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REVIEW

The Immunomodulatory Functions of BTK Inhibition in the Central Nervous System

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Abstract: Bruton's tyrosine kinase (BTK) is a central signaling node in B cells. BTK inhibition has witnessed great success in the treatment of B-cell malignancies. Additionally, in the immune system, BTK is also a prominent component linking a wide variety of immune-related pathways. Therefore, more and more studies attempting to dissect the role of BTK in autoimmune and inflammation progression have emerged in recent years. In particular, BTK expression was also found to be elevated within the central nervous system (CNS) during neuroinflammation. BTK inhibitors are capable of crossing the blood–brain barrier rapidly to modulate B cell functions, attenuate microglial activities and affect NLRP3 inflammasome pathways within the CNS to improve the outcome of diseases. Thus, BTK inhibition appears to be a promising approach to modulate dysregulated inflammation in the CNS and alleviate destruction caused by excessive inflammatory responses. This review will summarize the immunomodulatory mechanisms in which BTK is involved in the development of neurological diseases and discuss the therapeutic potential of BTK inhibition for the treatment of neuroinflammatory pathology.

Keywords: BTK, BTK inhibition, BTK inhibitors, neuroinflammation

Introduction

Bruton's tyrosine kinase (BTK), encoded by the BTK gene, is a cytoplasmic non-receptor tyrosine kinase of the Tec kinase family. As an integral part of BCR signaling, BTK plays vital roles in governing B cell development, proliferation and function. Its name originates from Ogden Bruton, who first described the disease X-linked agammaglobulinemia (XLA) in 1952[1]. This condition was characterized by recurrent bacterial infection because of the absence of antibodies in the serum. Further studies revealed an arrest of B cell development and differentiation in XLA patients and X-linked immunodeficiency (xid) mice.[2,3] Later, the mutation of BTK was identified as the culprit causing this humoral immunity deficiency in xid mice and XLA patients.[2,4] Due to the central role of BTK in B-cell maturation and function, various types of BTK inhibitors have been discovered and finally approved for the therapeutics of hematogenic malignancies, especially those related to B cells, such as chronic lymphocytic leukemia (CLL), Waldenstrom's macroglobulinemia (WM) and mantle cell lymphoma, etc.[5]

BTK-related signaling also participates in the cascade of autoimmunity and inflammation. In addition to B cells. BTK is also expressed in other immune cells including neutrophils, macrophages, mast cells and dendritic cells.[6,7] Microglia and astrocytes also exhibited elevated BTK activity during inflammatory response.[8,9] Except for BCR signaling, BTK also plays important roles cell-specifically in other immunological pathways, such as FcR signaling and TLR signaling.[10] Furthermore, a series of BTK inhibitors have been tested and/or applied for the treatment of inflammatory and autoimmune diseases, including rheumatoid arthritis (RA), Sjogren's syndrome (SS), multiple sclerosis (MS), systemic lupus erythematosus (SLE), urticaria, pemphigus, idiopathic thrombocytopenic purpura (ITP), IgG4-related disease (RD), etc.[11]

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Neuroinflammation is considered to be the driver of a broad spectrum of neurological disorders, including autoimmune, neurodegenerative and cerebral ischemic disorders.[12,13] Thus, modulating neuroinflammation was regarded as an effective way to alleviate disease progression. Therefore, more and more studies have emerged to test the possibility of BTK inhibition as a therapeutic approach to regulate neuroinflammatory responses and improve the outcome of diseases.

The Structure of BTK and BTK Inhibitors

BTK is a 659 amino acid protein and, as a member of the Tec family, is characterized by five domains: pleckstrin homology domain (PH) in N-terminal, TEC homology domain (TH), two Src homology domains 2 (SH2) and 3 (SH3), and the catalytic kinase C-terminal domain. The activation of BTK in BCR signaling involves several steps. Upon recruitment to membrane enabled by the PH domain through PIP_3, Y551 in the catalytic kinase domain is phosphorylated by SYK, resulting in subsequent autophosphorylation in Y233, which improves the catalytic activity of BTK and initiates downstream pathways (Figure 1).[14–16] Particularly, the site C481 in the kinase domain is the binding site of covalent BTK inhibitors including Ibrutinib, Acalabrutinib and Zanubrutinib, etc.[17]

BTK inhibitors (BTKis) are small molecules binding covalently or non-covalently to BTK to inhibit its activation. BTKis can cross the blood–brain barrier and penetrate into the CNS. A preclinical study demonstrated that Ibrutinib could rapidly enter the brain within an average of 0.29h and mainly accumulated in the ventricle area of the brain.[18] This result gives the opportunities that BTKis can exert functions locally within the CNS.

Covalent BTKis refer to BTK inhibitors that bind covalently and irreversibly to BTK C481 site.[19] At present, five covalent BTK inhibitors have been approved in the market, including Ibrutinib, Acalabrutinib, Zanubrutinib, Tirabrutinib and Orelabrutinib.

Ibrutinib was the first FDA-approved BTKi, which has been utilized for the treatment of chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), Waldenstrom's macroglobulinemia, relapsed or refractory (R/R) marginal zone lymphoma (MZL), and chronic graft versus host disease.[20] Although Ibrutinib showed efficacy and safety in many diseases, the issue of resistance and off-target effect preceded. The mutation of C481 residue, which is the binding site of Ibrutinib, and PLCγ2, the protein involved in BTK signaling, was identified in Ibrutinib-resistant patients, leading to reversible binding of Ibrutinib to BTK and auto-active of BCR signaling.[21] Additionally, an in vitro study demonstrated that CLL cells with del17p/*TP53*-mutation are less sensitive to Ibrutinib-induced apoptosis.[22] Ibrutinib also interacts with other kinases including epidermal growth factor receptor (EGFR)[23] and interleukin 2-inducible T cell kinase (ITK)[24] and C-terminal Src kinase (Csk),[25] causing a series of adverse effects including rash, diarrhea, bleeding and atrial fibrillation.[20,25] Optimizing the dose of Ibrutinib may be an effective way to reduce these side effects.[26]

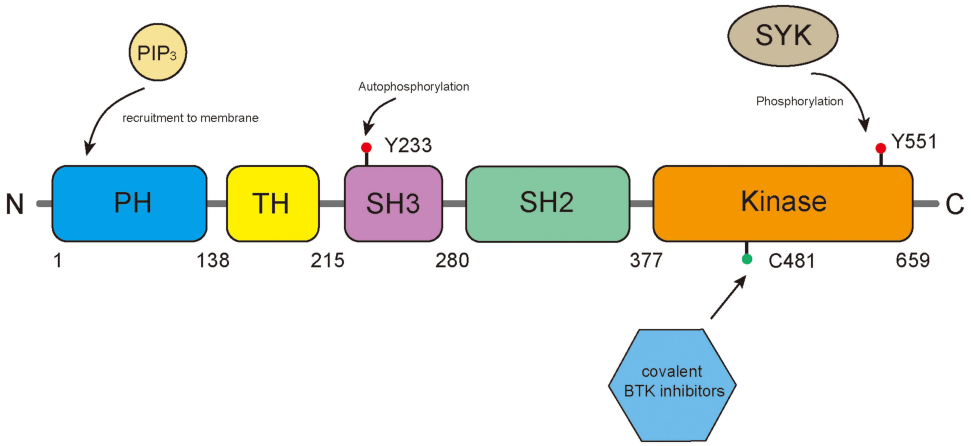

Figure 1 The structure of BTK. BTK consists of five protein domains from N to C terminal: a pleckstrin homology (PH) domain, a TEC homology (TH) domain, SRC homology (SH) domains SH2 and SH3, and a catalytic kinase domain. PIP3 interacts with the PH domain to recruit BTK to cell membrane. Next, SYK phosphorylates Y551 in the kinase domain, leading to autophosphorylation in Y233 in the SH3 domain to improve the catalytic activity of BTK. C481 is the binding site of covalent BTK inhibitors.

