Acta Pharmaceutica Sinica B 2024;14(12):5091−5105

Chinese Pharmaceutical Association
Institute of Materia Medica, Chinese Academy of Medical Sciences

Acta Pharmaceutica Sinica B

www.elsevier.com/locate/apsb
www.sciencedirect.com

REVIEW

Emerging interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitors or degraders as therapeutic agents for autoimmune diseases and cancer

Yifan Feng[a,†], Chengjuan Chen[a,†], Anqi Shao[b], Lei Wu[a], Haiyu Hu[a,*], Tiantai Zhang[a,*]

[a]*State Key Laboratory of Bioactive Substance and Function of Natural Medicines Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100050, China*
[b]*Department of Dermatology, Vagelos College of Physicians and Surgeons, Columbia University Irving Medical Center, New York, NY 10032, USA*

Received 6 May 2024; received in revised form 20 June 2024; accepted 26 July 2024

KEY WORDS

IRAK4;
IL-1R/TLRs signal pathway;
NF-κB;
Autoimmune diseases;
IRAK4 inhibitors;
Degraders;
Cancer

Abstract Interleukin-1 receptor-related kinase (IRAK4) is a widely expressed serine/threonine kinase involved in the regulation of innate immunity. IRAK4 plays a pivotal role as a key kinase within the downstream signaling pathway cascades of interleukin-1 receptors (IL-1R) and Toll-like receptors (TLRs). The signaling pathways orchestrated by IRAK4 are integral to inflammatory responses, and its overexpression is implicated in the pathogenesis of inflammatory diseases, autoimmune disorders, and cancer. Consequently, targeting IRAK4-mediated signaling pathways has emerged as a promising therapeutic strategy. Small molecule inhibitors and degraders designed to modulate IRAK4 have shown efficacy in mitigating related diseases. In this paper, we will provide a detailed description of the structure and function of IRAK4, the role of IRAK4 in related diseases, as well as the currently reported small molecule inhibitors and degraders of IRAK4. It is expected to provide new directions for enriching the clinical treatment of inflammation and related diseases.

*Corresponding authors.
E-mail addresses: ttzhang@imm.ac.cn (Tiantai Zhang), haiyu.hu@imm.ac.cn (Haiyu Hu).
[†]These authors made equal contributions to this work.
Peer review under the responsibility of Chinese Pharmaceutical Association and Institute of Materia Medica, Chinese Academy of Medical Sciences.

https://doi.org/10.1016/j.apsb.2024.09.008

1. Introduction

Inflammation is a common clinical-pathological response of the immune system to infection and injury. It serves as the immune system's defensive response to external or internal stimuli. However, an abnormal inflammatory response can be a causative factor[1−3]. Acute inflammatory responses are commonly triggered by viral and bacterial infections or other stimuli, such as disease-causing toxins or chemicals. They are particularly prevalent in patients diagnosed with chronic obstructive pulmonary disease (COPD) or asthma[4,5]. Chronic inflammatory responses can result in prolonged tissue destruction and disruption of systemic homeostasis[6], which contributes to the development of various related diseases, such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), psoriasis, multiple sclerosis (MS), and several others[7−10]. The association between chronic inflammation and cancer development has been well-established, as there is an abundance of inflammatory factors present at the location of malignant tumors[11], the production of these factors is induced through various signaling pathways, promoting tumor growth, metastasis, immunosuppression, and chemotherapy resistance[12,13].

TLRs are a family of transmembrane pattern recognition receptors (PRRs) that recognize specific signaling molecules produced by the body in response to stimulation by microorganisms or endogenous substances[14−17]. IL-1R can be activated by interleukin-1 (IL-1) to transmit inflammatory signals and initiate a cascade amplification of inflammatory responses[18,19]. IRAK4, a member of the IRAK family of intracellular serine-threonine kinases, holds a pivotal position as a key signaling node in the IL-1R/TLRs signaling pathway[20], and performs important functions in scaffold and phosphorylation processes[21,22]. The overexpression or activation of IRAK4 can result in the dysregulation of signaling pathways, which can lead to chronic inflammation in damaged tissues. Moreover, abnormalities of the signaling pathway can promote cell proliferation and differentiation, which lead to the development and progression of malignant tumors.

Given its involvement in the systemic inflammatory response, IRAK4 has gained recognition as a promising therapeutic target in the treatment of inflammatory diseases, autoimmune diseases, and cancer. Notable advancements have been made in the development of IRAK4 drugs with several candidates reaching different clinical stages. These drugs can be broadly classified into two categories: IRAK4 small-molecule inhibitors and degraders, which are proteolysis-targeting chimeras (PROTACs). Small molecule inhibitors, including PF-06650833, CA-4948, and BAY-1834845 have been developed and demonstrate excellent kinase inhibitory activity and selectivity. Degraders such as KT-474 have been designed to target the degradation of IRAK4, which further hinders scaffold and phosphorylation functions[23]. While noteworthy progress has been made, it is important to note that no drugs targeting IRAK4 are currently available on the market. Therefore, there is a pressing need to develop more promising inhibitors or degraders. In this article, we aim to provide a comprehensive review of the structure and function of IRAK4, signaling pathways mediated by IRAK4, and its relationship with diseases. Additionally, we will focus on the reported IRAK4 inhibitors or degraders, discussing their mechanisms of act and potential as therapeutic agents. A deeper understanding of IRAK4 and its inhibitors will contribute to the advancement of precision medicine and provide better therapeutic options for patients with IRAK4-related diseases.

2. IRAKs family and the structure and function of IRAK4

IRAKs are a class of serine threonine kinases consisting of four members: IRAK1, IRAK2, IRAK3 (IRAKM), and IRAK4[24,25]. They all share similar structural domains, including an N-terminal death domain (DD), a proline/serine/threonine (ProST) domain, a kinase domain (KD), and a C-terminal domain (CD) (except for IRAK4)[26]. The DD at the N-terminus of IRAK proteins plays a crucial role in dimerization and protein-protein interactions. It facilitates the interaction with other proteins containing the DD, such as myeloid differentiation primary response protein 88 (MyD88), an adapter protein in the IL-1R/TLRs pathway[27]. The ProST domain engages in regulating protein-protein interactions and contributes to the overall structural stability of IRAKs, IRAK1, in particular, undergoes phosphorylation events within this region that are mediated by IRAK4[28]. The KD of IRAKs is crucial for their catalytic activity. Within this domain, a conserved lysine residue is crucial for ATP binding and catalytic functions, and its disruption would lead to kinase inactivation, rendering the IRAK protein unable to phosphorylate downstream targets. Furthermore, IRAKs possess a unique tyrosine "gatekeeper" Tyr262, which distinguishes them from other kinase families. This gatekeeper residue helps maintain the active conformation of the protein and contributes to its functional activity. The CD is present in IRAK1, IRAK2, and IRAK3 but is absent in IRAK4. This domain interacts primarily with E3 ubiquitin-protein ligase TNF receptor-associated factor 6 (TRAF6) to initiate downstream nuclear factor-κ-gene binding (NF-κB) and c-Jun NH2-terminal kinase (JNK) activation, which occurs at the Pro−X−Glu−X−(Ar/Ac) motif[27] (Fig. 1).

