Mucosa-associated lymphoid tissue lymphoma of various sites: common molecular mechanisms but different players

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Abstract: Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) commonly arises from a background of chronic inflammatory disorder at various mucosal sites. The cause of the chronic inflammatory disorder is highly site dependent, ranging from microbial infection to autoimmune response. The adaptive immune responses generated by these different chronic inflammatory processes most likely have a critical impact on the clonal evolution of the lymphoma cells and their acquired somatic genetic changes. There is growing evidence showing biased usage of immunoglobulin genes, thus expression of stereotypic autoreactive B-cell receptor (BCR), in MALT lymphoma of various sites. There are also mounting data demonstrating distinct somatic genetic profiles among MALT lymphoma of different sites. More recent studies have revealed an association between biased immunoglobulin gene usage and somatic genetic changes that promote BCR signalling in ocular adnexal MALT lymphoma. Furthermore, there are distinct genetic changes in MALT lymphoma of the salivary gland and thyroid, which involve immune receptors and may enable them to gain more help signals from their microenvironment. In this review, I will summarise the recent research advances, advocating for a critical role of oncogenic cooperation between immunological drive and genetic changes for clonal evolution of MALT lymphoma cells.

Keywords: Mucosa-associated lymphoid tissue (MALT) lymphoma; immunological drive; genetic abnormalities; oncogenic cooperation

Introduction

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) lymphoma is a low-grade B-cell lymphoma originated from marginal zone B-cells. The lymphoma commonly arises in a background of a chronic inflammatory disorder at diverse anatomic sites typically devoid of any native lymphoid tissue (1). The cause of the chronic inflammation is highly site dependent, ranging from Helicobacter pylori infection in MALT lymphoma of the stomach to autoimmune responses in those of the salivary gland (Sjogren's syndrome) and thyroid (Hashimoto's thyroiditis). The inflammatory response results in development and accumulation of organised lymphoid tissue, i.e., acquired MALT. Like the secondary lymphoid tissue, the acquired MALT generates and maintains adaptive immune responses including T-cell dependent B-cell maturation. Thus, antigen primed B-cells actively undergo the germinal centre reaction, affinity maturation and differentiate into antigen experienced effective B-cells and plasma cells. Through this relentless dynamic process, reactive B-cells may undergo Darwinian selection based on their growth and survival capacity. This may lead to gradual clonal selection, expansion, and eventual malignant transformation of certain reactive B-cell clones. This is supported by the findings of multiple small clonal B-cell populations at reactive conditions, and their occasional progression and clonal expansion to develop an overt

lymphoma (2).

In general, MALT lymphoma only develops in a very small number of the patients with these common chronic inflammatory disorders. Apart from the host genetic and microbial virulent factors where indicated, the B-cell clone, which utmost undergoes malignant transformation, is most likely selected owing to its intrinsic properties, appropriate supporting microenvironments and cooperative somatic genetic changes. Although this is not yet fully understood, there is growing evidence indicating oncogenic cooperation among these three distinct components in the clonal evolution of MALT lymphoma. At the molecular level, all the three components affect the cellular signalling pathways critical for the biology of marginal zone B-cells. Nonetheless, there is a distinct difference in the players involved among MALT lymphomas of different sites. This review will focus on the recent advances that advocate for oncogenic cooperation between immunological drive and somatic genetic change in MALT lymphoma of various mucosal sites. To help the understanding of oncogenic role of various players in MALT lymphoma, I first briefly outline below the signalling pathways that are critical for the biology of marginal zone B-cells.

Cellular signalling critical for marginal zone B-cells

Marginal zone B-cells are post-germinal centre B-cells, their differentiation, migration and homing are tightly regulated by concerted actions of transcriptional network and surface receptor signalling. There are several signalling pathways including NF-κB and NOTCH, which are critical for marginal zone B-cells, and disruption of any of these signalling pathways impairs the development and/or function of marginal zone B-cells (3).

NF-κB signalling pathway

Nuclear factor (NF)-κB is a family of dimeric transcription factors, which are formed by various hetero or homodimers of RelA (p65), RelB, c-Rel, NF-κB1 (p50 and its precursor p105) and NF-κB2 (p52 and its precursor p100). They are kept inactive in the cytoplasm by their inhibitor (IκBα, IκBβ and IκBε) or in its dormant precursor form, but can be activated by various surface receptor signalling, enabling their nuclear translocation and transcriptional activities. There are two common pathways linking various surface receptor signalling to NF-κB activation, namely canonical

and non-canonical NF-κB pathway.

Canonical NF-κB pathway

This is characterised by activation of the IκB kinase (IKK) complex in response to upstream signalling, which phosphorylates IκB, triggering its K48-linked polyubiquitination and degradation by proteasome. NF-κB dimers are then free for nuclear translocation, enabling their transcriptional activities (*Figure 1*).