The second generation of BTKis, Acalabrutinib and Zanubrutinib, were approved by FDA in 2017 and 2019, respectively. Both drugs showed higher selectivity and safety and less toxicity in clinical trials compared with Ibrutinib.[27–29] Acalabrutinib is characterized by its reactive butynamide group binding covalently to C481 of BTK. This unique structure contributes to decreased off-targeted side effects compared with Ibrutinib. For instance, Acalabrutinib does not inhibit epidermal growth factor receptor (EGFR) and ITK.[27] Similarly, ITK is also not inhibited by Zanubrutinib.

Tirabrutinib was approved in Japan in 2020 for the treatment of recurrent or refractory primary central nervous system lymphoma. Compared with Ibrutinib, Tirabrutinib exhibited higher selectivity. Of note, the bone loss in mice induced by RANKL could be attenuated by ibrutinib, indicating that Tirabrutinib had potential therapeutic implications for osteoporosis and rheumatoid arthritis.[30]

Orelabrutinib, which was approved in China in 2020 for the treatment of MCL or CLL/SLL, is a highly selective, irreversible BTK inhibitor. A KINOMEscan assay demonstrated that BTK was the only target of Orelabrutinib (with >90% inhibition).[31] Off-target side effects were uncommon in patients receiving Orelabrutinib.[32]

Non-covalent BTK inhibitors do not bind to Cysteine 481 site on BTK, and their binding is reversible.[19] Instead, these molecules interact with a specific pocket located in the SH3 domain of BTK through reversible interactions, such as hydrogen bonds and hydrophobic interactions.[33] Therefore, they can be used as alternatives for patients acquiring resistance to covalent BTK inhibitors, especially those with BTK C481 mutations. Besides, they tend to exhibit fewer off-target effects. Non-covalent BTK inhibitors in clinical trials currently include Vecabrutinib, Fenebrutinib, ARQ 531, and LOXO-305, etc.[15]

Remarkable advances have been made in the therapy of malignant diseases targeting BTK.[15] Considering its central role in the signaling of B cells and other types of immune cells, the interest in BTK inhibition reasonably expanded to autoimmune diseases. Fenebrutinib is a non-covalent BTK inhibitor, and its efficacy and safety were tested in a Phase II, multicenter, randomized, placebo-controlled study in moderate-to-severe SLE patients. Although the treatment of Fenebrutinib reduced the level of auto-antibodies in the serum with acceptable adverse effects, the primary endpoint failed to be met.[34] Rilzabrutinib, an oral covalent BTK inhibitor, was investigated recently in an adaptive, dose-finding, open-label, Phase 1–2 clinical trial in immune thrombocytopenia patients. Rilzabrutinib showed rapid and long-term activity with a low level of toxicity. 400mg twice daily was identified as the optimal dosage.[35]

In conclusion, therapeutic approaches utilizing BTK as a target in many malignant diseases have achieved impressive success in recent decades.[15] Studies about the application of BTK inhibitors in autoimmunity are also gaining momentum.

BTK in Immunological Signaling Pathways

BCR Signaling Pathway

B cells are the main contributors to adaptive humoral immune reaction, playing vital roles in the human immune system. BTK is a prominent component of the BCR signaling pathway. BCR consists of IgM and a heterodimer of the Igα/β (CD79A/B). Upon antigen engagement on IgM, the immunoreceptor tyrosine-based activation motif (ITAM) on the tail of Igα/β is phosphorylated by the Src family, such as LYN, enabling the docking and activation of SYK protein.[36] Simultaneously, the cytoplasmic tail of co-receptor CD19 is phosphorylated by LYN and SYK, which subsequently recruits and activates PI3K. PI3K generates the second messenger PIP_3, which is responsible for localizing BTK to membrane through interaction with PH domain.[37] After being recruited to the membrane, BTK activation initiates with transphosphorylation at position Y551 by SYK and LYN, which contributes to BTK autophosphorylation at position Y223 in the SH3 domain.[7,14] The substrate of BTK includes PLCγ2. The activation of PLCγ2 generates two second messengers: diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 initiates Ca2+ mobilization and subsequently activates NFAT pathway. DAG mediates the activation of protein kinase Cβ (PKCβ), which activates the MAPK pathway and nuclear factor-κB (NF-κB) pathway.[11,14,16] These pathways are crucial for B-cell development, maturation and function.

Beyond BCR Signaling Pathway

Toll-like receptors (TLRs) were the first protein family identified in pattern recognition receptor (PRR) superfamily. TLRs recognize pathogen-associated molecular patterns (PAMPs) and endogenous damage-associated molecular patterns (DAMPs) to mediate innate immunity.[38] BTK participates in the recruitment of myeloid differentiation primary response 88 (MyD88) and MyD88 adaptor-like (MAL), which are downstream proteins in TLR pathway.[39] The interaction between TLRs and BTK has been seen in various immune cell types, including B cells,[40,41] macrophages,[42–45] dendritic cells,[46,47] neutrophils[48] and mast cells.[49] BTK is indispensable in TLR pathway to induce B-cell proliferation and differentiation.[10] The phagocytosis of macrophages to attack cancer cells could be enhanced by TLR-BTK activation.[45] Additionally, BTK regulated TLR4-mediated IL-10 production and TLR-7/8-mediated TNF production in macrophages.[43,44] However, the role of BTK in TLRs signaling in different subtypes of macrophages could be conflict. Although the lack of BTK and Tec in bone marrow-derived and thioglycolate-elicited peritoneal macrophages led to elevated expression of pro-inflammatory cytokines, the decreased secretion of pro-inflammatory cytokines in primary resident peritoneal macrophages was observed in the same context.[42] The pathogenetic activation of BCR signaling and TLR signaling synergistically promote the proliferation and survival of CLL cells.[50] Targeting BTK, a critical component of BCR signaling, has emerged as a promising therapeutic approach against CLL. Although BTK is also involved in TLR pathway, the single use of BTK inhibitors only partly dampened the activation of TLR pathway in CLL cells, which accounted for the low complete remission rate for CLL patients who received BTK inhibition treatment. The combinative use of Ibrutinib and TLR pathway inhibitor, IRAK1/4 inhibitor, was more effective than the usage of a single agent, which implicated that dual targeting of BCR signaling and TLR signaling had the potential to be a more effective strategy.[51]

Fc receptors, which harbor five variants (FcαRs, FcδRs, FcγRs, FcεRs, FcμRs), bind to the fragment crystallizable (Fc) domain of different isotypes of antibodies to initiate immune regulatory functions.[52] The activation of FcR pathway is dependent on BTK in myeloid cells.[53] As a part of FcεR pathway, BTK was involved in mast cell degranulation and BTK inhibition dampened the IgE-mediated histamine release in basophils.[10,54] BTK in FcR signaling is a promising therapeutic target for rheumatoid arthritis.[55] BTK inhibitors have exhibited efficacy in RA preclinical models.[56,57] However, off-target effects are likely to arise from BTK inhibition in FcR pathway. For example, Ibrutinib interfered with FcγRIIA pathway in platelets and impaired platelet activation against bacteria, increasing infection risk in CLL patients.[58]

