Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

Emerging targets in human lymphoma: targeting the *MYD88* mutation

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Abstract: B cell neoplasms co-opt the molecular machinery of normal B cells for their survival. Technological advances in cancer genomics has significantly contributed to uncovering the root cause of aggressive lymphomas, revealing a previously unknown link between TLR signaling and B cell neoplasm. Recurrent oncogenic mutations in *MYD88* have been found in 39% of the activated B cell-like subtype of diffuse large B cell lymphoma (ABC DLBCL). Interestingly, 29% of ABC DLBCL have a single amino acid substitution of proline for the leucine at position 265 (L265P), and the exact same variant has also been identified in a number of lymphoid malignancies. The MYD88 L265P variant was recently identified in 90% of Wadenstrom's macroglobulinemia patients. These recent developments warrant the need for novel diagnostic tools as well as targeted therapeutics. In this review, we discuss the physiological functions of MYD88 and focus on its role in B cell lymphomas, evaluating the potential for targeting oncogenic MYD88 in lymphoma.

Keywords: MYD88, *L265P* mutation, lymphoma, targeted therapy

Introduction

From one of the earliest detailed descriptions of lymphoma cases by Hodgkin in 1832, it was already evident that this group of cancer is very diverse.[1] Such heterogeneity poses significant challenges to the effective diagnosis, management and study of lymphomas. Following decades of progress in the understanding of the biology of white blood cells and 'the hallmarks of cancers', we now know lymphomas are characterized by neoplastic transformation of lymphocytes at various differentiation stages.[2,3] Given the diversity in the subsets of lymphocytes and the numerous differentiation stages, from the common hematopoietic stem cell precursor to distinct differentiated states, the diagnosis, treatment and study of lymphoid neoplasms remain central clinical challenges.

The current classification of lymphomas resulted from a major collaborative effort by the World Health Organization (WHO) synthesizing information about the immunophenotype, genetic features, and clinical characteristics, along with the traditionally used cell/tissue morphology to define specific clinically relevant diseases.[4] The WHO classification broadly segregates neoplasms based on myeloid and lymphoid lineages, followed by sub-categorization into functional or cell differentiation stages of the normal counterpart of each neoplasm. The 2008 WHO classification lists more than one hundred tumors of the hematopoietic and lymphoid tissues, for most of which the underlying causes are still unknown.

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Lymphoid neoplasms are the sixth most common cancer worldwide, with close to one million new cases expected to be diagnosed each year.[5] The most common hematopoietic tumors diagnosed are non-Hodgkin lymphoma, leukemia, multiple myeloma and Hodgkin's lymphoma. B lymphocyte neoplasms account for about 90% of all newly diagnosed cases, among which diffuse large B cell lymphoma (DLBCL) and follicular lymphoma are the most prevalent.[6]

B cell lymphomas are thought to co-opt the molecular features of normal B cells for their survival, such that the phenotype of malignant B cells mirror the state of differentiation from which they originate. During B cell development, B cells express a number of DNA-modifying enzymes such as recombinase-activating gene (RAG1 and RAG2), which primarily serves to increase diversity of antibodies in the repertoire.[7] A side consequence of such enzymes is the generation of chromosomal translocations, which may contribute to malignancy.[7] Another stage of differentiation at which B cells are very susceptible to genomic alterations is the transient germinal centre (GC) stage.[8] During the GC stage, B cells express activation-induced cytidine deaminase (AID), a DNA-modifying enzyme that is required for somatic hypermutation and class switching of antibodies.[9] The off-target effect of AID may also contribute to the oncogenic load in B cells.[10–12] Thus, GC B cells may give rise to several types of lymphoma, including the diffuse-large B cell lymphoma, follicular lymphoma and Burkitt's lymphoma.[13]

Diffuse large B cell lymphoma (DLBCL) is one of the most common forms of lymphoma, accounting for 30%–40% of all newly diagnosed cases.[6] DLBCL is also currently one of the least curable lymphoma, with about 50% success using a combination of chemotherapy and rituximab.[14] With the advent of genome-wide gene expression profiling, DLBCL has been subdivided into three molecular subtypes.[15] The activated B cell (ABC), germinal-center B cell (GCB) and the primary mediastinal B cell lymphoma (PMBL) subtypes are histologically indistinguishable, but differ in the expression of hundreds of signature genes.[15] The subdivision of DLBCL holds promise for better diagnosis and improved treatment regimes, even though the use of gene expression profiling is yet to be translated into clinical practice.