Canonical NF-κB pathway is activated by signalling from several surface receptors including B-cell receptor (BCR), Toll-like receptor (TLR), interleukin 1 receptor (IL1R) and tumour necrosis factor receptor (TNFR). Binding of these receptors by ligand triggers distinct cascade signalling, but converge on the canonical NF-κB activation pathway. For example, BCR engagement triggers phosphorylation of CD79A (Igα) and CD79B (Igβ) at their ITAM (immunoreceptor tyrosine-based activation motif) residues, which act as docking sites for LYN and SYK kinases, and their signal propagation (5). These kinases recruit the B-Cell Linker (BLNK), and coordinate the activation of Bruton's tyrosine kinase (BTK) and phospholipase Cg2 (PLCγ2). In turn, they trigger a signalling cascade that promote the assembly and activation of the CARD11/BCL10/MALT1 (CBM) signalosome complex (6,7), which links the BCR receptor signalling to the canonical NF-κB activation pathway. Apart from the canonical NF-κB pathway, the proximal BCR signalling also activate the PI3K–AKT and RAS-ERK activation pathways via different signalling cascades (5,8,9).

The signalling that leads to NF-κB activation is closely regulated by several negative regulators including TNFα inducible protein 3 (TNFAIP3, also known as A20), IκBα and CYLD (cylindromatosis) (10). Importantly, IκBα and TNFAIP3 are the transcriptional targets of NF-κB, and their expression could act as an auto-negative feedback to ensure appropriate level and length of NF-κB activation. Apart from immobilisation of NF-κB in the cytoplasm, IκBα harbours a nuclear export sequence and can promote NF-κB export from the cell nucleus to the cytoplasm (11). TNFAIP3 is an ubiquitin editing enzyme, can remove the K63-linked ubiquitin chain and catalyse the K48-linked polyubiquitination, which are modifications for protein activation and degradation respectively (12). Through these ubiquitin editing activities, TNFAIP3 can inactivate a number of NF-κB positive regulators including receptor-interacting protein-1/2 (RIP1/2), ubiquitin-conjugating enzyme 13 (Ubc13) and IKKγ (also known as NF-κB essential modulator, NEMO), thus attenuating the signalling
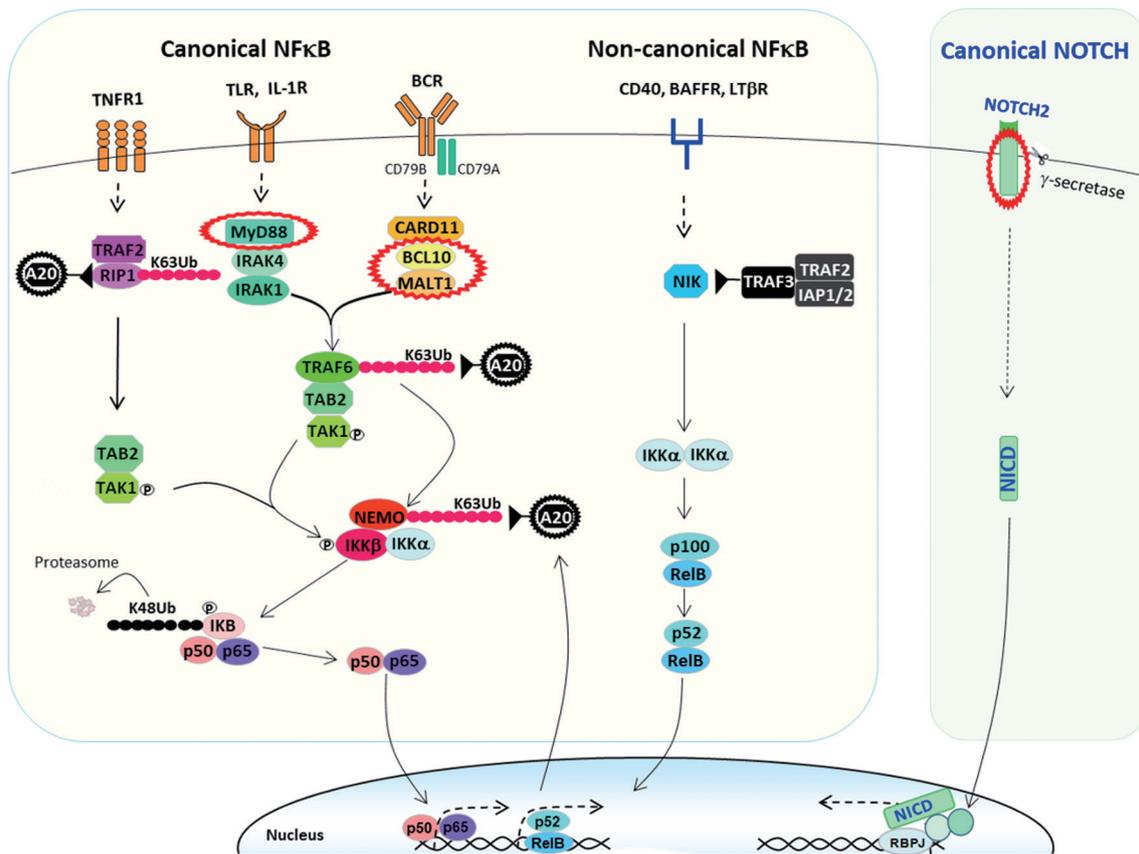
Figure 1 NF-κB and NOTCH activation pathways and their major regulators important for this review. The canonical NF-κB pathway is activated by signalling from the TNFR1, TLR, IL-1R, and antigen receptor (BCR), and characterised by activation of the IKK complex, phosphorylation and degradation of IκB. The non-canonical NF-κB pathway is activated by signalling from CD40, BAFFR and LTβR, and 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 NOTCH2 pathway is activated by ligand triggered proteolytic cleavage of the receptor, and generation of the active NOTCH2 intracellular domain (N2ICD). 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, Seminar in Cancer Biology 2016 (4). 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. RBPJ, recombination signal-binding protein for immunoglobulin kappa J region.

