoma cells in view of the evidence that a high proportion of MALT lymphoma of the stomach, ocular adnexa and skin show complete regression following anti-microbial treatment. Thus, the immune and inflammatory responses other than direct BCR stimulation, which are eliminated following anti-microbial treatment, may be the major player in sustaining the survival of lymphoma cells.

3.2. T-cell help and CD40 signalling

Among the many B-cell helper signals present in the microenvironment of MALT lymphoma, only T-cell help has been fairly investigated and this is largely based on studies of gastric MALT lymphoma. Although gastric MALT lymphoma is causatively linked to chronic *H. pylori* infection, *H. pylori* antigens do not directly stimulate the neoplastic B-cells, but rather activate *H. pylori* specific tumour infiltrating T-cells and through them to promote the survival and proliferation of lymphoma B-cells [62,72]. This involves cognate interaction between B and T-cells [73-75], and also bystander T-cell help via soluble ligands and cytokines, such as CD40L and BAFF, thus activating the non-canonical NF-κB pathway (Figure 1) [76]. In support of this, reactive B-cell follicles are invariably present in gastric MALT lymphoma, and these reactive components provide a setting for classical immunological responses that generate *H. pylori* specific T-cells. An enriched expression of proinflammatory cytokines such as IL8 and IL1β, molecules involved in B and T-cell interaction such as CD86, CD28 and ICOS is seen in gastric MALT lymphoma, particularly those without chromosome translocation [77]. In addition, in the mouse model of *Helicobacter* induced gastric MALT lymphoma, Th2 cytokines such as IL4, rather than CD40 signalling, have been thought to play a critical role in the proliferation of lymphoma cells [78].

Clearly, the immune and inflammatory responses are critical for the evolution and emergence of aurorective cells, their malignant transformation and subsequent clonal expansion. Although the survival of MALT lymphoma cells in a high proportion of cases is still highly dependent on such immunological drive, such an effect of immunological drive is likely additive or synergistic to those conferred by acquired genetic changes as immunological drive alone is not sufficient for malignant transformation.

4. Genetic abnormalities

The spectrum of genetic abnormalities underlying the molecular mechanisms of MALT lymphoma has not been explored by whole genome or whole exome sequencing, and thus remains to be fully investigated.

Despite this, various genetic abnormalities identified in MALT lymphoma to date have been shown commonly targeting the signalling pathways that regulate the NF-κB activities. These genetic abnormalities include chromosome translocations, somatic mutations and copy number changes, and intriguingly occur at remarkably variable frequencies in MALT lymphoma of different anatomic sites despite targeting the same or a similar molecular pathway.

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

This translocation occurs primarily in MALT lymphoma of the lung (9%) and stomach (4%) (Figure 3), and juxtaposes the *BCL10* gene under the regulatory control of the IG gene enhancer, leading to BCL10 over-expression (Figure 4) [79-81]. BCL10 is an essential component of the CARD11/BCL10/MALT1 signalosome complex that relays the antigen receptor signalling to the canonical NF-κB activation pathway (Figures 1 & 5) [6,82]. Over-expression of BCL10 causes its constitutive activation through oligomerisation via its N-terminal CARD/CARD interaction, and thus leads to enhanced NF-κB activities. Intriguingly, BCL10 protein 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 [79,83-86], suggesting a yet unappreciated role of nuclear BCL10 in the pathogenesis of MALT lymphoma.

Apart from the canonical NF-κB pathway as detailed above, there is also evidence for a role of BCL10 in the regulation of non-canonical NF-κB pathway. Bcl10 deficiency B-cells show a reduced expression of NF-κB2 (p100), and also a reduced nuclear accumulation of the non-canonical p52/RelB complex following BAFF stimulation [87]. In contrast, B-cells in Eμ-BCL10 mice exhibited constitutive activation of both canonical and non-canonical NF-κB signalling pathways, and the activation of non-canonical pathway was thought to be indirect via up-regulation of BAFF expression [86]. In keeping with these findings, BAFF has been shown to be over-expressed in MALT lymphoma [88,89].