BTK is also known as a component of chemokine receptor pathway. BTK and PLCγ2 synergistically regulate chemokine-mediated B cell migration and trafficking.[59] BTK inhibition by Evobrutinib impaired the ability of CXCR3+B cells to penetrate through human brain endothelial layers.[60]

The Immune-Related Mechanisms of BTK Inhibition in the Central Nervous System

Targeting B Cell

As mentioned above, BTK is a vital component of BCR signaling regulating B-cell functions. Targeting BTK has been widely studied and applied in the treatment of multiple sclerosis (MS).[61–63] Traditionally considered as a T cell-driven disease, MS has experienced a paradigm shift due to the success of anti-CD20 B cell-depleting therapy, which was regarded as a hallmark revealing the unneglectable role of B cells in MS pathogenesis.[64,65] Various B-cell-related mechanisms have been reported to contribute to MS development, including antigen presentation, antibody production, and cytokine secretion.[66,67] However, B-cell-depleting therapy has its limitations. As B cells are important functional immune cells in the human body, long-term pan-B-cell depletion alleviates the acute symptoms of MS at the cost of humoral deficiency.[68] In contrast to antibody-based therapy, BTK inhibition does not cause lasting damage to humoral immunity.[68,69] In addition, B cells are also present in meningeal inflammation areas, causing pathological changes in brain cortex.[70,71] BTK inhibition, but not anti-CD20 B-cell depletion, succeeded to eliminate B cells in the meningeal inflammation.[71] Therefore, BTK inhibition, with its selectivity and reversibility, is promising to serve as an alternative MS therapy. Furthermore, using B-cell depletion and BTK inhibition in sequence is likely to be an effective approach to

achieve rapid control of MS symptoms and avoid long-term compromising humoral immunity.[61,62,68] Although the increased expression level of BTK was observed in MS patients,[60,69] the exact mechanisms in which BTK involves in the development of MS remain to be further illustrated. Therefore, several studies have emerged in an attempt to address this question.

Weber et al[68] demonstrated that BTK inhibition could diminish the B-cell capacity as antigen-presenting cells (APCs). In EAE, BTK inhibition reduced the B-cell expression of MHC-II and costimulatory molecule CD86. B cells from Evobrutinib-treated mice exhibited a diminished ability to induce the differentiation of encephalitogenic T cells. Additionally, the B-cell function as antibody-secreting cells (ASCs) also implicates BTK involvement beyond BCR signaling. BTK was reported to be involved in CXCR3+ memory B cell differentiation. Evobrutinib could suppress the class-switching of B cells induced by INF-γ and TLR9 signaling pathway with T_{FH}-like stimulus (CD40L and IL-21). Evobrutinib also prevented memory B cell migration across the brain endothelial layer and maturation into ASCs, which can be considered a promising therapeutic approach to attenuate local antibody production in MS patients.[60]

A recent study shed new light on the regulatory function of BTKi on B cells in MS. Li et al[69] reported that the treatment of BTKi could inhibit mitochondrial respiration in human B cells in vitro, resulting in an anti-inflammatory shift in B cell properties. The expression of costimulatory molecules is reduced in B cells, limiting their function as antigen-presenting cells to activate pathogenic T cells. Notably, the result was further confirmed and complemented by using the samples from a Phase I clinical trial of a selective oral BTKi (BIIB091),[53] where health volunteers displayed diminished B cell activation and decreased proportion of memory B cell. This result supplemented the study in the EAE model and established the immunometabolic regulatory aspect of BTKi, which could be considered as a promising target for immune-related diseases.

Neuromyelitis Optica spectrum disorder (NMOSD) is an autoimmune demyelinating disease characterized by disturbed humoral immunity.[72] Auto-reactive B cells secret autoantigen to attack water channel protein aquaporin-4 (AQP4-IgG) on astrocytes foot processes and lead to CNS pathology.[73] BTK/NF-κB pathway was found to be activated in NMOSD patients in the acute phase, but not in the remission phase, compared with healthy controls.[70] This provided the preliminary evidence that BTK inhibition could be a potential therapy to ameliorate the pathological progression of NMOSDs. However, the precise mechanisms of BTK involvement are needed to be further confirmed.

Targeting Microglia

Microglia are resident macrophages in the CNS, which critically involve in the early development, homeostasis, and neuroprotection in the CNS.[74] Microglia serve as the front-line defense in clearing myelin debris and exogenous pathogens and preventing the accumulation of amyloid. However, in the duration of neuroinflammation, the dysregulation of "eat-me" and "Don't eat me" signals could lead to synapse loss due to microglia-mediated engulfment.[75]

BTK was reported to participate in the CCL5-induced pathway and increase the Ca2+ concentration in the microglia, potentially implicating the BTK involvement in controlling inflammatory phenotypes in microglia.[76] Recently, BTK in the FcR signaling in microglia was established using a novel and elegantly designed mice model. Fc-receptors (FcR) bind to antibodies to induce antibody-dependent cell cytotoxicity (ADCC) and phagocytosis (ADCP). Therefore, to specifically and efficiently engage FcRs in microglia in the CNS, mice were peripherally, not intracerebellarily, injected with anti-MOG antibodies. The reason to choose peripheral injection but not invasive central injection is that the latter would lead to the recruitment of platelets and complements, which is likely to interfere with the experiment results. As MOG is a well-known antigen that expresses abundantly in the CNS, the anti-MOG antibodies were detected throughout the mice brain. Rapid microglial proliferation response was observed in the brain and spinal cord. The microglial response enhanced in the BTK^{E41K} knock-in mice and was abrogated by BTK inhibitor.[77] All evidence converged to prove the importance of BTK in microglial activity. Thus, targeting BTK could be a feasible way to modulate the phenotypes and functions of microglia.

The positive effects of BTK inhibition to modulate microglial activity and alleviate inflammation damage have been demonstrated in many animal models. In 5xFAD mice, which is an animal model of Alzheimer's Disease, BTK inhibition diminished the phagocytic capacity of microglia and affected migration and cytokine secretion functions. The improved cognition was observed in mice treated with BTK inhibitors.[9] Ibrutinib, a BTK inhibitor, reduced proinflammatory

cytokine levels in BV2 microglia and primary microglia through TLR4 pathway in LPS-induced neuroinflammation model. This process partially involved ATK/STAT3 signaling pathway.[78] In addition, Ibrutinib attenuated the microglial and astrocyte activity in a traumatic spinal cord injury (SCI) mice model, which was associated with an improvement of motor functions.[8] The level of BTK was elevated majorly in microglia and partially in astrocytes in a demyelination model. Although BTK inhibition facilitated remyelination, the study could not completely exclude the effect from astrocytes.[79]

Recently, Tolebrutinib, a BTK inhibitor potently inhibiting microglial BTK activity, was evaluated in a phase 2b, randomized, double-blind, placebo-controlled, dose-finding trial in relapsing multiple sclerosis patients. Tolebrutinib dose-dependently attenuated new gadolinium-enhancing lesions in a 12-week treatment and 60mg was identified as the optimal dosage. The most common adverse effect during Tolebrutinib treatment was headache. It can be expected that in the future, more BTK inhibitors focusing on microglial modulation will advance into clinical trials. Notably, a potential limitation of the present studies on BTK and microglia is that most of these studies cannot distinguish accurately between microglia and CNS-associated macrophages (CAMs) in in vivo experiments. CAMs refer to macrophages located in CNS interface, including perivascular macrophages, meningeal macrophages, and choroid plexus macrophages, while microglia are located in brain parenchyma.[80] These two cell subsets share many common cell markers, making it challenging to target microglia accurately in in vivo studies. Therefore, the role of BTK inhibitors on microglia/CNS macrophages is required to be further dissected in future studies in combination with more specific cell markers.