from several surface receptors including BCR, TNFR, TLR and IL1βR (13-15).

Non-canonical NF-κB pathway
This is featured by activation of the NF-κB inducible kinase (NIK) in response to upstream signalling. The activated NIK phosphorylates and activates IKKα, which in turn triggers phosphorylation and partial proteolysis of NF-κB2

(p100), generating a functional active form p52 in complex with RelB. The p52/RelB dimer is then free for nuclear translocation and transcriptional function. The non-canonical NF-κB pathway is activated by signalling from surface receptors including CD40, B cell activating factor receptor (BAFFR), TNFRSF13B (also known as TACI) and lymphotoxin β receptor (LTβR). The pathway is modulated by controlling NIK degradation, which is mediated by an

ubiquitin ligase complex comprising TRAF3, TRAF2, and cIAP1/2 (API1/2) (16).

NOTCH2 signalling pathway

NOTCH2 is a surface receptor, composed of extracellular, transmembrane and intracellular domain. Binding of its extracellular domain by ligand triggers proteolytic cleavages of NOTCH2 by ADAM-type protease (S2) and γ-secretase (S3), and this releases the active NOTCH2 intracellular domain (N2ICD) (17). N2ICD is free to translocate to the nucleus, forms a transcriptionally active complex with RBPJ (CSL) and transactivate its target genes (17).

The above receptor signalling is important not only for the differentiation, but also for the function of marginal zone B-cell. This is supported by finding of expression of a range of ligands including BAFF, APRIL, CD40L and the Notch2 ligand Delta-like 1 (DLL1) by the innate lymphoid cells that reside in the marginal zone (18,19). These signalling, critical for normal marginal zone B-cells, are also operational in MALT lymphoma cells, and often affected by somatic genetic changes, together causing their constitutive activation.

Receptor signalling commonly implicated in MALT lymphoma of various sites

BCR signalling

Evidence of active BCR signalling in MALT lymphoma
A functional BCR is essential for the biology of B-cells, and this is also true if not more paramount for MALT lymphoma cells. The lymphoma cells invariably express surface IgM, and preserve the biological properties of reactive B-cells such as the ability to undergo blast transformation, plasma cell differentiation as well as the "germinal centre reaction", histologically known as follicular colonisation (20,21). Similar to germinal centre B-cells, MALT lymphoma cells frequently show intraclonal sequence variations in their rearranged IG genes, a likely consequence of their follicular colonisation (22-26). Importantly, crosslinking surface IgM on MALT lymphoma cells stimulates their proliferative responses to mitogens (27). As expected, inhibiting BCR signalling by BTK inhibitor induces durable responses in patients with previously treated marginal zone lymphoma including MALT lymphoma (28). Together, these observations indicate that BCR signalling is operational in MALT lymphoma cells.

Evidence of auto-reactivity of MALT lymphoma associated BCR

The specificity of immunoglobulin derived from MALT lymphoma has not been investigated in a large scale. Nonetheless, various studies using hybridoma or recombinant antibody technology consistently show that the immunoglobulin from MALT lymphoma of various anatomic sites is autoreactive rather than recognising antigens from infectious agents that are associated with the lymphoma development (*Figure 2A*). The auto-reactivity may range from polyreactive to various self-antigens to a high-affinity binding to IgG-Fc, a characteristic of rheumatoid factors (RF) (*Figure 2*). In fact, many of these MALT lymphoma derived immunoglobulins share the cardinal features of known autoantibodies, together providing the paradigm for sequence analysis of lymphoma derived immunoglobulin. This has considerably expanded our knowledge on the extent of autoreactivity of MALT lymphoma associated BCR.

A paradigm is the immunoglobulin displaying RF activities, which are generated commonly by IGHV1-69/J4, IGHV3-7/J3 and rarely by IGHV4-59/J2(J5) rearrangements (33-38). The vast majority of these IG gene rearrangements seen in MALT lymphoma of various anatomic sites show a high identity to those of classical RFs in their complementarity-determining regions (CDR) 3 sequences (*Figure 2B*). Interestingly, IGHV1-69/J4 is preferentially paired with IGKV3-20 rearrangement, while IGHV3-7/J3 is often paired with IGVK3-15 rearrangement, further emphasizing their selection for antigen binding (38).