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

This translocation occurs mainly in MALT lymphoma of the ocular adnexa (7%) and lung (6%) (Figure 3), and causes MALT1 over-expression [90-92]. MALT1 contains several functional domains including an N-terminal death domain, three immunoglobulin-like domains and a proteolytically active caspase-like domain (Figure 4). Through its two N-terminal Ig-like domains, MALT1 interacts with BCL10, triggering its own oligomerisation and activation, thus enhances canonical NF-κB signalling (Figures 1& 5) [93,94]. This is supported by a strong accumulation of both MALT1 and BCL10 in the cytoplasm of the lymphoma cells carrying t(14;18)(q32;q21)/*IGH-MALT1,* a very distinct expression pattern from those of MALT lymphoma with t(1;14)(p22;q32)/*BCL10-IGH* or t(11;18)(q21;q21)/*BIRC3* (*API2*)-*MALT1* [90].

Through its protease activities, MALT1 also regulates NF-κB activation by specific cleavage of several NF-κB regulators including TNFAIP3 (A20), CYLD, RelB and BCL10, thus inactivating the function of these proteins [95-98]. Among these, TNFAIP3, CYLD and RelB are NF-κB negative regulators and are thus particularly relevant in lymphoma pathogenesis [95-99]. For example, TNFAIP3 is a transcriptional target of NF-κB, serves as a "global" feedback regulator to attenuate NF-κB activity by inactivation of NEMO, TRAF6, and RIP1, thus negatively regulating several cellular signalling that activate the canonical NF-κB pathway (Figures 1& 5) [12,100-102]. Constitutive activation of MALT1 by translocation may abolish the above NF-κB negative regulators, eliminating the physiological auto-negative feedback and causing relentless NF-κB activation.

MALT1 also plays a role in regulation of non-canonical NF-κB activation pathway, and its deficiency in B-cells significantly reduces the BAFF-induced phosphorylation and degradation of NF-κB2 (p100), thus decreases transcriptionally active p52 [103]. Consequently, MALT1 deficiency significantly impairs BAFF-induced cell survival, and interestingly this affects only marginal zone B-cell, but not follicular B-cells [103]. These

findings suggest that over-expression MALT1 by chromosome translocation may also lead to dysregulation of the non-canonical NF-κB activation pathway.

In addition, MALT1 can directly interact with and activate caspase-8 in a protease independent manner, and direct its function to activate the NF-κB pathway rather than apoptosis pathway upon antigen receptor stimulation in T-cells [104,105]. It remains to be investigated whether this MALT1 function is also operational in B-cells, hence has a potential role in lymphoma pathogenesis.

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

This translocation occurs predominantly in MALT lymphoma of the stomach (24%), lung (38%) (Figure 3) [90,91], and causes a chimeric fusion between the N-terminal *API2* and the C-terminal *MALT1* (Figure 4) [106-108]. The resulting API2-MALT1 fusion product gains novel abilities to confer oncogenic activities via activation of both canonical and non-canonical NF-κB pathways (Figure 5).

The API2-MALT1 fusion products are also capable of auto-oligomerisation through heterotypic interaction between the BIR1 of the API2 moiety and the C-terminal region of MALT1, thus resulting in constitutive activation of the canonical NF-κB pathway [109,110]. Like MALT1, API2-MALT1 can also cleave TNFAIP3/A20 and CYLD and eliminate these physiological negative feedback regulations (Figure 5) [95,111]. In addition, the API2-MALT1 induced NF-κB activation may enhance its own expression since API2 is a transcriptional target of NF-κB [112]. In keeping with this speculation, high levels of polyubiquitination of NEMO 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 [110,113].

The API2-MALT1 fusion product also gains ability to activate the non-canonical NF-κB pathway (Figure 5). The API2 moiety of the fusion product recruits NIK and places it in close proximity with the activated MALT1 protease domain, leading to cleavage of NIK at arginine 325. This generates a C-terminal NIK fragment that retains kinase activity and resists to TRAF3 dependent proteasomal degradation, and consequently causes constitutive signalling to activate the non-canonical NF-κB pathway [114].

Furthermore, the API2-MALT1 fusion product 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, and generates a novel oncogenic LIM domain-only (LMO) fragment (Figure 5) [115]. Expression of the LMO fragment promotes survival and proliferation of primary B-cells *in vitro* and tumour formation in xenograft model [115], albeit its molecular mechanism remains to be investigated.