In the kinase family, IRAK1, consisting of 712 amino acid residues, was initially identified. The key residue Thr209 within the protein is responsible for its kinase activity. Phosphorylation of Thr209 initiates the activation of IRAK1 through a conformational change; however, mutations of Thr209 can lead to a complete loss of kinase activity[29]. IRAK1 plays a significant role in the IL-1R/TLRs signaling pathway, and its kinase activity is essential for the NF-κB pathway. However, the absence or inhibition of IRAK1 does not completely inhibit IL-1/TLR-induced NF-κB signaling[30]. IRAK2, consisting of 590 amino acids, is the second member discovered in its family, which is crucial in the IL-1R/TLRs signaling pathway[31]. IRAK2 has been considered a pseudo kinase due to the presence of asparagine residue rather than aspartic residue in its KD in the past. However, it has been found that the presence of lysine residues in IRAK2 is sufficient to make it active recently. In *in vitro* assays, it is found that IRAK2 can be phosphorylated by IRAK4 by stimulating TLR2. Furthermore, research shows that IRAK2 activates the NF-κB signal pathway through TLR3/4/8, with TLR3 being especially

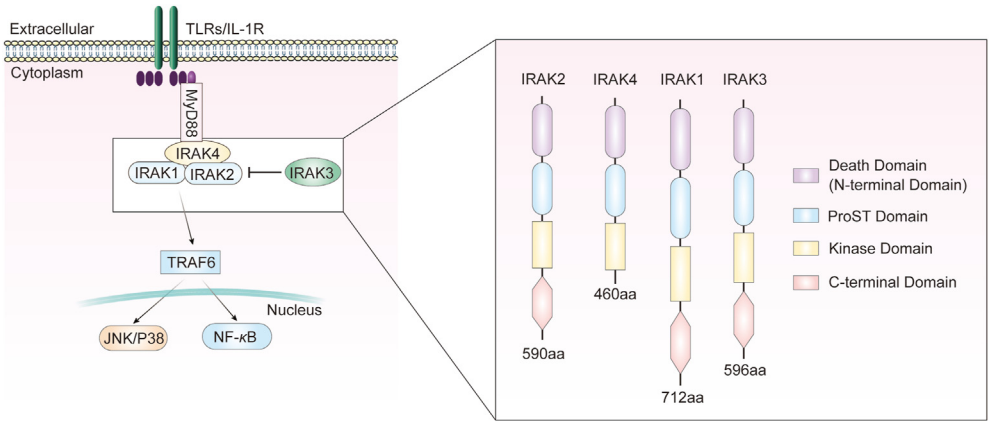


Figure 1 Members of the IRAK family. IRAKs belong to serine-threonine kinases, which consist of four members: IRAK1, IRAK2, IRAK3, and IRAK4. They include an N-terminal domain, a ProST domain, a kinase domain, and a C-terminal domain (except for IRAK4).

significant as it is not found in other IRAKs[31,32]. IRAK2 without DD will not be able to activate the NF-κB pathway. IRAK3 is the third discovered member, composed of 596 amino acids. As a pseudo kinase, its function is unique, and it is believed to play a negative feedback role in the TLR signaling pathway[33]. IRAK4, a recently discovered member of the IRAK family, is regarded as the primary IRAK due to its crucial role as a kinase in IL-1R/TLRs pathways[34]. IRAK4 possesses kinase activity and serves as the initiating factor for signal pathway activation. The downstream cascade signaling can only be initiated after IRAK4 undergoes self-phosphorylation. Furthermore, IRAK4 has a scaffolding function to form a complex with IRAK1 and MyD88, which is also critical for downstream signaling pathways[35]. The overactivation of IRAK4 has been shown to lead to aberrant activation of the NF-κB signaling pathway. Conversely, IRAK4 deficiency has been linked to recurrent childhood infections, while its impact in adults is minimal. These findings suggest that targeting IRAK4 may be safe. Given that IRAK4 is the initiator of phosphorylation within the signaling pathway, it is the most prominent member among the four IRAK family members[36].

IRAK1, IRAK2, and IRAK4 are found in a wide range of human immune cells. They engage in various immune signaling pathways and contribute to the regulation of immune responses. However, IRAK3 has a more restricted expression pattern, mainly limited to monocytes and macrophages[37].

IRAK4 is a protein kinase with a length of 460 amino acids and a molecular weight of approximately 52 kDa. It comprises several distinct domains, including a conserved N-terminal DD, a ProST domain, and a central KD[27,38,39]. The first crystal structure of the IRAK4 was reported simultaneously by Wang et al.[40] and Kuglstatter et al.[38] in 2006. It exhibits a characteristic kinase fold that consists of the N-terminus and C-terminus, with the active site in between. The unique gatekeeper Tyr262 interacts with Glu233, which is situated on helix α-C, forming a hydrogen bond (H-bond). By forming this H-bond, helix α-C is "pulled in," resulting in the maintenance of an active conformation of IRAK4. This conformational change is significant as it eliminates the hydrophobic pocket typically observed at the rear of the ATP-binding site. Glu233 has been exploited in structure-based drug design for the kinase-selective design of IRAK4[41]. Additionally, at the DD, there is an extended Schellman loop whose function remains unknown. Furthermore, in terms of the IRAK4 binding site, a hinge region is formed by Val263, Tyr264, and Met265, which holds significant potential for the design of IRAK4 inhibitors. Notably, the catalytic residue Lys213 is conserved across all catalytically active kinases[23,26] (Fig. 2).

It is worth noting that within the IRAK family, the two catalytic kinases IRAK4 and IRAK1 share an overall sequence similarity of 31%. Particularly in the region surrounding the ATP binding site, they exhibit a remarkable sequence similarity of 93%, indicating a high degree of sequence homology and suggesting potential similarities in ATP binding and catalytic activity. Upon detailed analysis, several differences have been identified between IRAK4 and IRAK1. One notable distinction lies at the top of the ATP binding site, where IRAK4 possesses Met192, while IRAK1 has an isoleucine residue in the same position. Furthermore, in IRAK4, the hinge region comprises Val263, Tyr264, and Met265, whereas IRAK1 features a glycine residue, a phenylalanine residue, and a leucine residue in its hinge region. Despite the high sequence homology, these subtle distinctions in sequence and composition provide a basis for developing selective IRAK4 inhibitors with improved therapeutic potential[41,42].