Another example is the immunoglobulin encoded by IGHV4-34 rearrangement, which is auto-reactive, binding to the carbohydrate I/i antigens composed of N-acetyl-lactosamine units. The hydrophobic residues ($Q^6W^7A^{24}V^{25}Y^{26}$) in the framework region 1 (FR1) of IGHV4-34 are essential for binding to *N*-acetyl-lactosamine residues, and introduction of mutations in these motifs impair the survival of the lymphoma cells expressing IGHV4-34 BCR (29,30). Remarkably, the germline FR1 hydrophobic patch is spared by somatic mutations in MALT lymphoma despite high levels of somatic mutations in other regions of the IGHV4-34 rearrangement (*Figure 2B*) (30,32,39).

Evidence of biased IG gene usage in MALT lymphoma

To date, sequencing studies of the rearranged IG genes in MALT lymphoma have been largely focused on IGH in those from the salivary gland, ocular adnexa and stomach. There is a clear evidence for a biased usage of IGH genes in

A

IG genes bias-used in MALT lymphoma	Known genetic features of IG rearrangement	IG properties by recombinant studies	References
VH1-69/JH4 (often with IGKV3-20)	– short CDR3 sequence frequently with high homology to those of rheumatoid factor; – variable mutations in VH with few intraclonal variations;	rheumatoid factors, – salivary gland – stomach self-polyreactive – stomach	(28-30,33,39,40)
VH3-7/JH3 (often with IGVK3-15)	– CDR3 sequence frequently with high homology to those of rheumatoid factor;	rheumatoid factors, – salivary gland – stomach self-polyreactive – stomach	(29,33,39,40)
VH3-23/JH4 (often with VK3-20)		self-polyreactive – ocular adnexa	(36)
VH3-30/JH3 (often with VK1-33)		rheumatoid factors – salivary gland self-polyreactive – salivary gland – ocular adnexa	(33) (36)
VH4-34 (often with VK3-20)	– Contains unique and conserved FR1 motif (Q^6W^7 and $A^{24}V^{25}Y^{26}$)	Binding to *N*-acetyl-lactosamine residues; polyreactive – ocular adnexa	(34-36)
IGHV4-59/JH2(JH5)		rheumatoid factors – salivary gland self-polyreactive – ocular adnexa	(32,36)

B

Figure 2 Features of MALT lymphoma associated BCR. (A) Summary of rearranged immunoglobulin genes from MALT lymphoma of various sites, which have been shown to be autoreactive by recombinant antibody technology with the site of MALT lymphoma indicated; (B) examples of IG gene rearrangements in MALT lymphoma of the ocular adnexa and salivary gland. Top panel shows the IGHV4-34 rearrangements in ocular adnexal MALT lymphoma. There is no or very rare mutation at the conserved VH FR1 $Q^6W^7A^{24}V^{25}Y^{26}$ residues (highlighted in yellow colour), which are essential for binding to N-acetyl-lactosamine residues (29). In contrast, mutations are commonly seen at the CDR2 N-link glycosylation site ($N^{52}H^{53}S^{54}$) and FR3 $K^{90}L^{91}S^{92}$ residues (both highlighted in light cyan colour), and these mutations are thought to improve the antigen binding affinity (30,31). Lower panel displays the IGH VDJ junction sequences from salivary gland MALT lymphoma, which have high identity to known RF (shown in bold). The gap in alignment is indicated by "-". Modified with permission from Moody *et al*, Journal of Pathology 2017 (32).
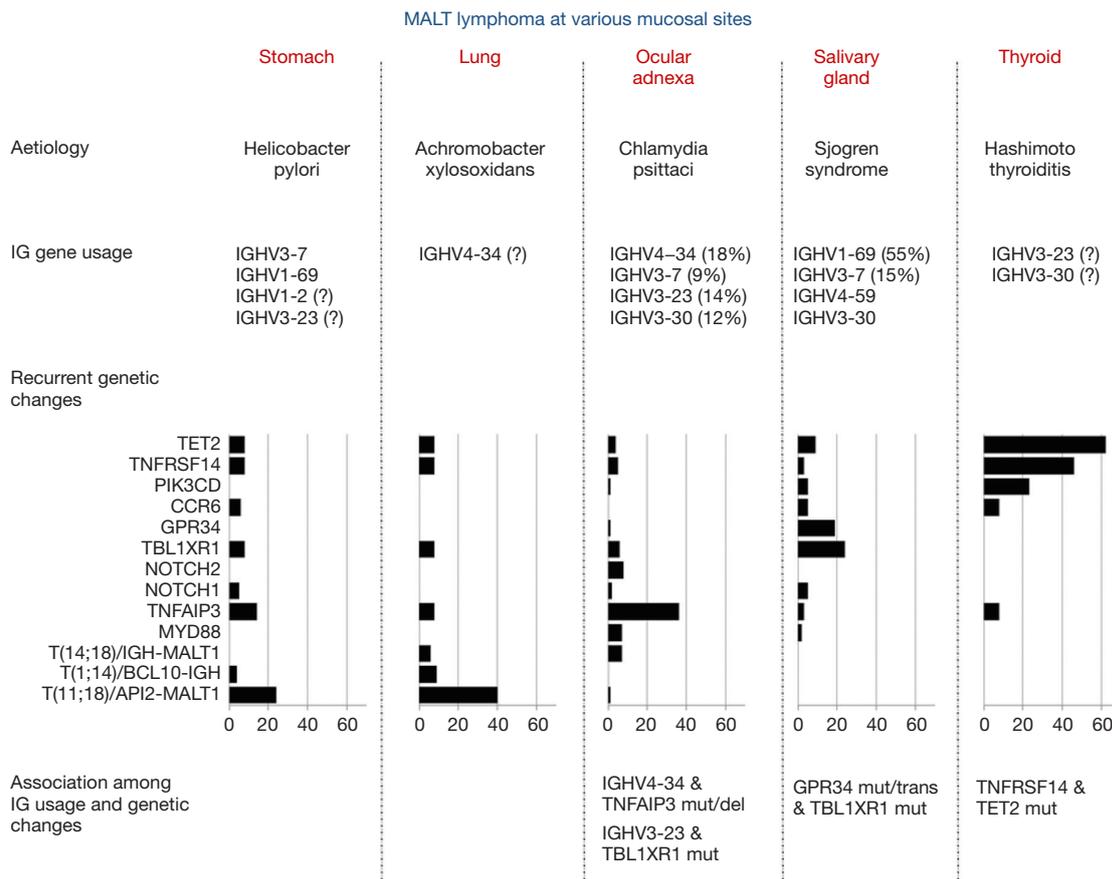
Figure 3 Aetiology, immunoglobulin gene usage, recurrent genetic abnormalities in MALT lymphoma of various sites. The *IGHV* gene usage in MALT lymphoma of various sites are based on the published literature (25,26,33,34,38,40-52). Where a IGHV member might be biased used, but not yet investigated extensively, is indicated by a question mark. Frequencies of genetic abnormalities in MALT lymphoma of different sites are based on published studies (32,53-63).