4.4. *TNFAIP3* (A20) inactivation

TNFAIP3 deletion and/or inactivation mutation are largely seen in MALT lymphomas of the ocular adnexa, salivary gland and thyroid, in which the above chromosome translocations are absent or rare (Figure 3) [116-120]. Unlike the above chromosome translocations that are specific to MALT lymphoma, *TNFAIP3/A20* deletion and inactivating mutations are also frequently seen in a range of other lymphoma entities [119-124]. 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 (Figure 4) [10,100]. Through removing the K63-linked ubiquitin chain, catalysing the K48-linked polyubiquitination and also direct binding to the linear polyubiquitin chain of its targets, TNFAIP3 can inactivate several NF-κB positive regulators including RIP1/2, TRAF6 and IKKγ (Figure 1) [12,101,102]. Thus, TNFAIP3 inactivation can potentially augment NF-κB activation triggered by signalling from multiple surface receptors.

4.5. *MYD88* mutation:

This occurs in ~5% of occular adnexal MALT lymphoma, and comprises novel inframe deletions as well as previously identified hotspot mutations such as L265P in the TIR domain, which is found frequently in several other B-cell lymphoma subtypes (Figures 3 & 4) [125-129]. These different mutations have been shown to be a gain-of-function change [125,127]. MYD88 mutants are constitutively active and capable of spontaneously assembling a protein complex containing IRAK1 and IRAK4, thus signalling to activate NF-κB, STAT3 and AP1 transcription factors (Figure 1) [125].

Somatic mutations in other NF-κB regulators: Although this has not yet been comprehensively investigated, several studies show that the somatic mutations of 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, are rare in MALT lymphoma [126-128,130-132]. The extent of common and unique genetic abnormalities between MALT lymphoma and other B-cell lymphomas characterised with constitutive NF-κB activities remains to be investigated.

4.6. Other chromosome translocations:

There are also several novel chromosome translocations including t(3;14)(p13;q32)/*FOXP1-IGH* [133-135], t(1;14)(p21;q32)/*CNN3-IGH*, t(5;14)(q34;q32)/*ODZ2-IGH*, t(9;14)(p24;q32)/*JMJD2C-IGH* [136] and t(X;14)(p11.4;q32)/*GPR34-IGH* [137,138], which are reported in isolated cases of MALT lymphoma. These translocations are predicted to cause over-expression of the oncogene involved as these are in association with the IGH gene locus, thus under the transcriptional control of the IG gene enhancer. The molecular mechanism underlying the oncogenic activities of these genetic events remains to be investigated.

5. Oncogenic cooperation among immunological stimulation and genetic changes

There is firm evidence that none of the genetic abnormalities in MALT lymphoma alone is sufficient for malignant transformation. Both Eμ-*BCL10* and Eμ-*API2-MALT1* mice develop splenic marginal zone hyperplasia but not lymphoma [86,113], while *TNFAIP3* (A20) deficiency in B-cells enhances B-cell proliferation with an excessive production of self-reactive autoantibodies [139]. However, stimulation of Eμ-API2-MALT1 mice with Freund's complete adjuvant leads to development of splenic marginal zone lymphoma-like lesion [140], suggesting oncogenic cooperation between genetic abnormalities and immunological stimulations.

As discussed above, there is a considerable overlap in the signalling pathways dysregulated by immunological stimulations and genetic changes (Figure 5). For example, the receptor signalling that leads to canonical NF-κB pathway activation, such as BCR and TLR (toll-like receptor), and those resulting in non-canonical NF-κB pathway activation such as BAFFR and CD40, are affected by both immunological stimulations and genetic changes. These signalling pathways and their concerted actions are known to be critical for the development and function of marginal zone B-cells [141,142]. Such biological cooperation among different receptor signalling is likely operational in MALT lymphoma cells, but in a remarkably dysregulated manner due to constitutive activations by auto-reactive BCR and genetic changes. For example, the constitutive activation of both canonical and non-canonical NF-κB pathways by chromosome translocation can be further augmented by chronic stimulation of surface BCR, TLR, BAFFR and CD40 [77]. Similarly, the BCR and TLR receptor signalling conferred by microenvironment milieu can be enhanced by *TNFAIP3* (A20) inactivation via genetic changes. Clearly, the extent of potential oncogenic cooperation among immunological responses and genetic abnormalities is very much underestimated due to incomplete understanding of the signalling for marginal zone B-cell development as well as incomplete characterisation of the genetics of MALT lymphoma.