Currently, studies have reported at least 20 mutations in the IRAK4 gene (C877T, G958T, A86C, Q29P, etc.). Bi-allelic recessive mutations in IRAK4 result in the production of nonfunctional proteins that block the IL-1R/TLRs signaling pathway, making the organism susceptible to infections by pyogenic bacteria, such as Streptococcus pneumonia. In children under 8 years old, the mortality rate is high; however, it decreases significantly after the age of 8 years, and beyond the age of 14 years, these mutations no longer have a significant effect[43]. Current research on mutations in IRAK4 focuses on the pediatric stage[44]. The missense mutation of IRAK4 is poorly studied to date.

Furthermore, studies have shown that the MyD88 L265P mutation forms the myddosome complex with IRAK4 and IRAK1, resulting in the hyperactivation of IRAK4. This hyperactivation has been linked to the pathogenesis of ABC-DLBCL and CLL, among other diseases.

3. IL-1R/TLRs signaling pathway and the role of IRAK4

The IRAK4-mediated IL-1R/TLRs signaling pathway has emerged as a prominent area of research. TLRs recognize pathogen-associated molecular patterns (PAMPs) generated by

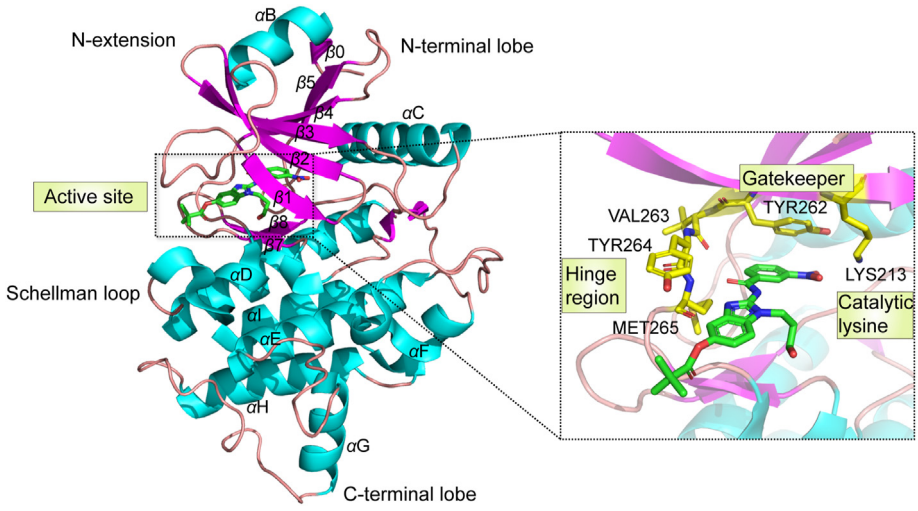


Figure 2 The first crystal structure features of IRAK4. (PDB ID: 2NRU). IRAK4 is a protein kinase with a length of 460 amino acids and a molecular weight of approximately 52 kDa. It includes a conserved N-terminal death domain, a ProST domain, and a kinase domain. The active site is located in between. Tyr262 as gatekeeper is unique, Val263, Tyr264, and Met265 form a kinase hinge region, and Lys213 is a catalytically active kinase.

various exogenous microbial stimuli such as bacteria, fungi, yeast, and viruses[45,46]. Normally, activation of TLRs is strictly regulated to prevent excessive or prolonged inflammation. Negative regulators, such as IRAK3, help to dampen the signaling cascade and maintain immune homeostasis. However, abnormal activation of TLRs triggers infiltration of inflammatory cells, the release of inflammatory factors, and subsequent sustained inflammatory tissue damage[23,47,48]. Currently, 12 members of the TLR family have been identified and described in mice, and 10 members have been characterized in humans[49]. IL-1R recognizes endogenous damage-associated molecular patterns (DAMPs) generated by damaged or injured cells[46,50,51]. When IL-1R binds to DAMPs, it initiates a cascade amplification effect that triggers inflammation, potentially contributing to the development of various diseases[52]. IL-1R and TLRs share a common signaling pathway due to their highly similar cytoplasmic portions, known as the toll/interleukin-1 receptor (TIR) structural domain, which is essential for recruiting the downstream protein MyD88[53–55]. When IL-1R/TLRs are activated by the DAMPs and PAMPs, their TIR structural domains recruit MyD88, which further promotes IRAK4 dimerization, trans-autophosphorylation, and activation, leading to the formation of the myddosome complex[35]. Subsequently, the MyD88–IRAK4 complex recruits the substrate IRAK2, which then brings in IRAK1 for its initial activation. Following this, the autophosphorylation of IRAK1 in its activation loop leads to full activation[31,42,56,57]. As activated IRAK1 recruits and activates the downstream effector TRAF6 (ubiquitin-protein ligase), IRAK1 and TRAF6 dissociate from the complex. This is followed by the binding to transforming growth factor-β-activated kinase 1 (TAK1) and TGF-β-activated kinase 1 binding protein 2 (TAB2), which activate TAK1 and inhibitor of κB-kinase (IKK) complex (IKKα, IKKβ, and IKKγ), as well as mitogen-activated protein kinases (MAPKs). Activated IKK complex further induces NF-κB activation and regulates the transcription of pro-inflammatory genes. The pathway activation is followed by extensive degradation of IRAK1 and TRAF6[54,58]. In addition, activation of MAPKs by TAK1 can further activate JNK and p38, inducing the expression of activator protein 1 (AP-1) genes. The combined effects of NF-κB and AP-1 lead to the production of pro-inflammatory factors (IL-1, IL-6, IL-8, etc.), tumor necrosis factor (TNF), adhesion molecules, etc[45,59,60].

Specifically, the TLR4 signaling pathway involves an additional pathway known as the MyD88 non-dependent-TLR3 signaling pathway[61]. TLR3 is located in intracellular compartments such as endosomes. Upon activation of TLR3, its TIR structural domain recruits and stimulates the downstream junctional protein TIR-domain-containing adapter-inducing IFN-β (TRIF), which can interact with TRIF-associated connector molecules (TRAM) located downstream of TLR4[48]. Upon activation, TRIF partners with TANK-binding kinase 1 (TBK1) and IKKε to form a signaling vesicle, initiating the phosphorylation of interferon regulatory factors 3 and 7 (IRF3 and IRF7). This phosphorylation triggers homodimerization, enabling them to enter the nucleus and stimulate IFN-inducible genes, which ultimately leads to the release of IFN-α and IFN-β[62,63]. Besides the above pathways, TRIF also facilitates the recruitment of TRAF6 in the principal pathway of TLR4 by activating RIP1, thereby ultimately triggering the activation of NF-κB. This pathway is known as the MyD88 non-dependent pathway or TRIF–RIP–IKK pathway[64] (Fig. 3).