MALT lymphoma of the salivary gland and ocular adnexa (*Figure 3*). Over 70% of salivary gland MALT lymphomas harbour IGHV1-69/J4 (~55%) or IGHV3-7/J3 (~15%) rearrangements (32,33,35,38). This together with other less encountered (IGHV4-59/J2(J5) and IGHV3-30/JH4) rearrangements indicates that most salivary gland MALT lymphomas express BCR that potentially bears RF activities. Ocular adnexal MALT lymphomas show a biased usage of IGHV4-34 (18%), followed by *IGHV*3-23 (12–17%), I*GHV*3-30 (10-14%) and IGHV3–7 (9%) (32,40,41). In contrast, gastric MALT lymphomas generally display more diversified IGH gene usages, but are nonetheless enriched by those coding for autoantibodies. The difference in IG gene usage among MALT lymphoma of different anatomic sites is mostly likely the outcome of adaptive response and clonal selection caused by their distinct aetiologies, hence

different antigen exposures (64).

T-cell help and receptor signalling to non-canonical NF-κB pathway

Marginal zone B-cells develop via a T-cell dependent B-cell maturation process. Studies largely based on gastric MALT lymphoma indicate a critical role of T-cell help in the lymphoma development, which may represent a common mechanism for MALT lymphoma as a whole. Early studies show that *H. pylori* primed tumour infiltrating T-cells stimulate the proliferation of gastric lymphoma B-cells *in vitro* via cognate interaction involving CD40/CD40L co-stimulating molecules (65-67). These observations are reinforced by animal model studies, showing that depletion of CD4 positive T-cells can block the tumour growth

in vivo (68,69). As there is no evidence that the BCR expressed by human gastric MALT lymphoma recognises *H. pylori* associated antigens, it is unclear how lymphoma B-cells interact with *H. pylori* specific T-cells without recognising a common antigen. Alternatively, the stimulation of lymphoma B-cells is mediated through bystander T-cell help via soluble ligands and cytokines, such as CD40L and BAFF (*Figure 1*) (70-72). In support of this speculation, 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 or responsive to *H. pylori* eradication therapy (73-76). Such bystander T-cell help by *H. pylori* specific T-cells could be generated by classical immunological responses through reactive B-cell compartments which are always present in gastric MALT lymphoma. Regardless of the mechanistic details, these receptor signalling are critical for the survival of gastric MALT lymphoma cells as 70% of cases show complete lymphoma regression by *H. pylori* eradication therapy alone (77-79).

Genetic abnormalities

Although there are extensive investigations of genome-wide copy number changes (80,81), there are only three whole exome studies on a small number of MALT lymphoma from the ocular adnexa (n=23), salivary gland (n=14) and thyroid (n=13) (53-55), and several targeted sequencing studies of small gene panels (32,53,54,56). Hence, our understanding of the mutation profile in MALT lymphoma is far from comprehensive. Nonetheless, the data available to date show that there are considerable variations in the incidence and spectrum of genetic abnormalities among MALT lymphoma of different sites (*Figure 3*). Interestingly, most of these changes affect several common pathways.