Targeting NLRP3 Inflammasome

The NACHT, LRR, and PYD domain-containing protein 3 (NLRP3) inflammasome is a multiple protein complex, consisting of NLRP3 protein as a sensor, apoptosis-associated speck-like protein (ASC) as an adaptor and caspase-1 as an effector.[81]

Typically, the assembly of NLRP3 inflammasome requires a priming stage and activation. The priming of the formation of NLRP3 inflammasome needs upstream signals as the first signal from the engagement of pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) with TLR, NOD2, IL-1R, or tumor necrosis factor receptor (TNFR), which subsequently triggers the upregulation of NLRP3 and pro-inflammatory cytokines: pro-interleukin (IL)-1β and pro-IL-18 via NF-κB pathway. Before subsequent activation, NLRP3 protein exists as a monomer. After receiving stimuli as the second signal, NLRP3 oligomerizes and the NACHT domain of NLRP3 is activated by ATP and NEK7 binding.[81,82] Next, the PYD domain recruits the adaptor ASC through PYD-PYD interaction. The caspase recruitment domain (CARD) of ASC binds to pro-caspase-1 via CARD–CARD interaction, converting pro-caspase-1 to caspase-1, which finally forms the NLRP3–ASC–caspase-1 protein complex, known as NLRP3 inflammasome. The downstream effects include the maturation and release of pro-inflammatory cytokines IL-1β and IL-18. However, there are alternative pathways of NLRP3 inflammasome activation, such as caspase-11-dependent pathway.[83] In the central nervous system, NLRP3 inflammasome is expressed in microglia, astrocytes and neurons. As mentioned above, NLRP3 inflammasome response can be primed by DAMPs. DAMPs can be released from brain cells damaged by mechanical or immune injury, subsequently triggering NLRP3 inflammasome response, which exacerbates inflammatory destruction to the brain.[84,85] In fact, several studies have demonstrated the role of NLRP3 inflammasome in many CNS diseases, including MS, traumatic brain injury, stroke and neurodegenerative diseases (Alzheimer's Disease and Parkinson's Disease).[82] All these studies converged to highlight that neuroinflammation is a key part of the pathogenesis of various CNS conditions.

Numerous studies proved that BTK was a component of NLRP3 inflammasome pathway. A molecular study revealed that BTK directly phosphorylated four conserved tyrosine residues in the NLRP3 polybasic linker motif and NLRP3 inflammasome oligomerization, ASC association, and IL-1β expression could be promoted by BTK, which provided strong evidence about BTK regulation of NLRP3 inflammasome.[86] The association between BTK and NLRP3 inflammasome was also established within the CNS by a series of animal experiments concerning brain ischemia. Post-ischemic inflammation is the main contributor to ischemic stroke injury, where NLRP3 inflammasome appears to be one of the drivers.[87,88] BTK inhibition suppressed NLRP3 inflammasome activity in infiltrating macrophages and neutrophils and attenuated infarct volume growth in the transient middle cerebral artery occlusion (tMACO) mice model.[89] This result

was complemented by another study where NLRP3 expression in ischemic hemisphere neurons elevated in the early phase of cerebral ischemia and pharmacological blocking utilizing inflammasome inhibitors was able to reduce infarct volumes and immune cell infiltration. The inhibition of NLPR3 inflammasome exhibits neuroprotection function against ischemic inflammatory response. However, there are no NLRP3 inhibitors approved for clinical therapy. In contrast, many types of BTK inhibitors have been approved by FDA. Thus, BTK appeared to be a promising and druggable target for ischemia-related inflammation.[87]

In conclusion, BTK inhibition links different pathways to regulate immune responses and inflammation reactions in the scope of neurological diseases (Figure 2).

BTK Inhibition in Primary Central Nervous System Lymphoma

Primary central nervous system lymphoma (PCNSL) is a rare but aggressive subtype of diffuse large B cell lymphoma (DLBCL). The invasion of PCNSL confines to the central nervous system including brain, eyes, cerebrospinal fluid (CSF), or spinal cord.[90] PCNSL is highly associated with mutations of the BCR subunit CD79B (CD79B) and the Toll-like receptor adaptor protein MYD88 (MYD88). Moreover, both CD79B and MYD88 L265P mutations were observed much more frequently in PCNSL than in systemic DLBCL.[91] These mutations lead to chronic activation of NF-κB signaling pathway, promoting malignant proliferation of B cells.[92] BTK is a critical signaling node linking BCR and TCR pathways, and BTK inhibitors process excellent pharmacokinetics in terms of brain distribution.[18,93] Therefore, it is reasonable to hypothesize that PCNSL is sensitive to BTK inhibition. BTK inhibition has been considered as a promising therapeutic approach for PCNSL, as proposed by Zhai et al.[94] Currently, except for malignant B cells, Ibrutinib, in combination with XPO1 inhibitor selinexor, also converted the phenotype of tumor-associated macrophages (TAMs), resulting in diminished expression of two regulatory checkpoint receptors on TAMs, PD-1 and SIRPα, which enhanced the anti-tumoral activity of TAMs.[95]

Ibrutinib was the first BTK inhibitor evaluated in the trials of PCNSL. In vitro and in vivo studies demonstrated that Ibrutinib was more effective than Zanubrutinib and Tirabrutinib for the treatment of PCNSL with an ideal pharmacokinetic property in brain distribution.[96] Ibrutinib monotherapy exhibits impressive clinical activity and safety with the

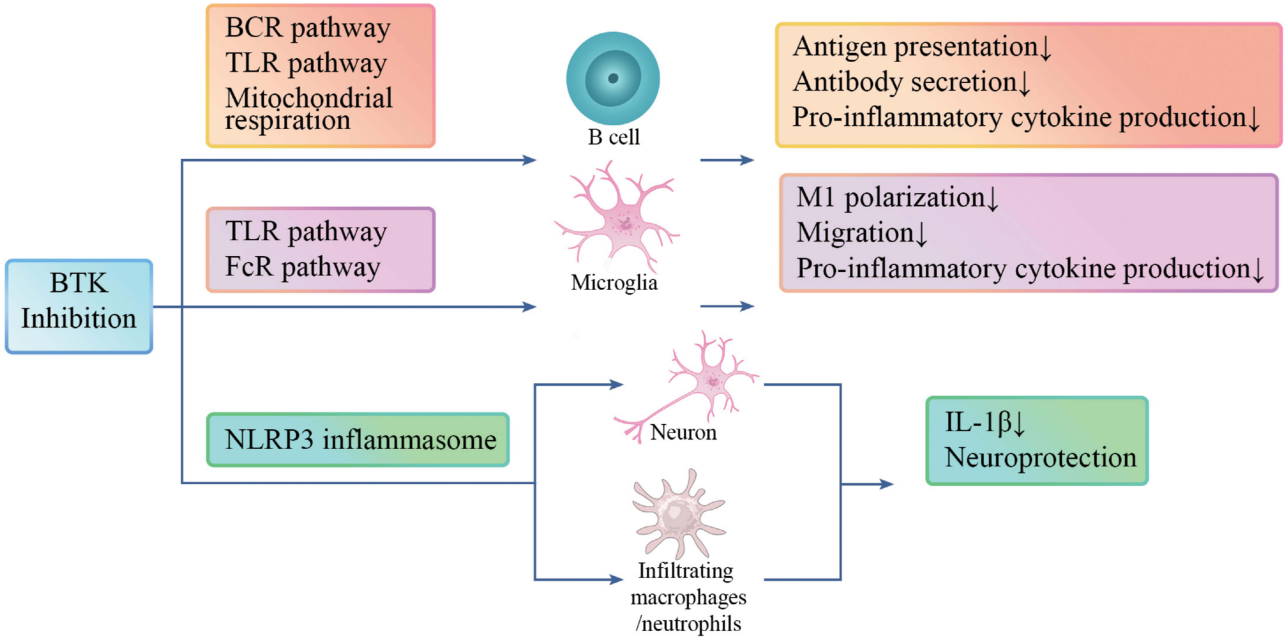

Figure 2 The overview of immunomodulatory mechanisms of BTK inhibition within CNS. In B cells, BTK inhibition dampens the capacity of antigen presentation, antibody secretion and pro-inflammatory cytokines production through BCR, TLR pathway and regulation of mitochondrial respiration. The M1 polarization toward a more pro-inflammatory profile, migration and pro-inflammatory cytokines production of microglia can be diminished by BTK inhibition. The activation of NLRP3 inflammasome in neurons and infiltrating macrophages/neutrophils can be inhibited by BTK inhibition, leading to decreased IL-1β production and neuroprotection.