It is important to highlight that IRAK3 is predominantly expressed in macrophages and monocytes. Within the IRAK4-mediated signaling pathway, IRAK3 functions to inhibit the dissociation of IRAK1 from MyD88, thereby hindering the subsequent formation of the IRAK1–TRAF6 complex. This negative regulation helps to modulate the immune response[65]. However, recent studies have found that IRAK3 can interact with the MyD88–IRAK4 complex to form myosin super assemblies that mediate TLR7-induced NF-κB activation[33].

IRAK4 plays dual roles in the IL-1R/TLRs signaling pathway. Firstly, it exhibits kinase activity, enabling the phosphorylation of downstream proteins including IKKs and JNK/p38. Secondly, it contributes to the assembly of the multimeric myddosome complex, serving as a scaffolding protein[61]. Scaffolding functions as a platform for facilitating protein-protein interactions, thereby regulating and enhancing signaling pathways *via* positive and negative feedback mechanisms[23]. IRAK4 utilizes its scaffolding

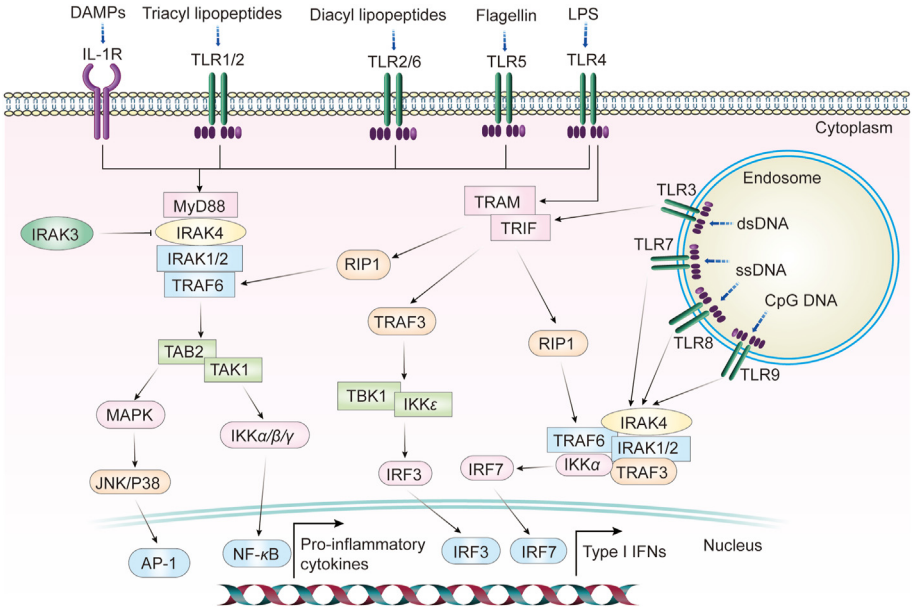


Figure 3 The IL-1R/TLRs signal transduction pathway. When IL-1R/TLRs are activated by DAMPs and PAMPs, MyD88 is recruited, which further recruits IRAK4 dimerization, and the MyD88−IRAK4 complex recruits IRAK2 and IRAK1. As activated IRAK1 recruits and activates TRAF6, IRAK1, and TRAF6 dissociate from the complex, in turn, bind to TAK1 and TAB2 to activate TAK1 and IKKα, IKKβ, and IKKγ, further inducing NF-κB to enter the nucleus to regulate the transcription of pro-inflammatory genes. In addition, activation of MAPKs by TRAF6 can further activate JNK and p38, inducing the expression of AP-1.

function to assemble the myddosome complex, which initiates the activation of TRAF6. This activation leads to the induction of the NF-κB and MAPK pathways, subsequently facilitating the expression of anti-inflammatory factors[42]. In the realm of small molecule inhibitors, although they can inhibit the activity of IRAK4, they may not completely halt the signaling pathway or cytokine production. This highlights the importance of IRAK4's scaffolding function in the development of drug strategies. The emergence of PROTACs in recent years has become a promising approach that can effectively target both kinase activity and scaffolding function, enabling comprehensive inhibition of the relevant signaling pathways, and leading to significant anti-inflammatory and anti-tumor effects[66].

IRAK4 serves as the fundamental protein responsible for the initiation and activation of the comprehensive signaling pathway, whereby the downstream proteins are activated upon IRAK4's autophosphorylation. It is evident that IRAK4 plays an indispensable role in the signaling pathway. Therefore, targeting IRAK4 for drug design holds immense scientific importance. By leveraging its kinase activity and scaffolding function, developing inhibitors and degraders specifically targeting IRAK4 opens up potential therapeutic opportunities for a variety of inflammatory and autoimmune diseases, as well as cancers.

4. The role of IRAK4 in the development of autoimmune diseases and cancer

Normal signaling pathways are intricate networks of molecular interactions that regulate and coordinate various cellular processes. These pathways allow cells to respond to stimuli and maintain homeostasis. However, aberrant IL-1R/TLRs signaling pathways contribute to long-term chronic inflammatory responses[67−69]. When tissue undergoes injury and infection, local antigen-presenting cells (APCs), such as macrophages and dendritic cells (DCs), identify DAMPs or PAMPs and initiate the activation of IL-1R/TLRs on the cell membrane. This activation subsequently triggers the NF-κB signaling pathway, resulting in the release of pro-inflammatory factors such as IL-1β, IL-6, and TNF. These cytokines then facilitate the recruitment and differentiation of $CD4^+$ T cells into Th1/17 cells, ultimately leading to the persistence of inflammatory damage at the tissue site (Fig. 4a).

Inflammatory response has a dual role in cancer, with the potential of anti-tumor immune response on one hand, while potentially promoting tumor growth and metastasis on the other[12,70]. It has been found that NF-κB plays a significant role as an endogenous tumor activator, which is believed to be involved in the pathogenesis of cancer through the IL-1R/TLRs signaling pathway. NF-κB pathway is activated within tumor cells, triggering the production of pro-inflammatory factors. The activation leads to the recruitment of immune cells ($CD4/8^+$ T cells, B cells, macrophages, neutrophils, etc.), which secret various pro-inflammatory factors and provide a rich environment for promoting angiogenesis and tumor growth[71,72]. The activation of IL-1R/TLRs results in IRAK4 overexpression in tumor cells, which shows that targeted inhibition of IRAK4 is an effective therapeutic strategy for hematologic malignancies and other tumors[73] (Fig. 4b).