Genetic abnormalities that enhance NF-κB signalling

There are several chromosome translocations involving the adaptor molecules that connect the BCR signalling to the NF-κB activation pathway. T(1;14) (p22;q32) and t(14;18) (q32;q21) juxtapose the *BCL10* and *MALT1* gene under the regulatory control of the IG gene enhancer respectively, causing their over-expression. These translocations are primarily seen in MALT lymphoma of the stomach, lung and ocular adnexa, but at low frequencies (*Figure 3*) (57). BCL10 and MALT1 over-expression triggers their

oligomerisation, hence constitutive activation, leading to enhanced signalling to activate the canonical NF-κB pathway (6,82). MALT1 activation also elicits its protease activities, causing specific cleavage and inactivation of NF-κB negative regulators including TNFAIP3 and CYLD, thus further enhancing NF-κB activation (83-87). BCL10 and MALT1 over-expression may also promote the activation of non-canonical NF-κB pathway via up-regulation of BAFF expression (88,89).

T(11;18)(q21;q21) generates a chimeric fusion between the N-terminal *BIRC3* (*API2*) and the C-terminal *MALT1*, and is frequently seen in MALT lymphoma of the stomach (24%) and lung (40%) (4,58,90). Through interaction between the BIR1 of the API2 moiety and the C-terminal region of MALT1, the fusion products undergo oligomerisation, become constitutively active, thus triggering signalling to activate the canonical NF-κB pathway (91-93). The API2-MALT1 fusion product can also cleave TNFAIP3 and CYLD through MALT1 protease activities, thus abolishing their negative feedback regulation (83,94). Theoretically, the API2-MALT1 induced NF-κB activation can enhance its own expression since API2 is a transcriptional target of NF-κB (95). Moreover, the API2-MALT1 fusion product gains novel function to activate the non-canonical NF-κB pathway by cleaving NIK at arginine 325, and generating a C-terminal fragment that retains kinase activity and resists to TRAF3 mediated proteasomal degradation (96). Finally, the fusion product can also cleave the tumour suppresser protein LIMA1 (LIM domain and actin-binding protein-1) and generates a novel oncogenic LIM domain-only (LMO) fragment (97). In support of the above observations, MALT lymphomas with *BCL10* or *MALT1* translocation show strong signature of NF-κB target gene expression (76,98).

Additionally, there are several other signalling molecules, including MYD88, CARD11 and CD79B, which are activated by mutation (32,99-104). Among these, *MYD88* mutation, mainly L265P, is relatively frequent, but primarily in ocular adnexal MALT lymphoma, and the mutation enables MYD88 spontaneously assembling an active complex containing IRAK1 and IRAK4, triggering signalling cascade to activate NF-κB, STAT3 and AP1 transcription factors (*Figure 1*) (104).

Apart from the above positive regulators activated by chromosome translocation or mutation, several negative regulators of the NF-κB signalling pathway are inactivated by mutation and/or deletion, and they include *TNFAIP3*, *TRAF3*, *TINIP1* and *NFKBIA*. Among these changes,

TNFAIP3 inactivation by mutation and deletion is more frequent, but primarily in MALT lymphoma of the ocular adnexa (36%) and dura (67%) (*Figure 1*) (59,60,105-109). TNFAIP3 inactivation can enhance the activation of the canonical NF-κB pathway triggered by signalling from several receptors including BCR, TLR and TNFR1 due to loss of negative regulation on several signalling molecules (IKKγ, TRAF6 and RIP1/2) downstream of their receptors (*Figure 1*) (13,110,111). Similarly, TRAF3 inactivation promotes the activation of the non-canonical NF-κB pathway due to impaired control on NIK degradation (*Figure 1*).

Genetic changes that enhance NOTCH signalling

Only a few of studies investigated NOTCH signalling pathway for mutation in MALT lymphoma, mainly in those from the ocular adnexa and dura. Nonetheless, these studies revealed recurrent mutations in *NOTCH1* and *NOTCH2* (56,109,112), and the majority of the observed mutations predict a truncated NOTCH1/2 product lacking the C-terminal PEST domain which regulates the protein stability and degradation. Thus, these mutations are activation changes, most likely enhancing NOTCH stability and prolonging its activity (113).