ORR reaching 77% in a phase I clinical trial.[97] Similar positive results were obtained in another phase I trial.[93] In a multicenter, Phase II study, Ibrutinib achieved an ORR of 52% after two 28-day treatments. The relatively decreased ORR may be related to lower Ibrutinib dosage (560mg/day).[98] Furthermore, the tolerability and efficacy of Ibrutinib were further validated by a meta-analysis including eight clinical studies.[99] However, Ibrutinib resistance was also observed due to mutations in CARD11 and CD79B.[97] Therefore, combinative therapy seemed to be a more feasible way. The combination of ibrutinib with high-dose methotrexate (HD-MTX) and rituximab reached an 80% clinical response rate without dose-limiting toxicity.[100] A retrospective study of rituximab/lenalidomide/ibrutinib combination demonstrated complete response in 4 of 14 and partial response in 4/14 relapsed/refractory (R/R) primary CNS lymphoma (PCNSL) patients, and toxicity was acceptable.[101] The usage of Ibrutinib combined with radiotherapy also generated promising outcomes, achieving the highest response rate for PCNSL and secondary central nervous system lymphoma (SCNSL) patients (2/3 for PCNSL, 3/3 for SCNSL).[102]

In addition to Ibrutinib, other BTK inhibitors were also under investigation in clinical trials. Particularly, Tirabrutinib, an oral, covalent BTK inhibitor, has been approved in Japan for the clinical therapy of recurrent or refractory primary central nervous system lymphoma.[30] Compared with Ibrutinib, Tirabrutinib is more specific with higher safety and tolerability.[103] The pathological evidence of the efficacy of Tirabrutinib was provided by a recent post-mortem autopsy report, demonstrating that tumor cells were completely eliminated by Tirabrutinib in the brain of the patients, who died because of suspected pneumocystis pneumonia in the duration of Tirabrutinib treatment.[104] The efficacy of the BTK inhibitor, Orelabrutinib, combined with rituximab, methotrexate, temozolomide and lenalidomide was analyzed in a retrospective study. Among fifteen patients, the overall response rate (ORR), disease control rate (DCR) and complete remission (CR) rate were 86.7%, 73.3% and 93.3%, respectively.[105]

Conclusion

BTK critically participates in the signaling pathways not only in B cells but also in other immune cells. Currently, BTK inhibitors have been widely accepted in the therapeutics of malignant diseases, especially B-cell malignancies. Besides, the application of BTK inhibitors in inflammatory and autoimmune diseases is also gaining momentum. Specifically, BTK is involved in the innate immunity (such as microglia) and adaptive immunity (such as B cells) and affects the production of inflammation mediators (NLRP3 inflammasome, etc.) in the central nervous system. Neuroinflammation is the main player in neuroimmune diseases and also a driver in other neurological diseases including neurodegenerative diseases and ischemic cerebral diseases, etc. BTK inhibition has been demonstrated as an effective way to alleviate dysregulated inflammation within the CNS to improve outcomes of neurological diseases. Although many BTK-related mechanisms and pathways have been illustrated in a wide range of neurological diseases, it has to be emphasized that these mechanisms are not independent of each other but form a complex network of modulation and interaction system to control the inflammation progression and disease development. There is no doubt that the application of BTK inhibition in the CNS will advance along with the evolving understanding of the relationship between neuroinflammation and neurological diseases.

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Disclosure

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References

1. Bruton OC. Agammaglobulinemia. *Pediatrics*. 1952;9(6):722–728. doi:10.1542/peds.9.6.722
2. Tsukada S, Saffran DC, Rawlings DJ, et al. Deficient expression of a B cell cytoplasmic tyrosine kinase in human X-linked agammaglobulinemia. *Cell*. 1993;72(2):279–290. doi:10.1016/0092-8674(93)90667-F