Among the three subtypes of DLBCL, the ABC subtype has been associated with the lowest success rates following standard treatment regimes.[14] Interestingly, gene expression profiling and drug inhibition studies revealed that the ABC subtype has a striking dependence on signaling pathways activating the transcription factor NFκB.[15,16] The constitutive NFκB activation in ABC DLBCL could contribute to the poor response following chemotherapy as the targets of this family of transcription factors prevent apoptosis.[17] These findings emphasized the need for the development of therapeutics targeting NFκB signaling for the treatment of aggressive lymphomas.

A recent wave of progress in cancer genomics triggered by next-generation sequencing technologies have significantly contributed to uncovering the root cause of the high NFκB activity in ABC DLBCL (Figure 1). The survival of this aggressive lymphoma subtype relies on signaling from the antigen receptor to the NFκB transcription factors, with CARD11, BCL10 and MALT1 being essential components of the signaling apparatus.[16] In approximately 10% of patients, gain-of-function mutations in the *CARD11* oncogene have been found to activate NFκB and prolong cell survival.[18] In addition, about 20% of ABC lymphomas have mutations in *CD79A* or *CD79B*, which are rare or absent in GCB and other lymphoma subtypes.[19] Loss of function mutations resulting in the inactivation of A20, a negative regulator of NFκB signaling, has been found to occur in 25% of ABC lymphomas.[20–22] Crippling the activity of A20 increases the activity of NFκB signaling in malignant B cells.[23]

More recently, high-throughput RNA resequencing of DLBCL has identified recurrent oncogenic mutations in *MYD88* in 39% of ABC DLBCL tumors.[24,25] These findings established a previously unknown link between TLR signaling and B cell lymphoma. Interestingly, 29% of ABC DLBCL have a single amino acid substitution of proline for the leucine at position 265 (L265P) in the TIR domain.[24,25] The MYD88 L265P variant has also been identified in a number of lymphoid malignancies (Table 1). The MYD88 L265P variant was recently identified in about 90% of Wadenstrom's macroglobulinemia patients, revealing a central pathogenic feature of this tumor.[26] These recent developments warrant the need for novel diagnostic tools as well as targeted therapeutics. In this review, we discuss the physiological functions of MYD88 and focus on its role in B cell lymphomas, evaluating the potential for targeting oncogenic MYD88 in lymphoma.

Physiological function of MYD88

MYD88 was originally identified as a myeloid differentiation primary response gene in hematopoiesis.[27] Following treatment of myeloid cell precursors with interleukin 6 (IL6), the levels of MYD88 transcript was found to increase as cells terminally differentiated.[27] MYD88 is essential for the mammalian innate immune response. Individuals with MYD88 deficiency suffer life threatening recurrent pyogenic