Genetic abnormalities affecting G protein-coupled receptor (GPR)

The extent of genetic abnormalities in GPR signalling pathways is unclear due to few studies by whole exome and targeted sequencing. Nonetheless, recurrent mutations are seen in *GPR34* and *CCR6*, with *GPR34* changes primarily restricted to salivary gland MALT lymphoma (53). The majority of mutations in these GPRs are nonsense changes or frameshift indels, which are clustered in their C-terminal region (53). These mutations predict a truncated GPR product that lacks the C-terminal phosphorylation motif, which is essential for interaction with β-arrestin and receptor desensitization (53). As expected, the GPR34 and CCR6 truncation mutants are more potent in activation of a range of downstream signalling pathways including NF-κB and MAPK/JNK than their wild type counterpart (unpublished data, April 2020). Apart from mutation, *GPR34* is also targeted by t(X:14)(p11.4;q32), which cause GPR34 over-expression. Like *GPR34* mutation, this translocation is also restricted to MALT lymphoma of salivary gland (114-116).

Genetic abnormalities that deregulate transcriptional control

Recurrent mutations have also been described in several transcriptional regulators including *TBL1XR1*, *TET2* and *CREBP*, again variably involved in MALT lymphoma of different sites (32,53,54,56,107). *TBL1XR1* mutation is frequently seen in MALT lymphoma of the salivary gland (24%), ocular adnexa (6%), while *TET2* mutation is biased toward to those of the thyroid (62%). Majority of *TBL1XR1* mutations are missense changes affecting regions or residues critical for interaction with NCoR, and may enhance TBL1XR1 binding to NCoR and facilitate its degradation, consequently promoting NF-κB and JUN target gene expression (53,54). While most *TET2* mutations are deleterious alterations, likely inactivating or impairing its dioxygenase activity, hence its role in DNA demethylation, consequently affecting a wide spectrum of gene expression (53,117). The biological impact of genetic change in these transcriptional regulators is likely broad, and their oncogenic impact most likely depends on concurrent cooperating events.

Genetic abnormalities that deregulate B and T cell interactions

Despite limited number of MALT lymphomas investigated by whole exome sequencing, studies to date have revealed frequent mutation in *TNFRSF14* (HVEM: herpesvirus entry mediator) particularly in thyroid MALT lymphoma (53,107). Majority of *TNFRSF14* mutations are deleterious changes such as nonsense, frameshift alterations, thus most likely inactivating or impairing the protein function (53). TNFRSF14 is a surface ligand for T lymphocyte attenuator (BTLA) expressed on T-helper cells, and binding of BTLA by TNFRSF14 attenuates T-cell function, restraining its help to B-cells through downregulation of CD40-CD40L interactions (118). In a mouse model study, Tnfrsf14 deficient B cells show an enhanced growth advantage due to exaggerated T-helper signals (119). Thus, TNFRSF14 inactivation by genetic change may enable malignant B-cells to gain more T-cell help, a molecular mechanism exemplified by early studies in gastric MALT lymphoma (*Figure 4*).

Distinct oncogenic cooperation among MALT lymphoma of different sites

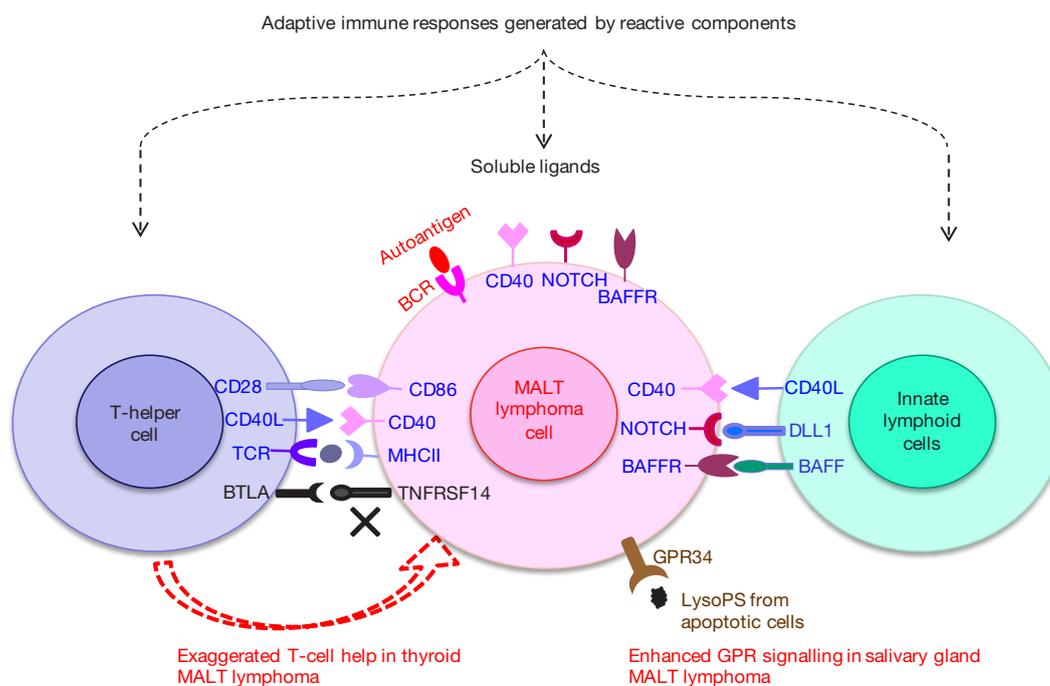As discussed above, there are distinct differences in the