6. Summary and future prospective

MALT lymphoma is a paradigm for illustration of oncogenic cooperation between immunological drive and genetic abnormalities in lymphoma genesis. There are significant differences in the aetiology, IG gene usage and acquired genetic changes in MALT lymphoma of different anatomic sites despite they all share certain common clinicopathological features, and such variations offer excellent opportunities for discovery research. Particularly, neither the immunological drive nor genetic changes have been comprehensively investigated in MALT lymphoma of different anatomic sites. It is imperative to perform whole genome or exome sequencing analysis to characterise the somatic mutation profile of MALT lymphoma of various anatomic sites and dissect their molecular oncogenic mechanisms. It is also important to comprehensively catalogue IG gene usage in MALT lymphoma of various anatomic sites, and characterise the properties of the lymphoma derived immunoglobulin. Finally, apart from T helper cells, it is important to investigate the potential role of other B-cell helper signals, such as those from dendritic cells, neutrophils and innate lymphoid cells, in the pathogenesis of MALT lymphoma, in light of their important role in the biology of normal B-cells [143,144]. A comprehensive investigation of these genetic and immunological properties will provide rich information and insights into the molecular mechanisms and oncogenic cooperation among somatic genetic abnormalities and immunological stimulations in MALT lymphoma.

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FIGURE LEGENDS:

Figure 1: NF-κB activation pathways and their major regulators. The signalling from the TNFR1, TLR, IL-1R, and antigen receptor (BCR) 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 non-canonical NF-κB pathway, which is featured by activation of NIK, proteolytic processing of p100 and generation of functional active p52. The canonical NF-κB pathway is negatively regulated by A20 (TNFAIP3), a target of NF-κB, while the non-canonical pathway is negatively controlled by TRAF3. The regulators that are activated by genetic changes in MALT lymphoma are highlighted by a red colour circle, while those that are inactivated by genetic changes are highlighted by a black colour circle. Modified with permission from Du MQ, Histopathology 2011 [148].

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.

Figure 2: Multistage development of MALT lymphoma.

Figure 3: Frequencies of genetic abnormalities in MALT lymphoma of different sites. The data are based on our previous studies [79,90,116,119,145-147].

Figure 4: Key features of MALT lymphoma associated oncogenes or tumour suppresser genes.

T(1;14)(p22;q32)/*BCL10-IGH* and t(14;18)(q32;q21)/*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. Modified with permission from [127,148].

Figure 5: 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* activate the canonical NF-κB 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 TNFAIP3/A20. 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. Over-expression of BCL10 or MALT1 may also indirectly enhance non-canonical NF-κB signalling via BAFFR. These genetic changes may potentially cooperate with the signalling from BCR, BAFFR and CD40, together causing constitutive activation of both canonical and non-canonical NF-κB pathways.

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 explains that most of translocation negative gastric MALT lymphomas are responsive to *H. pylori* eradication. Reproduced with permission from [148,149].

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.

Table 1: Examples of biased IG gene usage in MALT lymphoma of different anatomic sites.

Sites of MALT lymphoma	**Aetiology**	**Biased IG gene usage#**	**References**
Stomach	*Helicobacter pylori*	IGHV3-7 IGHV1-69 IGHV1-2 (?) IGHV3-23 (?)	[42,45-49]
Ocular adnexa	*Chlamydia psittaci*	IGHV4-34/IGKV3-20***** (~12%) IGHV3-7 (?) IGHV3-23 (?) IGHV3-30 (?)	[44,50-54]
Salivary glands	lymphoepithelial sialadenitis	IGHV1-69/IGKV3-20 (~50%)	[42,55,56]
Thyroid	Hashimoto thyroiditis	IGHV3-30 (?)	[57]
Skin	*Borrelia burgdorferi*	IGHV3-30 (?) IGHV1-69 (?)	[58-60]
Lung	Achromobacter xylosoxidans	IGHV4-34 (?)	[61]

#where a IGHV member might be biased used, but not yet investigated extensively, is indicated by a question mark;
*frequently in *Chlamydia psittaci* negative cases.