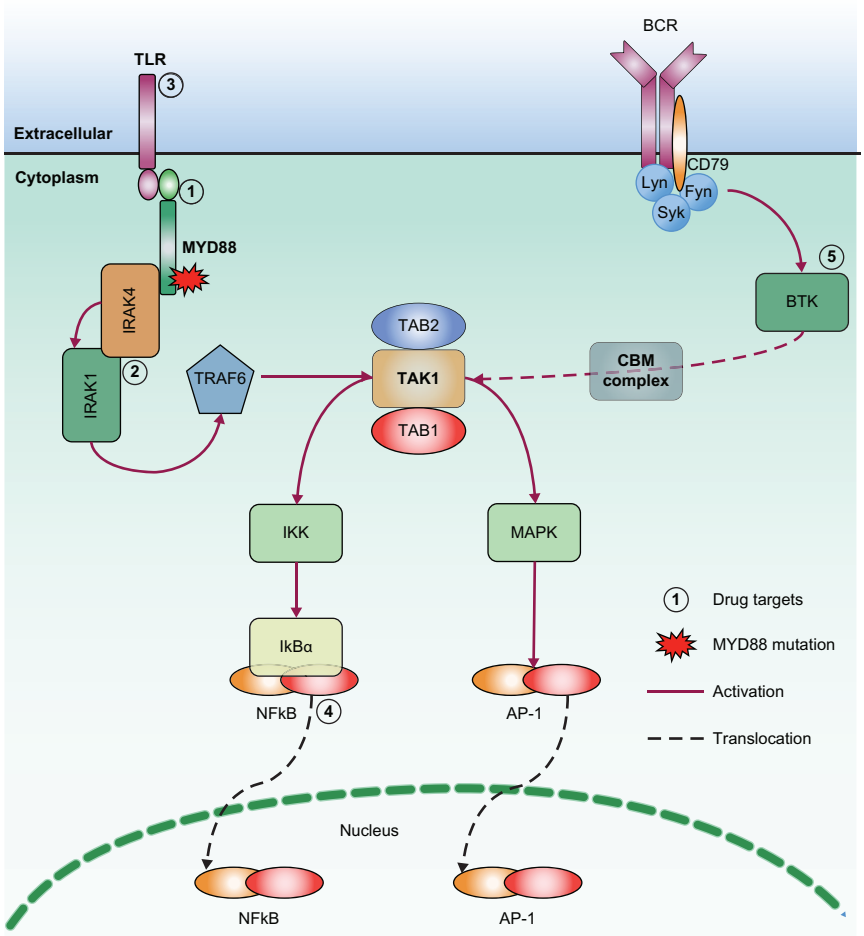

Figure 1 Oncogenic mutations targeting the NFκB pathway. Oncogenic mutations frequently target the MYD88, CD79, and CARD11 (part of the CMB complex) in aggressive lymphomas. Consequences of these mutations include disruption to normal cellular signal transduction events such as protein phosphorylation, ubiquitylation or deubiquitylation, which converge onto aberrant NFκB activity, a hallmark of lymphomas with L265P MYD88. Specific inhibitors targeting (**1**) MYD88, (**2**) IRAK4, (**3**) Toll-like receptor (TLR), (**4**) NFkB, and BTK are currently in clinical trials.

Note: Targeting these molecular pathways may provide effective treatment to patients.

Abbreviations: AP-1, activator protein 1; BCR, B cell receptor; BTK, Bruton tyrosine kinase; CBM, CARD11-BCL10-MALT1 complex; CD79, cluster of differentiation 79; Fyn, Src family protein tyrosine kinase Fyn; Lyn, Src family protein tyrosine kinase Lyn; IkBα, inhibitor of NFkB alpha; IKK, inhibitor of kB alpha kinase; IRAK1, interleukin 1 receptor associated kinase 1; IRAK4, interleukin 1 receptor associated kinase 4; MAPK, mitogen activated protein kinase; MYD88, myeloid differentiation factor 88; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells; Syk, spleen tyrosine kinase; TAB1, TGF beta activated kinase 1 binding protein 1; TAB2, TGF beta activated kinase 1 binding protein 2; TAK1, TGF beta activated kinase 1; TGF, transforming growth factor; TLR, Toll like receptor; TNF, tumor necrosis factor; TRAF6, TNF receptor associated factor 6.

bacterial infection by *Streptococcus pneumonia*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*, suggesting that MYD88 plays a crucial role in the innate immune response in the Toll/IL1 receptor pathways.[28,29] Furthermore, mice lacking MYD88 also show impaired Toll receptor and IL1/IL18 responses in addition to defects in T cell proliferation and Th1 response.[30] These defects result from the inability of signals to be transmitted from ligand activated receptors to the NFκB and JNK pathways.[30] Thus, MYD88 plays a central role as an adaptor molecule to transducing signals from receptors such as Toll-like receptor/IL-1 receptor to transcription factors.

A homolog of MYD88 in Drosophila, known as Tube, was initially described as an adaptor protein for Toll-Dorsal signaling and is essential for establishing dorsal-ventral polarity during embryogenesis.[31] Moreover, MYD88 deficient drosophila flies have crippled defense against fungal and microbial infections, and mammalian models of MYD88 deficiency have drastically poor defense against a plethora of pathogens.[32,33] Given the crucial role of MYD88 in the immune system of a wide range of organisms, it is not surprising that this adaptor molecule has been evolutionarily conserved.