4.1. IRAK4 and autoimmune disease

RA is an autoimmune disease characterized by inflammatory synovitis, which involves dysregulated immune responses and chronic inflammation in the joints[74,75]. The pathogenesis of RA is still not fully understood, and the mainstream view is that it is a multifactorial mechanism. The pathogenesis of RA involves both innate and adaptive immune responses. In synovial fluid, TLRs on monocytes/macrophages are activated by endogenous molecules,

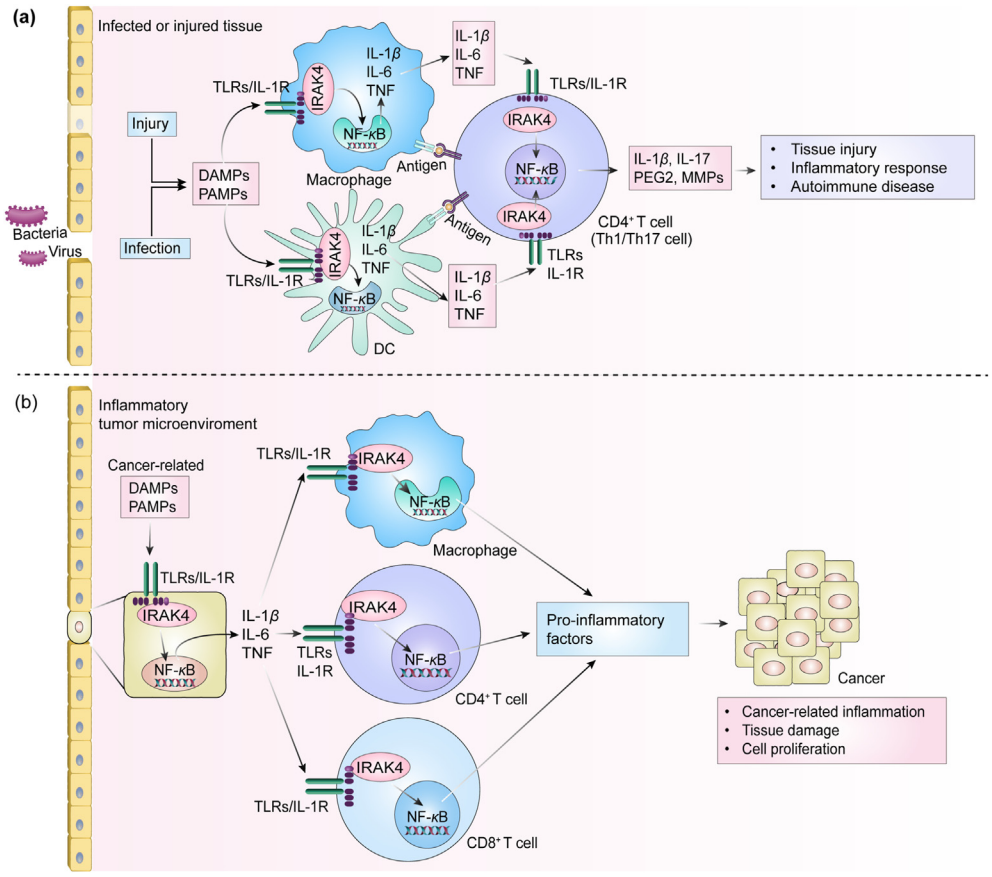


Figure 4 The role of IL-1R/TLRs−IRAK4−NF-κB signal pathway in the development of autoimmune diseases and cancer. (a) When tissues undergo injury and infection, APCs identify DAMPs or PAMPs and initiate the activation of IL-1R/TLRs, subsequently inducing the activation of NF-κB to release IL-1β, IL-6, and TNF, etc., followed by facilitating the recruitment and differentiation of $CD4^+$ T cells, ultimately leading to inflammatory damage at the tissue site. (b) NF-κB pathways are activated within tumor cells, triggering the production of pro-inflammatory factors, followed by immune cells ($CD4/8^+$ T cells, B cells, macrophages, neutrophils, etc.) are recruited, which secret various pro-inflammatory factors and provide a rich environment for promoting angiogenesis and tumor growth.

which induces NF-κB to secrete pro-inflammatory factors[76–78]. This, in turn, activates and induces the TLRs−NF-κB signaling pathway in fibroblast-like synoviocytes (FLS), leading to the expression of inflammatory and chemotactic factors. Consequently, immune cells are recruited, and inflammatory factors are released, ultimately leading to the development of a persistent and chronic inflammatory response[79]. Furthermore, IRAK4 has been shown to play a significant role in the pathogenesis of RA. In experimental models, IRAK4 knockout mice (IRAK4-KO) have exhibited reduced production of NF-κB induction by IL-1β. This suggests that IRAK4 is involved in the activation of NF-κB downstream of IL-1β signaling[80]. In RA patients, high levels of IL-1 can be found in joint fluid, and treatment with IL-1 in animal arthritis models exacerbates symptoms[81]. Moreover, studies have shown that antagonizing the TLR4 signaling pathway can reduce IL-1 secretion and alleviate arthritis symptoms in mice[82,83]. IRAK4 is an essential component of the TLR4 signaling pathway, and interfering with or inhibiting IRAK4 could be a potential strategy for treating chronic arthritic diseases[84,85].

The role of TLR2 and TLR4 signaling pathways has also been investigated in SLE, an autoimmune disease that can manifest as damage to the kidneys, joints, skin, and nervous system[86]. Activation of TLR2/4 signaling pathways can lead to the release of pro-inflammatory cytokines, such as IL-6 and TNF-α, and the production of autoantibodies, which can deposit in various tissues, triggering inflammation and tissue damage[87]. In addition, PAMPs and DAMPs may also be involved in the pathogenesis of SLE by stimulating the TLR7/9 signaling pathways on DCs. Studies have shown that autoimmune-sensitized mice deficient in MyD88, a key adaptor protein in the TLR signaling pathway, exhibit fewer SLE symptoms compared to control animals[88]. Furthermore, IRAK4, which plays a significant role in the pathogenesis of SLE, has been targeted in animal models, demonstrating promising results in reducing disease manifestations and alleviating symptoms. BMS-986126 has been developed for treating SLE and is currently in the preclinical stage[88].

Alcoholic liver disease (ALD) is a class of inflammatory diseases in which ethanol introduces direct damage to hepatocytes and triggers an inflammatory response that induces liver injury[89]. The IL-1R/TLRs signaling pathway participates in the development of this disease[90]. Increased intestinal permeability after alcohol intake leads to the accumulation of low levels of TLR ligand LPS. These ligands can be recognized by IL-1R/TLRs in the liver's Kupffer cells (stellate macrophages), which recruits MyD88 and IRAKs family members to form a complex that induces NF-κB activation, leading to the transcription of inflammatory factors. After transcription, IL-1β is secreted and can function as an endogenous mediator by interacting with the IL-1R

pathway on hepatocytes. This interaction leads to the release of various inflammatory factors and interferons and contributes to the development of diseases such as fatty liver, hepatocyte cell death, and liver injury. It was found that phosphorylated IRAK4 levels were increased in patients with alcohol-induced liver injury compared to normal liver tissue, and administration of IRAK4 inhibitors attenuated ethanol-induced liver injury. Therefore, targeting the IRAK4 activity of hepatocytes may be an effective strategy for the treatment of ALD[91,92].