3. Khan WN, Alt FW, Gerstein RM, et al. Defective B cell development and function in Btk-deficient mice. *Immunity*. 1995;3(3):283–299. doi:10.1016/1074-7613(95)90114-0
4. Rawlings DJ, Saffran DC, Tsukada S, et al. Mutation of unique region of Bruton's tyrosine kinase in immunodeficient XID mice. *Science*. 1993;261(5119):358–361. doi:10.1126/science.8332901
5. Liang C, Tian D, Ren X, et al. The development of Bruton's tyrosine kinase (BTK) inhibitors from 2012 to 2017: a mini-review. *Eur J Med Chem*. 2018;151:315–326. doi:10.1016/j.ejmech.2018.03.062
6. Zhu S, Gokhale S, Jung J, et al. Multifaceted Immunomodulatory Effects of the BTK inhibitors ibrutinib and acalabrutinib on different immune cell subsets - beyond B lymphocytes. *Front Cell Dev Biol*. 2021;9:727531. doi:10.3389/fcell.2021.727531
7. McDonald C, Xanthopoulos C, Kostareli E. The role of Bruton's tyrosine kinase in the immune system and disease. *Immunology*. 2021;164 (4):722–736. doi:10.1111/imm.13416
8. Yu CG, Bondada V, Iqbal H, et al. Inhibition of Bruton tyrosine kinase reduces neuroimmune cascade and promotes recovery after spinal cord injury. *Int J Mol Sci*. 2021;23:1. doi:10.3390/ijms23010355
9. Keaney J, Gasser J, Gillet G, Scholz D, Kadiu I. Inhibition of Bruton's tyrosine kinase modulates microglial phagocytosis: therapeutic implications for alzheimer's disease. *J Neuroimmune Pharmacol*. 2019;14(3):448–461. doi:10.1007/s11481-019-09839-0
10. Zarrin AA, Bao K, Lupardus P, Vucic D. Kinase inhibition in autoimmunity and inflammation. *Nat Rev Drug Discov*. 2021;20(1):39–63. doi:10.1038/s41573-020-0082-8
11. Zhang D, Gong H, Meng F. Recent advances in BTK inhibitors for the treatment of inflammatory and autoimmune diseases. *Molecules*. 2021;26:16.
12. Hirsch EC, Standaert DG. Ten unsolved questions about neuroinflammation in parkinson's disease. *Mov Disord*. 2021;36(1):16–24. doi:10.1002/mds.28075
13. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol*. 2021;17 (3):157–172. doi:10.1038/s41582-020-00435-y
14. Corneth OBJ, Klein Wolterink RGJ, Hendriks RW. BTK Signaling in B cell differentiation and autoimmunity. *Curr Top Microbiol Immunol*. 2016;393:67–105.
15. Gu D, Tang H, Wu J, Li J, Miao Y. Targeting Bruton tyrosine kinase using non-covalent inhibitors in B cell malignancies. *J Hematol Oncol*. 2021;14(1):40. doi:10.1186/s13045-021-01049-7
16. Pal Singh S, Dammeijer F, Hendriks RW. Role of Bruton's tyrosine kinase in B cells and malignancies. *Mol Cancer*. 2018;17(1):57. doi:10.1186/s12943-018-0779-z
17. Burger JA. Bruton Tyrosine Kinase Inhibitors: present and Future. *Cancer J*. 2019;25(6):386–393. doi:10.1097/PPO.0000000000000412
18. Goldwirt L, Beccaria K, Ple A, Sauvageon H, Mourah S. Ibrutinib brain distribution: a preclinical study. *Cancer Chemother Pharmacol*. 2018;81(4):783–789. doi:10.1007/s00280-018-3546-3
19. Zain R, Vihinen M. Structure-function relationships of covalent and non-covalent BTK Inhibitors. *Front Immunol*. 2021;12:694853. doi:10.3389/fimmu.2021.694853
20. Liu J, Chen C, Wang D, Zhang J, Zhang T. Emerging small-molecule inhibitors of the Bruton's tyrosine kinase (BTK): current development. *Eur J Med Chem*. 2021;217:113329. doi:10.1016/j.ejmech.2021.113329
21. Woyach JA, Furman RR, Liu TM, et al. Resistance mechanisms for the Bruton's tyrosine kinase inhibitor ibrutinib. *N Engl J Med*. 2014;370 (24):2286–2294. doi:10.1056/NEJMoa1400029
22. Amin NA, Balasubramanian S, Saiya-Cork K, Shedden K, Hu N, Malek SN. Cell-intrinsic determinants of ibrutinib-induced apoptosis in chronic lymphocytic leukemia. *Clin Cancer Res*. 2017;23(4):1049–1059. doi:10.1158/1078-0432.CCR-15-2921
23. Robert C, Soria J-C, Spatz A, et al. Cutaneous side-effects of kinase inhibitors and blocking antibodies. *Lancet Oncol*. 2005;6(7):491–500. doi:10.1016/S1470-2045(05)70243-6
24. Dubovsky JA, Beckwith KA, Natarajan G, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. *Blood*. 2013;122(15):2539–2549. doi:10.1182/blood-2013-06-507947
25. Xiao L, Salem JE, Clauss S, et al. Ibrutinib-mediated atrial fibrillation attributable to inhibition of C-terminal src kinase. *Circulation*. 2020;142 (25):2443–2455. doi:10.1161/CIRCULATIONAHA.120.049210
26. Zimmerman SM, Peer CJ, Figg WD. Ibrutinib's off-target mechanism: cause for dose optimization. *Cancer Biol Ther*. 2021;22(10–12):529–531. doi:10.1080/15384047.2021.1980313
27. Barf T, Covey T, Izumi R, et al. Acalabrutinib (ACP-196): a Covalent Bruton Tyrosine Kinase Inhibitor with a Differentiated Selectivity and In Vivo Potency Profile. *J Pharmacol Exp Ther*. 2017;363(2):240–252. doi:10.1124/jpet.117.242909
28. Syed YY. Zanubrutinib: first Approval. *Drugs*. 2020;80(1):91–97. doi:10.1007/s40265-019-01252-4
29. Ghia P, Pluta A, Wach M, et al. ASCEND: phase III, randomized trial of acalabrutinib versus idelalisib plus rituximab or bendamustine plus rituximab in relapsed or refractory chronic lymphocytic leukemia. *J Clin Oncol*. 2020;38(25):2849–2861. doi:10.1200/JCO.19.03355
30. Dhillon S. Tirabrutinib: first Approval. *Drugs*. 2020;80(8):835–840. doi:10.1007/s40265-020-01318-8
31. Dhillon S. Orelabrutinib: first Approval. *Drugs*. 2021;81(4):503–507. doi:10.1007/s40265-021-01482-5
32. Robak T, Witkowska M, Smolewski P. The role of Bruton's kinase inhibitors in chronic lymphocytic leukemia: current status and future directions. *Cancers*. 2022;14:3. doi:10.3390/cancers14030771
33. Tasso B, Spallarossa A, Russo E, Brullo C. The development of BTK inhibitors: a five-year update. *Molecules*. 2021;26:23. doi:10.3390/molecules26237411
34. Isenberg D, Furie R, Jones NS, et al. Efficacy, safety, and pharmacodynamic effects of the Bruton's tyrosine kinase inhibitor fenebrutinib (GDC-0853) in systemic lupus erythematosus: results of a phase II, randomized, double-blind, placebo-controlled trial. *Arthritis Rheumatol*. 2021;73 (10):1835–1846. doi:10.1002/art.41811
35. Kuter DJ, Efraim M, Mayer J, et al. Rilzabrutinib, an Oral BTK Inhibitor, in Immune Thrombocytopenia. *N Engl J Med*. 2022;386 (15):1421–1431. doi:10.1056/NEJMoa2110297
36. Rolli V, Gallwitz M, Wossning T, et al. Amplification of B cell antigen receptor signaling by a Syk/ITAM positive feedback loop. *Mol Cell*. 2002;10(5):1057–1069. doi:10.1016/S1097-2765(02)00739-6