Toll like receptors (TLR) play essential roles as the danger sensing molecular detector in an innate immune response.[34] TLRs are type I transmembrane protein that share homology with the interleukin-1 receptor. In total, ten different members of TLRs are differentially expressed amongst different immune cell subtypes, each responding to a different type of stimulus.[35]

Table 1 Frequency of somatic *MYD88* mutations in B cell neoplasm

Disease	*MYD88* mutation	Frequency (case/sample)	Reference
ABC DLBCL	L265P	29%#	24
ABC DLBCL	Others	10%#	24
BL	Other	5%#	24
CBCL	L265P	69% (11/16)	70
CLL	L265P	2.9% (9/310)	71
CLL	M232T	2.2% (2/91)	72
CLL	P258L	1.1% (1/91)	72
CLL	L265P	6.6% (6/91)	72
GCB DLBCL	Other	6%#	24
IgM MGUS	L265P	10% (2/21)	73
LPL	L265P	91% (49/54)	73
MALT	L265P	9%#	24
MALT	L265P	3.8% (2/53)	74
MALT	27 bp deletion*	1.9% (1/53)	74
MZL	L265P	6.5% (3/46)	75
PCNSL	L265P	36% (5/14)	76
PCNSL	L103L	7% (1/14)	76
PCNSL	Q143E	7% (1/14)	76
PCNSL	L265P	38% (11/29)	77
SMZL	L265P	13% (6/46)	78
SMZL	L265P	5.1% (6/117)	79

Notes: #Percentage in published text inconsistent with calculated percentage from biopsy number; *deletion occurred between gene sequence 1039–1065, resulting in amino acid deletion between V286-T294.

Abbreviations: ABC-DLBCL, activated B-cell like diffuse large B-cell lymphoma; BL, Burkitt's lymphoma; CBCL, cutaneous diffuse large B-cell lymphoma (leg type); CLL, chronic lymphocytic leukemia; GCB-DLBCL, germinal center B-cell like diffuse large B cell lymphoma; IgM MGUS, IgM monoclonal gammopathy of undetermined significance; LPL, lymphoplasmacytic lymphoma (Waldenström's Macroglobulinemia or non-IgM LPL); MALT, gastric mucosa-associated lymphoid tissue lymphoma; MZL, marginal zone lymphoma; PCNSL, primary central nervous system lymphoma; SMZL, splenic marginal zone lymphoma.

Different combinations of adaptor molecules create distinct signaling platforms, which recruit additional signal transduction molecules giving rise to a range of responses governed by differential gene expression.[34] Signaling by all TLRs, with the exception of TLR3, requires MYD88 as an adaptor molecule.[34]

During bacterial infections, macrophages form an important first line of defense as part of the innate immune response. Macrophages can be potently activated by lipopolysaccharide (LPS), a major component of the Gram-negative bacteria outer membrane, through the stimulation of Toll-like receptor 4.[34] Stimulated macrophages produce various cytokines such as tumor necrosis factor alpha (TNFα), IL1, IL6/10 and inflammatory effector chemokines.[36] By using MYD88 deficient mice, Akira and colleagues elucidated the role of MYD88 in macrophage activation in response to endotoxin.[37] MYD88 deficient mice fail to produce proinflammatory cytokines such as TNFα, IL1 and IL6 after LPS challenge.[37] Cultured macrophages from MYD88 deficient mice show no increase in mRNA level in proinflammatory cytokines upon LPS treatment, highlighting the importance of MYD88 in response to bacterial infection.[37]

MYD88 signaling in B lymphocytes

B lymphocytes have also been shown to respond to LPS through their Toll-like receptors, resulting in proliferation and production of cytokines such as IL1, IL6, IL8 and TNFα.[38] LPS activated B cells also enhance their antigen presentation capacity through increased MHC II expression as well as secretion of large amounts of LPS-neutralizing antibodies, such that in response to LPS MYD88 deficient B cells have impaired MHC II upregulation as well as poor proliferation and antibody secretion.[37,38] The response following recognition of bacterial DNA by TLR9 through a specific CpG motif,[39,40] requires MYD88 as B cells without the adaptor molecule fail to proliferate in response to CpG DNA.[41] MYD88 plays central role in the response of B cells following various stimuli through the Toll-like receptors.