In addition, inflammatory bowel disease[93], psoriasis[94], neuroinflammatory diseases[41], and Sjogren's syndrome[95]—all disorders shown to involve the IL-1R/TLRs signaling pathway—have also highlighted the importance of IRAK4 as a therapeutic target.

4.2. *IRAK4 and cancer*

Currently, IRAK4 inhibitors have been designed for the treatment of a variety of cancers, such as activated myelodysplastic syndromes (MDS), B-cell diffuse large B-cell lymphoma (ABC-DLBCL), chronic lymphocytic leukemia (CLL)[96,97], and acute myelogenous leukemia (AML), colon, breast, lung cancers[98].

In the activated ABC-DLBCL cells, a mutation in L265P of MyD88 was found to induce a non-dependent oligomerization of the myddosome complex composed of MyD88 and members of the IRAK family[99–101]. This oligomerization leads to IRAK4 activation, which further induces NF-κB activation into the nucleus to regulate the transcription of inflammatory factors and ultimately promote the proliferation and survival of B cells[102,103].

Low-risk MDS encompasses a diverse range of myeloid clonal disorders originating from hematopoietic stem cells. These disorders are characterized by abnormalities in myeloid differentiation and development, resulting in ineffective hematopoiesis, refractory hematopoiesis, hematopoietic failure, and a heightened risk of progression to AML[49]. TLRs are found to be expressed in hematopoietic stem and progenitor cells (HSPCs)[104,105]. Typically, the adaptive immune response induced by the TLR4−IRAK4−NF-κB signaling pathway effectively responds to acute infections or injuries and can regulate basal hematopoiesis[104,106]. However, abnormal or enhanced signaling of TLRs leads to disturbances in the hematopoietic system and causes hematopoietic disorders. For example, in MDS patients, TLRs are found to be overexpressed/mutated, leading to downstream IRAK4 being overexpressed/hyperactivated, affecting the HSPC's function and leading to the development of MDS[107,108].

5. The action characteristic of IRAK4 inhibitors or degraders

Currently, there are two main directions in the development of IRAK4-targeted drugs: IRAK4 inhibitors and PROTACs that act as degraders. For the small molecule inhibitor drug design strategy, the IRAK4 protein folds to form a unique ATP binding "pocket-like" structure, enabling it to bind ATP and fulfill its protein phosphorylation function. Consequently, most inhibitors have been developed to competitively bind to this ATP pocket, thereby inhibiting IRAK4's phosphorylation activity. A potent IRAK4 inhibitor can effectively enter the ATP-binding site, establishing $\pi-\pi$ interactions with the gatekeeper Tyr262 and forming hydrogen-bonding interactions with the hinge region and the catalytic Lys213, which enables it to occupy the ATP-binding site in a highly efficient manner[22].

PROTACs are considered a novel strategy for drug research, which was first reported in 2001 as heterodimeric bifunctional molecules consisting of three components: a portion that binds to the protein of interest (POI), a linker, and a portion that binds to an E3 ubiquitin ligase[109]. PROTAC molecules work by forming a ternary complex between the POI, linker, and E3 ligase[110]. It simultaneously binds to both the E3 ligase and the target protein, bringing them into proximity, which facilitates the transfer of ubiquitin from the E3 ligase to the target protein, labeling it for proteasomal degradation[66,111]. This process effectively hijacks the ubiquitin proteasome system (UPS), leading to the degradation of the ubiquitinated target proteins. In eukaryotic cells, the UPS is a major mechanism for maintaining protein homeostasis by removing and degrading defective and damaged proteins through substrate-specific ubiquitination recognition[112]. By selectively degrading IRAK4, this strategy aims to inhibit its function and disrupt the downstream inflammatory signaling pathway[61]. For example, Kymera's KT-474 can block both kinase activity and scaffolding function by selectively degrading IRAK4 to achieve pathway inhibition and exert good anti-tumor activity.

6. IRAK4 inhibitors or degraders in clinical development

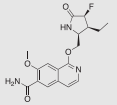
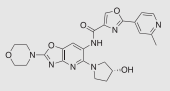
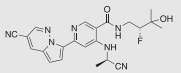
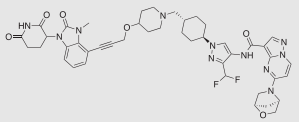
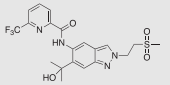
Currently, the research direction of developing drugs targeting IRAK4 is dominated by small-molecule inhibitors. However, in recent years, PROTACs have emerged as an increasingly popular alternative approach for IRAK4 drugs research. According to statistics, over 50 IRAK4 drugs are currently in the clinical trials, with most in the early stages, although none have yet reached the market. In terms of therapeutic indications, the most extensively developed applications are for autoimmune diseases, followed by malignant tumors, and also involved in hidradenitis suppurativa (HS), atopic dermatitis (AD), chronic kidney disease (CKD), etc. (Table 1).

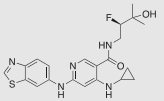
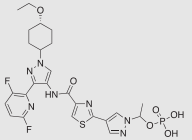
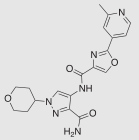
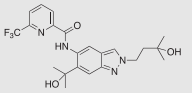
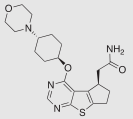
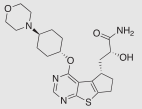
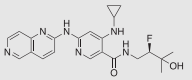
6.1. *IRAK4 inhibitors for the treatment of autoimmune disease*

6.1.1. *Rheumatoid arthritis*

PF-06650833 (Zimlovisertib) was the first IRAK4 inhibitor to enter clinical trials in 2014. In preclinical studies, PF-06650833 demonstrated favorable *in vivo* and *in vitro* ADME characteristics, exhibiting a notable dose-dependent inhibition of LPS-induced TNF[113] and reduced antibody levels in lupus mice. Additionally, it demonstrated a protective effect in CIA rats[114]. Ten out of eleven conducted clinical trials have been completed. Two phase I studies demonstrated that PF-06650833 was well tolerated and safe in healthy subjects and exhibited favorable PK properties. PF-06650833 provided pharmacological evidence firstly by observing IFN levels (increased in SLE) and CRP levels (increased in RA)[115]. Subsequently, Singh et al.[116] revealed that PF-06650833 has rapid absorption following oral administration. The primary route of excretion and its metabolites was through bile, while renal excretion was minimal. A phase II study evaluated the efficacy and safety of PF-06650833 in patients with moderate-to-severe RA who had a poor response to MTX. Results showed that the use of different doses of PF-06650833 was superior to placebo in patients with moderate to severe RA, efficacy was favorable, and the clinical response rate at 12 weeks after administration was consistent with the reported response rate of tofacitinib. The most common AEs were infections and infestations, and there were no deaths[83,114,117]. In addition,

Table 1 The development status of IRAK4 inhibitors in the clinical study.