Table 2: Properties of IG gene rearrangements and their encoded BCR in MALT lymphoma.

IG genes bias-used in MALT lymphoma	Known genetic features of IG rearrangement	Known IG properties	References
IGHV1-69	– short CDR3 sequence frequently with high homology to those of rheumatoid factor; – variable mutations in IGHV with few intraclonal variations;	rheumatoid factors, self-polyreactive	[42,48,54,56]
IGHV3-7	– CDR3 sequence frequently with high homology to those of rheumatoid factor;	rheumatoid factors, self-polyreactive	[42,48,54]
IGHV3-23/IGKV3-20	n/a	self-polyreactive	[43]
IGHV3-30 /IGKV1-33	n/a	self-polyreactive	[43]
IGHV4-34/ IGKV3-20*	– Contains unique and conserved FR1 motif ($Q^{6}W^{7}$ and $A^{24}V^{25}Y^{26}$)	Binding to *N*-acetyl-lactosamine residues; polyreactive	[43,64,65]

n/a: not available yet

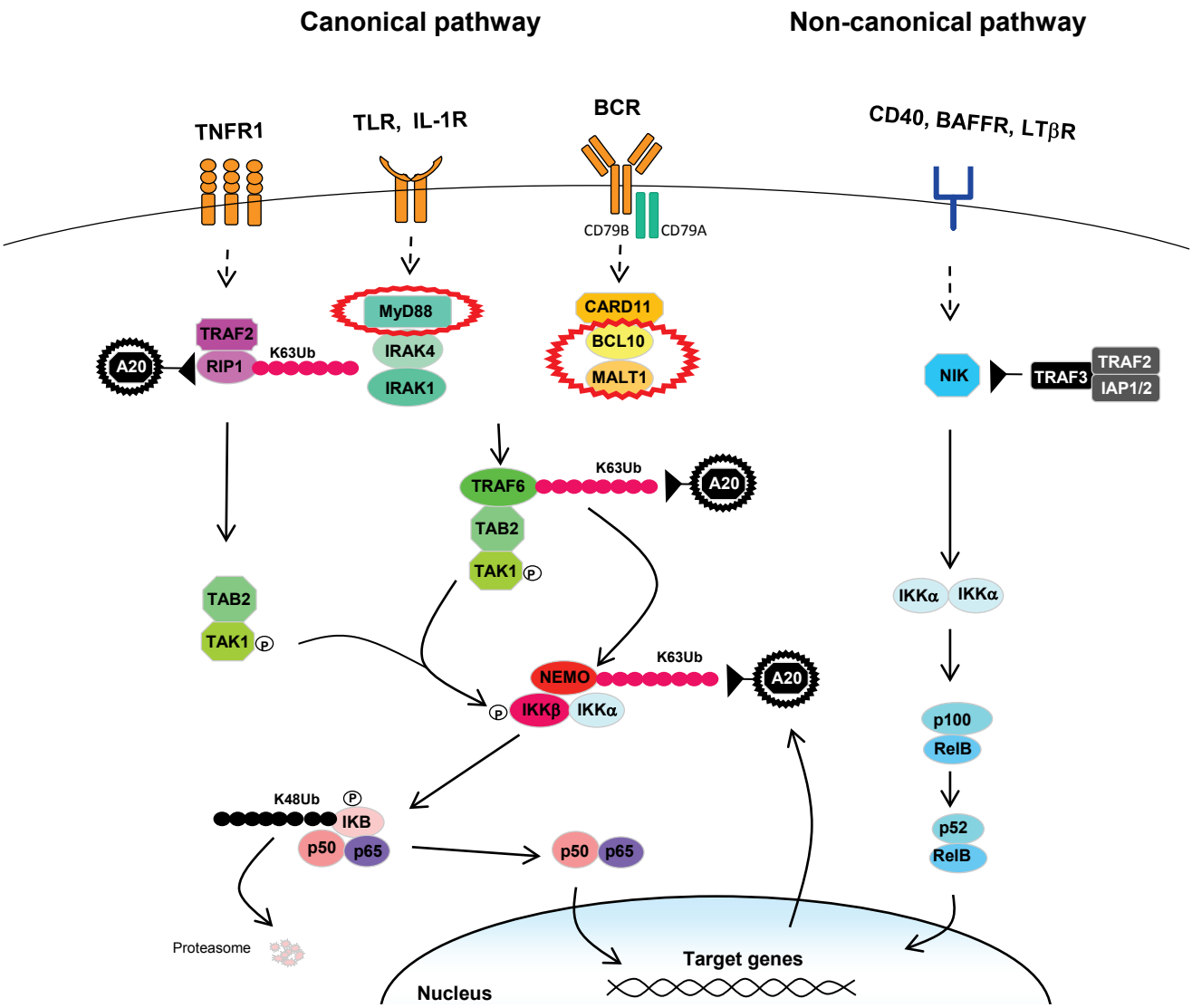

Figure 1. NF-κB activation pathways and their major regulators.

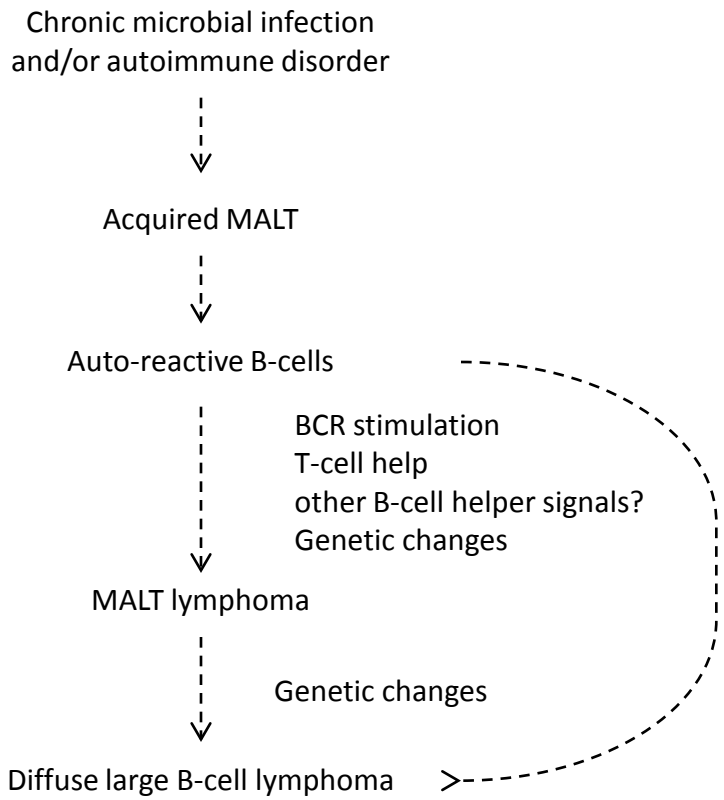

Figure 2: Multistage development of MALT lymphoma.

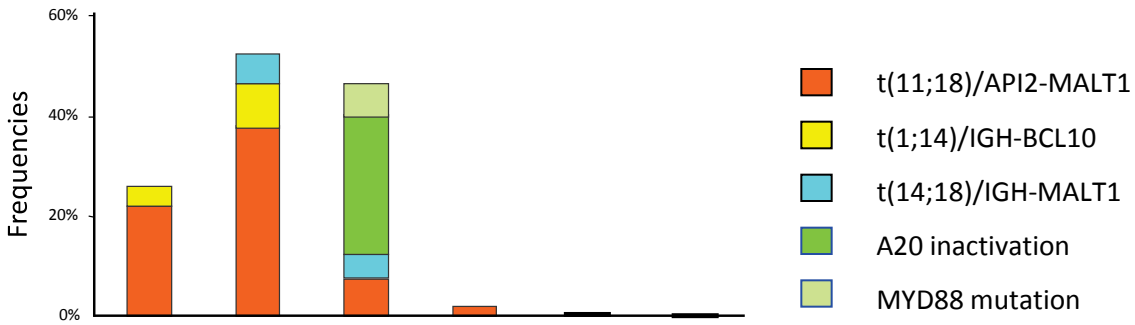

Figure 3: Frequencies of genetic abnormalities in MALT lymphoma of different sites.