37. Saito K, Scharenberg AM, Kinet JP. Interaction between the Btk PH domain and phosphatidylinositol-3,4,5-trisphosphate directly regulates Btk. *J Biol Chem*. 2001;276(19):16201–16206. doi:10.1074/jbc.M100873200
38. Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. *Cell*. 2020;180(6):1044–1066. doi:10.1016/j.cell.2020.02.041
39. Jefferies CA, Doyle S, Brunner C, et al. Bruton's tyrosine kinase is a Toll/interleukin-1 receptor domain-binding protein that participates in nuclear factor kappaB activation by Toll-like receptor 4. *J Biol Chem*. 2003;278(28):26258–26264. doi:10.1074/jbc.M301484200
40. Morbach H, Schickel J-N, Cunningham-Rundles C, et al. CD19 controls Toll-like receptor 9 responses in human B cells. *J Allergy Clin Immunol*. 2016;137:3. doi:10.1016/j.jaci.2015.08.040
41. Corzo CA, Varfolomeev E, Setiadi AF, et al. The kinase IRAK4 promotes endosomal TLR and immune complex signaling in B cells and plasmacytoid dendritic cells. *Sci Signal*. 2020;13:634. doi:10.1126/scisignal.aaz1053
42. Tampella G, Kerns HM, Niu D, et al. The tec kinase-regulated phosphoproteome reveals a mechanism for the regulation of inhibitory signals in murine macrophages. *J Immunol*. 2015;195(1):246–256. doi:10.4049/jimmunol.1403238
43. Schmidt NW, Thieu VT, Mann BA, Ahyi A-N-N, Kaplan MH. Bruton's tyrosine kinase is required for TLR-induced IL-10 production. *J Immunol*. 2006;177(10):7203–7210. doi:10.4049/jimmunol.177.10.7203
44. Page TH, Urbaniak AM, Espirito Santo AI, et al. Bruton's tyrosine kinase regulates TLR7/8-induced TNF transcription via nuclear factor-κB recruitment. *Biochem Biophys Res Commun*. 2018;499(2):260–266. doi:10.1016/j.bbrc.2018.03.140
45. Feng M, Chen JY, Weissman-Tsukamoto R, et al. Macrophages eat cancer cells using their calreticulin as a guide: roles of TLR and Btk. Proc Natl Acad Sci U S A. 2015;112(7):2145–2150.
46. Liu X, Zhan Z, Li D, et al. Intracellular MHC class II molecules promote TLR-triggered innate immune responses by maintaining activation of the kinase Btk. *Nat Immunol*. 2011;12(5):416–424. doi:10.1038/ni.2015
47. Lougaris V, Baronio M, Vitali M, et al. Bruton tyrosine kinase mediates TLR9-dependent human dendritic cell activation. *J Allergy Clin Immunol*. 2014;133:6. doi:10.1016/j.jaci.2013.12.1085
48. Marron TU, Rohr K, Martinez-Gallo M, Yu J, Cunningham-Rundles C. TLR signaling and effector functions are intact in XLA neutrophils. *Clin Immunol*. 2010;137(1):74–80. doi:10.1016/j.clim.2010.06.011
49. Zorn CN, Keck S, Hendriks RW, Leitges M, Freudenberg MA, Huber M. Bruton's tyrosine kinase is dispensable for the Toll-like receptor-mediated activation of mast cells. *Cell Signal*. 2009;21(1):79–86. doi:10.1016/j.cellsig.2008.09.010
50. Kennedy E, Coulter E, Halliwell E, et al. TLR9 expression in chronic lymphocytic leukemia identifies a promigratory subpopulation and novel therapeutic target. *Blood*. 2021;137(22):3064–3078. doi:10.1182/blood.2020005964
51. Dadashian EL, McAuley EM, Liu D, et al. TLR signaling is activated in lymph node-resident CLL cells and is only partially inhibited by ibrutinib. *Cancer Res*. 2019;79(2):360–371. doi:10.1158/0008-5472.CAN-18-0781
52. Kim J, Lee JY, Kim HG, Kwak MW, Kang TH. Fc receptor variants and disease: a crucial factor to consider in the antibody therapeutics in clinic. *Int J Mol Sci*. 2021;22:17.
53. Bame E, Tang H, Burns JC, et al. Next-generation Bruton's tyrosine kinase inhibitor BIIB091 selectively and potently inhibits B cell and Fc receptor signaling and downstream functions in B cells and myeloid cells. *Clin Transl Immunology*. 2021;10(6):e1295. doi:10.1002/cti2.1295
54. Hata D, Kawakami Y, Inagaki N, et al. Involvement of Bruton's tyrosine kinase in FcepsilonRI-dependent mast cell degranulation and cytokine production. *J Exp Med*. 1998;187(8):1235–1247. doi:10.1084/jem.187.8.1235
55. Wu Y, Pan W, Hu X, Zhang A, Wei W. The prospects for targeting FcR as a novel therapeutic strategy in rheumatoid arthritis. *Biochem Pharmacol*. 2021;183:114360. doi:10.1016/j.bcp.2020.114360
56. Haselmayer P, Camps M, Liu-Bujalski L, et al. Efficacy and pharmacodynamic modeling of the BTK inhibitor evobrutinib in autoimmune disease models. *J Immunol*. 2019;202(10):2888–2906. doi:10.4049/jimmunol.1800583
57. Liu Y-T, Ding -H-H, Lin Z-M, et al. A novel tricyclic BTK inhibitor suppresses B cell responses and osteoclastic bone erosion in rheumatoid arthritis. *Acta Pharmacol Sin*. 2021;42(10):1653–1664. doi:10.1038/s41401-020-00578-0
58. Naylor-Adamson L, Chacko AR, Booth Z, et al. Bruton's tyrosine kinase inhibitors impair FcγRIIA-Driven platelet responses to bacteria in chronic lymphocytic leukemia. *Front Immunol*. 2021;12:766272. doi:10.3389/fimmu.2021.766272
59. de Gorter DJJ, Beuling EA, Kersseboom R, et al. Bruton's tyrosine kinase and phospholipase Cgamma2 mediate chemokine-controlled B cell migration and homing. *Immunity*. 2007;26:1. doi:10.1016/j.immuni.2006.11.012
60. Rijvers L, van Langelaar J, Bogers L, et al. Human T-bet+ B cell development is associated with BTK activity and suppressed by evobrutinib. *JCI Insight*. 2022;7. doi:10.1172/jci.insight.160909
61. García-Merino A. Bruton's tyrosine kinase inhibitors: a new generation of promising agents for multiple sclerosis therapy. *Cells*. 2021;10:10. doi:10.3390/cells10102560
62. Torke S, Weber MS. Inhibition of Bruton's tyrosine kinase as a novel therapeutic approach in multiple sclerosis. *Expert Opin Investig Drugs*. 2020;29(10):1143–1150. doi:10.1080/13543784.2020.1807934
63. Montalban X, Arnold DL, Weber MS, et al. Placebo-controlled trial of an oral BTK inhibitor in multiple sclerosis. *N Engl J Med*. 2019;380(25):2406–2417. doi:10.1056/NEJMoa1901981
64. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med*. 2008;358(7):676–688. doi:10.1056/NEJMoa0706383
65. Li R, Patterson KR, Bar-Or A. Reassessing B cell contributions in multiple sclerosis. *Nat Immunol*. 2018;19(7):696–707. doi:10.1038/s41590-018-0135-x
66. Häusser-Kinzel S, Weber MS. The role of B cells and antibodies in multiple sclerosis, neuromyelitis optica, and related disorders. *Front Immunol*. 2019;10:201. doi:10.3389/fimmu.2019.00201
67. Cencioni MT, Mattoscio M, Magliozzi R, Bar-Or A, Muraro PA. B cells in multiple sclerosis - from targeted depletion to immune reconstitution therapies. *Nat Rev Neurol*. 2021;17(7):399–414. doi:10.1038/s41582-021-00498-5
68. Torke S, Pretzsch R, Häusler D, et al. Inhibition of Bruton's tyrosine kinase interferes with pathogenic B-cell development in inflammatory CNS demyelinating disease. *Acta Neuropathol*. 2020;140(4):535–548. doi:10.1007/s00401-020-02204-z
69. Li R, Tang H, Burns JC, et al. BTK inhibition limits B-cell-T-cell interaction through modulation of B-cell metabolism: implications for multiple sclerosis therapy. *Acta Neuropathol*. 2022;143(4):505–521. doi:10.1007/s00401-022-02411-w