Figure 4 The proposed model of molecular pathogenesis of MALT lymphoma. The development of MALT lymphoma is the consequence of oncogenic cooperation between immunological drive and genetic abnormalities. The adaptive immune responses not only promote the generation of autoreactive B-cells and their malignant transformation through acquisition of genetic changes, but also provide a supporting microenvironment that promotes the growth and survival of the lymphoma cells. The latter may involve provision of active help signalling from T-cells, possibly innate lymphoid cells (remained to be ascertained in future research), and soluble ligands. There are emerging data suggesting reciprocal influence between the lymphoma cells and their supporting environment. In thyroid MALT lymphoma, TNFRSF14 inactivation in malignant B-cells may impair their negative regulation to T-helper cells, thus enabling them to enjoy more exaggerated T-cell help. Similarly, GPR34 activation by mutation or translocation in salivary gland MALT lymphoma may enable the lymphoma cell more sensitive to the stimulation by ligand lysophosphatidylserine (LysoPS), which is likely enriched by apoptotic cells of lymphoepithelial lesion.

aetiology and genetic profile among MALT lymphoma of different sites. Different aetiologies clearly trigger disparate adaptive immune responses, which are prone to generate autoreactive B-cells with distinct specificity, and influence their clonal expansion. Different aetiologies also generate distinct microenvironments, which may give rise to different spectrum of genotoxic damages and influence pathogenic event selection, leading to distinct mutation profile seen in MALT lymphoma of various sites. There is mounting evidence showing significant association between certain intrinsic B-cell properties and genetic changes in MALT lymphoma of various sites, suggesting Darwinian selection of these events during the lymphoma cell clonal evolution.

In ocular adnexal MALT lymphoma, there is a significant association between IGHV4-34 usage and *TNFAIP3* inactivation, and also between IGHV3-23 usage and *TBL1XR1* mutation (32). Both IGHV4-34 and IGHV3-23

rearrangements generate BCR that are likely autoreactive, hence persistent signalling to activate the canonical NF-κB pathway. The chronic BCR signalling is likely further enhanced by loss of downstream negative regulation, i.e., TNFAIP3 inactivation or enhanced degradation of the transcriptional repressor NCoR by mutated TBL1XR1 (54). The acquisition of TNFAIP3 and TBL1XR1 mutation in these autoreactive clones could be the consequence of Darwinian selection for cooperative oncogenic events during their clonal evolution.

In salivary gland MALT lymphoma, the IGHV1-69 usage is mutually exclusive from the genetic changes identified so far, and the genetic event that cooperates with BCR signalling remains to be identified. Nonetheless, there is a significant association between *GPR34* mutation/translocation and *TBL1XR1* mutation in cases not using the IGHV1-69 gene (53). As discussed above, *GPR34* mutation/

translocation enhances its receptor signalling, leading to enhanced NF-κB and MAPK/JNK activities, and this could be further enhanced by *TBL1XR1* mutations. The ligand for GPR34 is lysophosphatidylserine, which is generated by hydrolysis of membrane phosphatidyserine, and enriched on the surface of apoptotic cells (120). In light of the prominent lymphoepithelial lesions in salivary gland MALT lymphoma and the early appearance of neoplastic B-cells always surrounding these apoptotic cells, it is pertinent to speculate that this is the special niche favouring the survival and expansion of neoplastic cells carrying *GPR34* mutations/translocation (*Figure 4*).

Finally in thyroid MALT lymphoma, there is a significant correlation between *TNFRSF14* and *TET2* mutation (53). As discussed above, *TNFRSF14* inactivation by mutation enables lymphoma B-cells gain more T-cell help as the mutation attenuates the negative regulation by B-cells to T-helper cells (*Figure 4*) (119). How such enhanced T-cell help, such as CD40 signalling, cooperate with TET2 inactivation is unclear. Nonetheless, TET2 mediated demethylation is critical for expression of lineage specific genes that regulate T-dependent B-cell maturation (117,121,122). Thyroid MALT lymphomas with *TET2* mutation show a high level of extensive DNA methylation, particularly in the promoter regions, than those with wild type *TET2* (107). Thus, there is an ample scope for oncogenic cooperation between TET2 inactivation and CD40 and other receptor signalling mediated by T-helper cells.

Future prospective

MALT lymphoma is a paradigm for illustration of oncogenic cooperation between adaptive immune responses and acquired somatic genetic changes in the selection, expansion and malignant transformation of the neoplastic clone. Distinct aetiologies and different mutation profiles among MALT lymphoma of various sites provide a dynamic model to explore the interaction between lymphoma cells and their microenvironments during the multi-stages of the lymphoma development. As neither the immmunogenetic nor the somatic genetic profile has been comprehensively investigated in MALT lymphoma of various sites, the lymphoma remains to be a fertile research area for scientific discoveries in the near future. Finally, the recent advances in characterisation of innate lymphoid cells in the marginal zone provide a further avenue to interrogate the interaction between lymphoma cells and their residential microenvironment.

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