IRAK4 inhibitor	Target	Mechanism	Structure	Status	Indication	Study number	R&D Company
Zimlovisertib (PF-06650833)	IRAK4	Small molecule inhibitor		Phase II	Rheumatoid arthritis, COVID-19 pneumonia and exuberant inflammation	NCT02224651 (Phase I) NCT02609139 (Phase I) NCT02224651 (Phase I) NCT03308110 (Phase I) NCT02996500 (Phase II) NCT04933799 (Phase II) NCT04575610 (Phase II)	Pfizer
Emavusertib (CA-4948)	IRAK4/FLT3	Small molecule inhibitor		Phase II	Relapsed or refractory hematologic malignancies	NCT05187182 (Phase I) NCT05685602 (Phase I) NCT02478768 (Phase I/II) NCT03328078 (Phase I/II) NCT05669352 (Phase I/II) NCT05178342 (Phase II)	Aurigene/Curis
Edecesertib (GS-5718)	IRAK4	Small molecule inhibitor		Phase II	CLE, RA	NCT04809623 (Phase I) NCT05629208 (Phase II) NCT05165771 (Phase II)	Gilead
EVO-101	IRAK4	Small molecule inhibitor	—	Phase II	Eczema, atopic dermatitis	NCT05579899 (Phase II)	Evommune Inc.
KT-474	IRAK4	PROTAC		Phase II	Atopic dermatitis (AD) or hidradenitis suppurativa (HS)	NCT04772885 (Phase I) NCT06028230 (Phase II) NCT06058156 (Phase II)	Kymera Therapeutics Inc.
Zabedosertib (BAY-1834845)	IRAK4	Small molecule inhibitor		Phase II	Moderate-to-severe atopic dermatitis, psoriasis, pelvic inflammatory disease	NCT03054402 (Phase I) NCT03244462 (Phase I) NCT03493269 (Phase I) NCT05003089 (Phase I) NCT05656911 (Phase II)	Bayer
MY-004	IRAK4	Small molecule inhibitor	Not disclosed	Phase II	Psoriasis, glomerulonephritis (IGA), rheumatoid arthritis	CTR20211804 (Phase I) CTR20221570 (Phase I) CTR20222675 (Phase I) CTR20222849 (Phase I) CTR20230953 (Phase I) CTR20231762 (Phase II)	Shanghai Meiyue Biotechnology Development Co., Ltd.
TQH3821	IRAK4	Small molecule inhibitor	Not disclosed	Phase II (China)	Rheumatoid arthritis	CTR20221068 (Phase I) CTR20231260 (Phase II)	Chia Tai Tianqing Pharmaceutical Group
KT-413	IRAK4	PROTAC	Not disclosed	Phase I	Non-Hodgkin's lymphoma, diffuse large B-cell lymphoma	NCT05233033 (Phase I)	Kymera Therapeutics Inc.
LT-002-158	IRAK4	PROTAC	Not disclosed	Phase I	Atopic dermatitis (AD) or hidradenitis auppurativa (HS), autoimmune	NCT06082323 (Phase I)	Leadingtac Biopharmaceutical Technology Co., Ltd.

					diseases		
BMS-978299	IRAK4	Small molecule inhibitor		Phase I	Immune disorders	–	Bristol-Myers Squibb
R835 (IRAK4/1 dual inhibitors)	IRAK4/1	Small molecule inhibitor	Not disclosed	Phase I	Inflammatory diseases	–	Rigel
R289 (IRAK4/1 dual inhibitors)	IRAK4/1	Small molecule inhibitor		Phase I	LR-MDS	NCT05308264 (Phase I/II)	Rigel
AS-2444697	IRAK4	Small molecule inhibitor		Phase I	Chronic kidney disease (CKD)	–	Astellas Pharma Inc.
BAY-1830839	IRAK4	Small molecule inhibitor		Phase I	Inflammatory diseases, rheumatoid arthritis	NCT05003089 (Phase I)	Bayer
AZD6793	IRAK4	Inhibitor	Not disclosed	Phase I	Inflammatory diseases	NCT05662033 (Phase I)	AstraZeneca
AK-179	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Inflammatory diseases	–	Vernalis
GS-6791	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Rheumatoid arthritis, inflammatory diseases	–	Gilead Sciences Inc.
ND-2110	IRAK4	Small molecule inhibitor		Pre-clinical	Rheumatoid arthritis, diffuse large B-cell lymphoma	–	Nimbus Therapeutics LLC
ND-2158	IRAK4	Small molecule inhibitor		Pre-clinical	Inflammatory diseases, diffuse large B-cell lymphoma	–	Nimbus Therapeutics LLC
ND-346	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Autoimmune disease	–	Nimbus Therapeutics LLC
AU-2807	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Diffuse large B-cell lymphoma	–	Aurigene
PF-05388169	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Rheumatoid arthritis	–	Pfizer
BMS-986126	IRAK4	Small molecule inhibitor		Pre-clinical	Systemic lupus erythematosus	–	BMS
BMS-986236	IRAK4	Small molecule inhibitor	Not disclosed	Pre-clinical	Inflammatory diseases	–	BMS

PF-06650833 was also used for severe inflammation caused by COVID-19. Although PF-06650833 has a very satisfactory therapeutic effect on autoimmune diseases, there is also a high clearance rate (rat $t_{1/2}$ is 0.6 h) that can lead to the momentary disappearance of the inhibitory effect on IRAK4.

GS-5718 (Edecesertib) is an IRAK4 inhibitor used to treat RA and CLE. Pharmacokinetic studies conducted in humans demonstrated that GS-5718 has a median half-life of 25−33 h, with a steady state reached after 5−7 days of administration. Co-administration of GS-5718 with food did not significantly affect its exposure. However, when used in combination with omeprazole, GS-5718 exposure was reduced. Overall, the administered doses were well tolerated[83,118]. The above data supports GS-5718 for further development in inflammatory diseases.