70. Qiao H, Mao Z, Wang W, et al. Changes in the BTK/NF-κB signaling pathway and related cytokines in different stages of neuromyelitis optica spectrum disorders. *Eur J Med Res*. 2022;27(1):96. doi:10.1186/s40001-022-00723-x
71. Bhargava P, Hartung HP, Calabresi PA. Contribution of B cells to cortical damage in multiple sclerosis. *Brain*. 2022;145:3363–3373. doi:10.1093/brain/awac233
72. Weinshenker BG, Wingerchuk DM. Neuromyelitis spectrum disorders. *Mayo Clin Proc*. 2017;92(4):663–679. doi:10.1016/j.mayocp.2016.12.014
73. Li J, Bazzi SA, Schmitz F, et al. Molecular level characterization of circulating aquaporin-4 antibodies in neuromyelitis optica spectrum disorder. *Neurol Neuroimmunol Neuroinflamm*. 2021;8:5. doi:10.1212/NXI.0000000000001034
74. Prinz M, Jung S, Priller J. Microglia biology: one century of evolving concepts. *Cell*. 2019;179(2):292–311. doi:10.1016/j.cell.2019.08.053
75. Borst K, Dumas AA, Prinz M. Microglia: immune and non-immune functions. *Immunity*. 2021;54(10):2194–2208. doi:10.1016/j.immuni.2021.09.014
76. Shideman CR, Hu S, Peterson PK, Thayer SA. CCL5 evokes calcium signals in microglia through a kinase-, phosphoinositide-, and nucleotide-dependent mechanism. *J Neurosci Res*. 2006;83(8):1471–1484. doi:10.1002/jnr.20839
77. Pellerin K, Rubino SJ, Burns JC, et al. MOG autoantibodies trigger a tightly-controlled FcR and BTK-driven microglia proliferative response. *Brain*. 2021;144(8):2361–2374. doi:10.1093/brain/awab231
78. Nam HY, Nam JH, Yoon G, et al. Ibrutinib suppresses LPS-induced neuroinflammatory responses in BV2 microglial cells and wild-type mice. *J Neuroinflammation*. 2018;15(1):271. doi:10.1186/s12974-018-1308-0
79. Martin E, Aigrot MS, Grenningloh R, et al. Bruton's tyrosine kinase inhibition promotes myelin repair. *Brain Plast*. 2020;5(2):123–133. doi:10.3233/BPL-200100
80. Kierdorf K, Masuda T, Jordão MJC, Prinz M. Macrophages at CNS interfaces: ontogeny and function in health and disease. *Nat Rev Neurosci*. 2019;20(9):547–562. doi:10.1038/s41583-019-0201-x
81. Blevins HM, Xu Y, Biby S, Zhang S. The NLRP3 inflammasome pathway: a review of mechanisms and inhibitors for the treatment of inflammatory diseases. *Front Aging Neurosci*. 2022;14:879021.
82. Piancone F, La Rosa F, Marventano I, Saresella M, Clerici M. The role of the inflammasome in neurodegenerative diseases. *Molecules*. 2021;26:4. doi:10.3390/molecules26040953
83. Huang Y, Xu W, Zhou R. NLRP3 inflammasome activation and cell death. *Cell Mol Immunol*. 2021;18(9):2114–2127. doi:10.1038/s41423-021-00740-6
84. Jing X, Yao Y, Wu D, et al. IFP35 family proteins promote neuroinflammation and multiple sclerosis. *Proc Natl Acad Sci U S A*. 2021;118:32.
85. Yang T, Velagapudi R, Terrando N. Neuroinflammation after surgery: from mechanisms to therapeutic targets. *Nat Immunol*. 2020;21(11):1319–1326. doi:10.1038/s41590-020-00812-1
86. Bittner ZA, Liu X, Mateo Tortola M, et al. BTK operates a phospho-tyrosine switch to regulate NLRP3 inflammasome activity. *J Exp Med*. 2021;218:11. doi:10.1084/jem.20201656
87. Franke M, Bieber M, Kraft P, Weber ANR, Stoll G, Schuhmann MK. The NLRP3 inflammasome drives inflammation in ischemia/reperfusion injury after transient middle cerebral artery occlusion in mice. *Brain Behav Immun*. 2021;92:223–233. doi:10.1016/j.bbi.2020.12.009
88. Zhu H, Jian Z, Zhong Y, et al. Janus kinase inhibition ameliorates ischemic stroke injury and neuroinflammation through reducing NLRP3 inflammasome activation via JAK2/STAT3 pathway inhibition. *Front Immunol*. 2021;12:714943. doi:10.3389/fimmu.2021.714943
89. Ito M, Shichita T, Okada M, et al. Bruton's tyrosine kinase is essential for NLRP3 inflammasome activation and contributes to ischaemic brain injury. *Nat Commun*. 2015;6:7360. doi:10.1038/ncomms8360
90. Schaff LR, Grommes C. Primary central nervous system lymphoma. *Blood*. 2021;5:8.
91. Ngo VN, Young RM, Schmitz R, et al. Oncogenically active MYD88 mutations in human lymphoma. *Nature*. 2011;470(7332):115–119. doi:10.1038/nature09671
92. Schaff LR, Grommes C. Update on novel therapeutics for primary CNS lymphoma. *Cancers*. 2021;13:21. doi:10.3390/cancers13215372
93. Lionakis MS, Dunleavy K, Roschewski M, et al. Inhibition of B cell receptor signaling by ibrutinib in primary CNS lymphoma. *Cancer Cell*. 2017;31:6. doi:10.1016/j.ccell.2017.04.012
94. Zhai Y, Zhou X, Wang X. Novel insights into the biomarkers and therapies for primary central nervous system lymphoma. *Ther Adv Med Oncol*. 2022;14:17588359221093745. doi:10.1177/17588359221093745
95. Jiménez I, Carabia J, Bobillo S, et al. Repolarization of tumor infiltrating macrophages and increased survival in mouse primary CNS lymphomas after XPO1 and BTK inhibition. *J Neurooncol*. 2020;149(1):13–25. doi:10.1007/s11060-020-03580-y
96. Yu H, Kong H, Li C, et al. Bruton's tyrosine kinase inhibitors in primary central nervous system lymphoma-evaluation of anti-tumor efficacy and brain distribution. *Transl Cancer Res*. 2021;10(5):1975–1983. doi:10.21037/tcr-21-50
97. Grommes C, Pastore A, Palaskas N, et al. Ibrutinib unmasks critical role of Bruton tyrosine kinase in primary CNS Lymphoma. *Cancer Discov*. 2017;7(9):1018–1029. doi:10.1158/2159-8290.CD-17-0613
98. Soussain C, Choquet S, Blonski M, et al. Ibrutinib monotherapy for relapse or refractory primary CNS lymphoma and primary vitreoretinal lymphoma: final analysis of the phase II 'proof-of-concept' iLOC study by the Lymphoma study association (LYSA) and the French oculo-cerebral lymphoma (LOC) network. *Eur J Cancer*. 2019;117:121–130. doi:10.1016/j.ejca.2019.05.024
99. Lv L, Sun X, Wu Y, Cui Q, Chen Y, Liu Y. Efficacy and safety of ibrutinib in central nervous system lymphoma: a PRISMA-compliant single-arm meta-analysis. *Front Oncol*. 2021;11:707285. doi:10.3389/fonc.2021.707285
100. Grommes C, Tang SS, Wolfe J, et al. Phase 1b trial of an ibrutinib-based combination therapy in recurrent/refractory CNS lymphoma. *Blood*. 2019;133(5):436–445. doi:10.1182/blood-2018-09-875732
101. Houillier C, Chabrot CM, Moles-Moreau MP, et al. Rituximab-lenalidomide-ibrutinib combination for relapsed/refractory primary CNS lymphoma: a case series of the LOC network. *Neurology*. 2021;97(13):628–631. doi:10.1212/WNL.0000000000012515
102. Lewis KL, Chin CK, Manos K, et al. Ibrutinib for central nervous system lymphoma: the Australasian lymphoma alliance/MD Anderson cancer center experience. *Br J Haematol*. 2021;192(6):1049–1053. doi:10.1111/bjh.16946
103. Munakata W, Tobinai K. Tirabrutinib hydrochloride for B-cell lymphomas. *Drugs Today*. 2021;57(4):277–289. doi:10.1358/dot.2021.57.4.3264113

104. Okita Y, Kano-Fujiwara R, Nakatsuka S-I, Honma K, Kinoshita M. Histological verification of the treatment effect of tirabrutinib for relapsed/refractory primary central nervous system lymphoma. *Exp Hematol Oncol*. 2021;10(1):29. doi:10.1186/s40164-021-00222-5
105. Yang C, Cui Y, Ren X, et al. Orelabrutinib combined with lenalidomide and immunochemotherapy for relapsed/refractory primary central nervous system lymphoma: a retrospective analysis of case series. *Front Oncol*. 2022;12:901797. doi:10.3389/fonc.2022.901797