MYD88 acts as a key adaptor protein linking danger signals from Toll-like receptors to transcription factors, which regulate cellular gene expression. Molecular studies revealed that MYD88 forms a protein complex with interleukin 1 receptor (IL1R) and interleukin 1 receptor-associated kinase (IRAK), a serine threonine protein kinase, in the presence of IL1.[42,43] MYD88 is first recruited to the cytoplasmic tail of IL1R or TLRs following their engagement via homophilic TIR interactions and the formation of a homodimer.[44] IRAK4 is then recruited to the site of activation through the interactions between the death domains, resulting in the activation of IRAK4 and the phosphorylation of the downstream protein kinase IRAK1.[42] Subsequently, phosphorylated IRAK1 associates with TRAF6 in the cytoplasm and leads to the activation of the NFκB and MAPK pathways (Figure 1).[34] Through a poorly defined mechanism, following IRAK1 mediated phosphorylation, TRAF6 disassociates from the receptor complex and forms a cytoplasmic complex that consists of TRAF6/TAB2/TAK1.[34] Activated TAK1 phosphorylates both the β subunit of IKK and MAPK kinase 6.[34] Activated IKKβ in turn phosphorylate IκBα, leading to its ubiquitylation and proteasomal degradation, allowing the NFκB dimer to translocate to the nucleus and activate gene transcription that regulates cell activation, proliferation and immune responses.[34]

Oncogenic *MYD88* in lymphoma

MYD88 forms an important link in the activation and proliferation of B cells under a number of different extra-

cellular stimuli. It is thus not surprising that defects in this critical signal relay molecule may result in pathology in B cell activation and proliferation that result from aberrant NFκB and MAPK activity.[34] ABC DLBCL has characteristically constitutive NFκB activity that enhances the proliferation and survival of the affected B cell populations. Sequencing studies of DLBCL samples and RNA interference screens using human lymphoma cell lines revealed *MYD88* mutations are present in 39% of samples.[24] MYD88 was found to be required for the survival of the cell lines through constitutive activation of NFκB signaling.[24]

The MYD88 L265P variant was recently identified in about 90% of Wadenstrom's macroglobulinemia patients, constituting a significant clinical feature for this disease.[26] Albeit at lower frequencies, L265P MYD88 was also found in cases of chronic lymphocytic leukemia, splenic marginal zone lymphoma, primary central nervous system lymphoma and gastric mucosa-associated lymphoid tissue lymphoma (Table 1). The *L265P* mutation affects the MYD88 TIR domain, which is responsible for recruiting the protein to the cytoplasmic tail of TLRs to form an active complex, which subsequently activates the kinases IRAK1 and IRAK4 to signal downstream.[45] A hyperphosphorylated slow migrating isoform of IRAK1 associates strongly with the *L265P* mutant MYD88 but not wild type MYD88 suggesting a gain-of-function activity in the *L265P* mutant.[24] The *MYD88 L265P* mutation was also found to be a potent driver of high NFκB activity, which is characteristic of ABC DLBCL.[24]

Interestingly, in addition to enhancing NFκB signaling, MYD88 L265P seems to increase JAK-STAT signaling and interferon production, indicating the potential involvement of a niche microenvironment important for tumor survival.[24] STAT3 signaling induced by cytokines such as IL6 could provide additional survival signals sustaining lymphoma survival, given that transgenic mice expressing supraphysiological amounts of IL6 develop a range of lymphoid malignancies, including DLBCL.[46] Thus, IL6 and IL10 production potentially form an important autocrine feedback loop that activates JAK-STAT signaling to enhance the survival of ABC DLBCL.[24,47] Interestingly, overexpression of the L265P MYD88 variant has recently been associated with reduced disease free survival and increased disease recurrence in DLBCL patients.[48] These recent developments highlight MYD88 as a specific target for therapeutic intervention, and warrants the development of inhibitors targeting the MYD88-NFκB signaling axis.