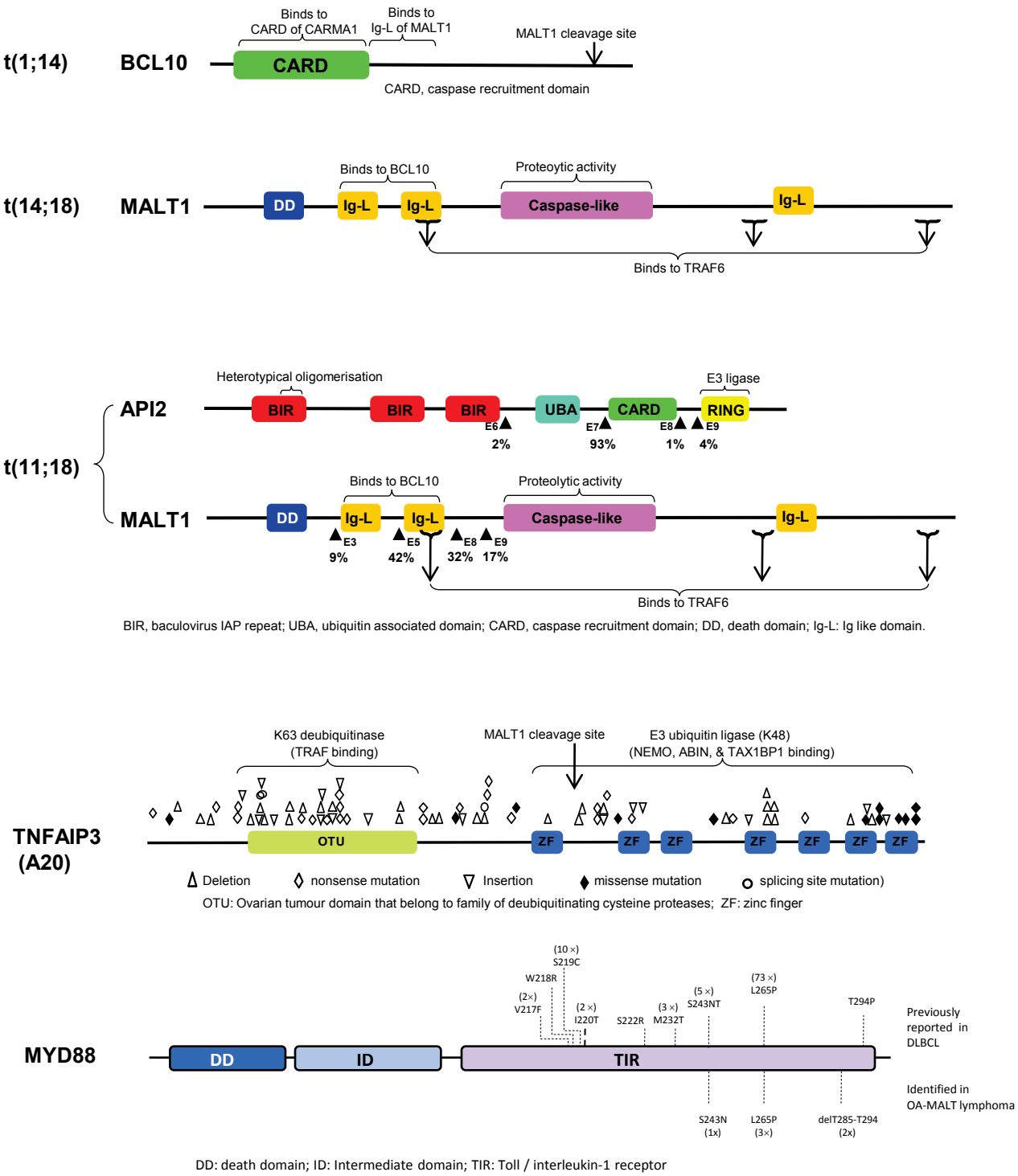

Figure 4: Key features of MALT lymphoma associated oncogenes or tumour suppresser genes.