Targeting oncogenic *MYD88*

Aberrant NFκB activation has been associated with poor clinical outcomes in many lymphomas and leukemia. Thus, effective therapeutic agents targeting the NFκB pathway may allow the achievement of desirable outcome for a subset of patients. Given the large proportion of lymphoid neoplasms with aberrant TLR signaling, targeting the MYD88 pathway is becoming an attractive option for clinicians and researchers.

Direct inhibition of MYD88

A critical event in MYD88 mediated signaling is the homodimerization of MYD88 through its TIR and DD domains.[49] The dimerization of MYD88 promotes its recruitment to the plasma membrane and docking with the TIR domain of the cytoplasmic tails of TLRs or IL1R, as well as the recruitment of IRAK4 and IRAK1 through the interaction between their DD domains.[43,50] Given signal transduction through MYD88 requires its homodimerization and lymphoma associated *MYD88* mutations occur exclusively in the TIR domain, one appealing option would be to 'switch off' this signaling relay event so that MYD88 homodimerization and downstream signaling is inhibited.

TIR-TIR interaction in MYD88 is achieved by distinct conserved residues in a structure known as the BB-loop that lies between the second β-strand and the second α-helix.[51] The interference of this interaction was successfully achieved by the use of heptapeptides mimicking BB-loop by Sette and colleagues.[51] When this dimerization is inhibited, significant reduction in NFκB activity is achieved in cells stimulated with IL1 or TLR agonists but not poly(I:C), a TLR3 agonist, suggesting this component selectively inhibits MYD88 dependent signaling.[51] The same group also identified a novel synthetic compound, ST2825, which mimics the heptapeptide in the BB-loop of MYD88 and this compound is currently undergoing preclinical evaluations.[52]

Alternative options to specifically target MYD88-MYD88 and MYD88-receptor interactions through the TIR domain would be to use small molecule inhibitors such as Hydrocinnamoyl-L-valyl pyrrolidine (compound 4a).[53] This particular low molecular weight compound is cell membrane permeable and specifically disrupts MYD88-receptor interactions by inhibiting TIR domain interactions. Another peptide Pepinh-MYD developed by InvivoGen, which carries a 26 amino acid MYD88 homodimerization motif, could also potentially be used to treat lymphoma patients with L265P MYD88. However, these potential MDY88-specific therapeutic options are yet to be trialed in large clinical cohorts.

Targeting IRAK4, downstream of receptor-MYD88 signaling

Interleukin receptor-associated kinases (IRAKs) are a key component of the signal transduction pathways downstream of IL1 receptor or TLRs, and are required for the activation of NFκB and MAPKs in response to the activation of these receptors.[34] In particular, IRAK4 serves as the "master IRAK" by having the ability to phosphorylate and activate other IRAKs. The *MYD88 L265P* mutation result in a constitutively activated signaling complex, which includes IRAK4 and phosphorylated IRAK1.[24] Since ABC DLBCL lines depend on kinase activity of IRAK4, but not IRAK1, inhibiting IRAK4 kinase activity could be a potent way of 'tuning down' aberrant NFκB and MAPK pathways activated by *MYD88* mutations.

The activation of IRAK4 is regulated by the autophosphorylation of three serine and threonine sites in its activation loop.[54] The autophosphorylation of these key activating residues confer a conformation change to allow the ATP-binding site to become activated.[54] The kinase activity of IRAK4 is thus often targeted by small molecular inhibitors that bind to the ATP-binding site. In ABC DLBCL cell lines carrying the *MYD88 L265P* mutation, disrupting IRAK4 signaling by a small molecule inhibitor led to the decreased phosphorylation of IRAK1, IκBα, NFκB p65 and STAT3 (unpublished data). Two small molecule IRAK4 inhibitors (ND-2110 and ND-2158) developed by Nimbus Discovery are highly selective against more than 300 kinases and seem promising, although these drugs are still in the preclinical stage.

Targeting the two ends-inhibiting TLRs and the NFκB signaling

It has long been speculated that cognate antigen stimulation might contribute to lymphomagenesis.[55] Since MYD88 physiologically serves as an adaptor molecule for TLR sensing pathogens, it is an attractive idea that lymphomas with *MYD88* mutations need external or internal signals from TLRs for their survival. However, it remains unclear whether oncogenic mutant MYD88 proteins require upstream signaling from ligand-activated receptors for enhancing its activity. But, in the potential scenario where ligand-TLR engagement would be required for oncogenic MYD88 activation, inhibiting TLR signaling upstream of MYD88 can be a potential therapeutic target for treating B cell malignancies carrying *MYD88* mutations. TLR antagonists which are currently under preclinical and clinical evaluation could be potentially used to inhibit receptor signaling.[56]

An alternative point at which signaling from oncogenic MYD88 could be interrupted would be through direct inhibition of NFκB activity. In recent years, more than 800 drugs that inhibit NFκB signaling have been developed, and their mechanisms of action have been characterized.[57,58] For instance drugs such as emetine, bithionol, narasin and lestaurtinib inhibit NFκB signaling via inhibition of IkBα phosphorylation, a critical step required for activation of NFκB, while drugs such as bortezomib and Carfilzomib inhibit NFκB activity by dampening proteosomal degradation of IkBα.[59] Even though a number of NFκB inhibitors are FDA-approved for use in particular cancer types, inhibition of this particular family of transcription factors would be accompanied by a number of undesired side-effects. NFκB is known to have a critical role across many cellular processes including cell proliferation, apoptosis, immune responses to infection, and inflammation, such that the beneficial effects and potential collateral damage must be carefully examined.[60]

Combination therapy

Lenalidomide (Revlimid®, Celgene Corporation, Summit, NJ, USA), a derivative of thalidomide, is an immunomodulatory drug and currently used as a treatment of multiple myeloma and myelodysplastic syndromes.[61,62] Although the mechanism of action still remains unclear, clinical trials showed lenalidomide is effective against most lymphomas. ABC DLBCL had a significantly higher response rate to the thalidomide analog compared to GC DLBCL, indicating that one of its actions is a suppressive effect on the NFκB pathway.[63]

A recent study from Staudt et al found synergistic effects between lenalidomide and a BTK inhibitor, ibrutinib.[64] They found that lenalidomide was partially toxic to ABC DLBCL lines by inhibiting NFκB, JAK and MYD88 signaling as well as augmenting IFN beta signature.[64] IFN beta production and upregulation of IFN beta-responsive genes is characteristic of ABC DLBCL harboring *MY88* mutations, although its pathological roles are still unclear since IFN beta is known to induce cell cycle arrest and apoptosis paradoxically.[65] IFN beta production is induced by IRF7 in a positive-feedback manner and IRF4/SPIB transcription factor network represses IFN beta production by downregulating IRF7.[66] Ibrutinib cooperates with lenalidomide to kill ABC DLBCL lines, presumably due to inducing IFN beta pathway by changing the balance between IRF7 and IRF4/SPIB.[64]

Another potential strategy of combination therapy would be to block IRAK4 signaling and BTK signaling in synergy. This strategy is consistent with the observation that survival of ABC DLBCL cell lines require a signal through both the

TLR and the BCR as knocking down CD79 molecule of the BCR signaling compartment synergistically kills ABL-DLBCL cell lines with MYD88 knockdown.[24] Therefore synergistic killing of lymphoid neoplasms with L265P MYD88 using a combination of IRAK inhibitor and BTK inhibitor strongly indicate that most potent therapy should target both the TLR and BCR pathways simultaneously.

Concluding remarks

Recent discoveries have uncovered the involvement of L265P MYD88 in a number of diseases, but the effects of this oncogenic variant remain unclear. Future research would help elucidate the effects of deregulated MYD88 on cellular signaling pathways, the activity of transcription factors, and gene expression changes. However, from the initial biochemical characterization of oncogenic MYD88, it is apparent that several key signaling pathways are disrupted such that effective therapeutic strategies would involve multi-pronged approaches with combination of specific agents targeting biochemically distinct pathways simultaneously. Such therapeutic regimes remain to be evaluated in large cohorts of patients, and a factor central to evaluation of the effectiveness of such treatment regimes would be the appropriate selection of patients. Recently, a number of diagnostic tools have been developed to specifically detect the presence of the L265P MYD88 variant in clinical samples.[67–69] With the refinement of these diagnostic methods and the development of targeted therapeutics, clinicians would, in the near future, be in a better position to provide treatment options to previously incurable diseases.

Disclosure

The authors have no conflict of interest to declare.

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