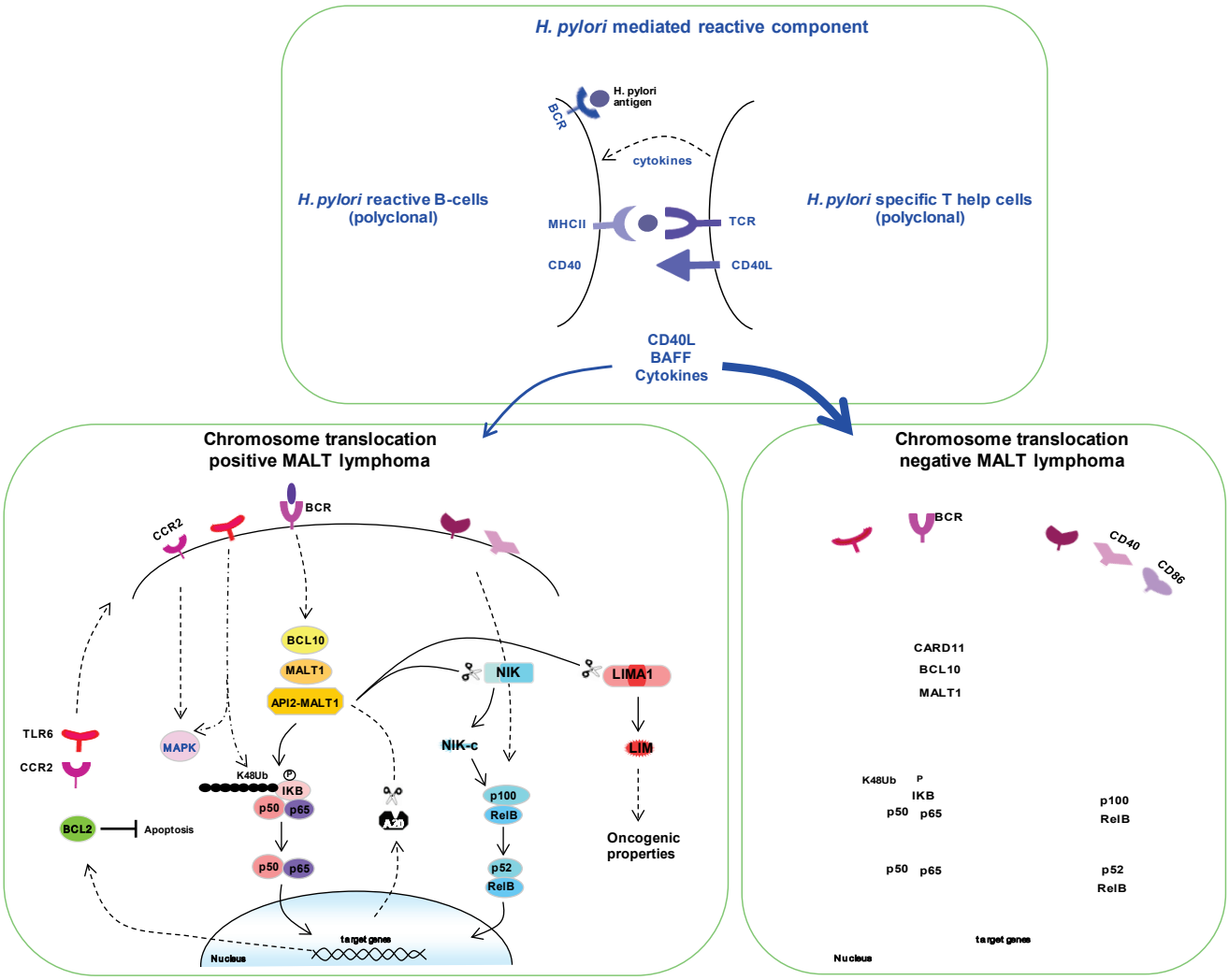

Figure 5: The proposed model of molecular pathogenesis of gastric MALT lymphoma with and without chromosome translocation.