6.1.2. *Systemic lupus erythematosus*

BMS-986126 is the first IRAK4 inhibitor studied in a lupus erythematosus mouse model. It exhibits remarkable selectivity in inhibiting TLR2-induced IL-6, TLR7-induced IL-6 and IFN-α, TLR9-induced IFN-α, as well as TLR7-induced skin inflammation *in vitro*. However, it does not demonstrate inhibitory effects on TLR4-induced IL-6 and TLR3-induced cytokines. Furthermore, BMS-986126 demonstrated the ability to inhibit cytokine production triggered by IL-1β and IL-18. Due to the association of TLR7 and TLR9 with diseases such as lupus and psoriasis, Dudhgaonkar et al.[119] conducted studies using the MRL/Lpr model and the NZB/NZW model of lupus. BMS-986126 showed strong therapeutic efficacy, particularly by inhibiting the expression of the iconic regulatory genes IFIT1 and MX1 in lupus, indicating that BMS-986126 can serve as a new treatment method for lupus patients. In addition, the combined use of BMS-986126 and prednisolone enhances the effect by 10-fold[119]. However, the absence of a substantial inhibitory effect of BMS-986126 on cytokines in human PBMCs is attributed to the activation of type-I interferon (IFN) production through the TRIF-dependent pathway. These findings indicate that the TRIF pathway may play a crucial regulatory role in these responses, specifically in human cells.

6.1.3. *Eczema and atopic dermatitis*

EVO-101 is a heterocyclic IRAK4 inhibitor. It is currently in phase II trials for treating eczema and atopic dermatitis[20]. In March 2022, a phase I study for the treatment of skin disorders was conducted. Following this, in September 2022, a phase II study was initiated to evaluate the efficacy and safety of EVO-101 for treating mild-to-moderate atopic dermatitis. This study involved the application of EVO-101 Topical Cream at a concentration of 0.1%, administered twice daily for 8 weeks.

BAY-1834845 (Zabedosertib) and BAY-1830839 are highly potent, highly selective IRAK4 inhibitors developed by Bayer, each characterized by a remarkable PK profile. Both clinical compounds have shown significant inhibitory effects on IL-1R/TLRs-induced inflammatory factors[120]. Currently, BAY-1834845 is in phase II for the treatment of AD, with five clinical studies conducted to date; four of these studies have been completed, including a phase I study for the treatment of pelvic infection. BAY-1830839 is currently in phase I for the treatment of RA and inflammatory disease[83].

6.1.4. *Chronic kidney disease*

AS2444697 holds promise as a therapeutic agent for chronic kidney disease (CKD) and is currently in phase I. AS2444697 exhibited low induction potential for CYP3A4 and CYP1A2 enzymes and demonstrated excellent metabolic stability in human and rat liver microsomes. Additionally, AS2444697 had low plasma clearance and high oral bioavailability, indicating efficient absorption[121]. Furthermore, AS2444697 was evaluated in 5/6 nephrectomized (Nx) rats (CKD model) and showed that urinary protein excretion was significantly reduced in a dose-dependent manner, and inflammatory factors produced by nephritis were significantly inhibited[122]. However, further studies are needed to assess its efficacy and safety in inflammatory functions.

6.2. *IRAK4 inhibitors for the treatment of cancer*

CA-4948 (Emavusertib) is the first IRAK4 inhibitor used in malignant tumors. One noteworthy feature of CA-4948 is that it has an inhibitory effect on FLT3, a tyrosine-protein kinase receptor. CA-4948 displayed favorable ADME and PK properties and exhibited tumor growth inhibition in relevant tumor models[123]. Additionally, in toxicity studies, CA-4948 exhibited satisfactory tolerance[124]. In April 2021, CA-4948 received orphan drug designation from the FDA for the treatment of acute myeloid leukemia (AML) and myelodysplastic syndromes (MDS). To date, CA-4948 has been involved in six clinical studies evaluating its potential in treating various malignant tumors, such as esophageal cancer, metastatic melanoma, and gastric cancer. A phase I/IIa study demonstrated favorable tolerability and efficacy in patients with relapsed/refractory (R/R) AML and high-risk MDS (HR-MDS), especially in patients with U2AF1/SF3B1/FLT3 mutations. This indicates the potential suitability of CA-4948 for combination therapy[125]. In patients with R/R NHL, the $t_{1/2}$ was approximately 6 h, and the exposure exhibited a correlation with the dosage. PD data showed decreased secretion of NF-κB-related factors such as IL-6 following TLR stimulation *in vitro*[126]. Subsequently, synergistic inhibition of B-cell NHL was found in a preclinical mouse model using a combination of CA-4948 with a BTK inhibitor. Hence, Joffe et al.[127] combined CA-4948 with ibrutinib in patients with relapsed or refractory malignant hematological disorders, finding that the combination was both well-tolerated and efficacious. The above-mentioned evidence demonstrated the therapeutic efficacy of IRAK4 inhibitors in B-cell lymphoma and suggests its potential to overcome resistance to BTK inhibitors[128]. Additionally, CA-4948 shows promising results in a study treating melanoma brain metastasis (MBM), highlighting IRAK-4 as a potent candidate for targeted therapy against MBM[129]. Monotherapy with CA-4948 significantly reduced the proliferation of invasive MBM, improving survival rates[130]. In addition, CA-4948 has also been utilized in combination with trastuzumab in the treatment of untreated, unresectable gastroesophageal cancer[131]. The remarkable therapeutic efficacy of CA-4948 in a broad spectrum of malignant tumors underscores the need for further clinical and translational evaluation.

ND-2158 and ND-2110 are two novel IRAK4 inhibitors for malignant hematomas. *In vitro* experiments have shown that both inhibitors can suppress LPS-induced TNF production, alleviate collagen-induced arthritis, and prevent gout formation in mouse models. Research has found that 30% of ABC-DLBCL cases carry the L265P mutation of MyD88[132]. Hence, in the ABC-DLBCL xenograft model, IRAK4 inhibitors not only inhibit tumor growth as a single agent but also produce a synergistic effect when used in combination with BTK inhibitors. However, the inhibitors are not effective against ABC-DLBCL strains with MyD88 mutations other than L265P[133]. In another study, ND2158 significantly reduces the proliferation of CLL cells in a dose-

dependent manner, with consistent effects across both MYD88-mutated (3%) and unmutated cases[97]. However, it also accelerates the exhaustion of effector $CD8^+$ T cells simultaneously and has a moderate negative impact on tumor suppression. Thus, combining it with drugs that improve T-cell function may improve therapeutic outcomes.

Besides, Rigel's R289 and Aurigene's AU-2807, though still in the preclinical phase, are being developed to treat malignant tumors.

6.3. IRAK1/4 dual inhibitors

R835 is an IRAK1/4 dual inhibitor. In the preclinical study, R835 demonstrated a dose-dependent inhibition of cytokine production induced by LPS and IL-1β. The administration of R835 demonstrated significant suppression in knee edema and pain in the human gouty arthritis rat model. Additionally, in CIA, R835 exhibited a substantial inhibitory effect that effectively blocked the occurrence and progression of the disease[134]. Most notably, R835 works by blocking LPS/TLR4 signaling to inhibit inflammatory cytokines[135]. R835 also dose-dependently reduced TLR7-induced cytokine production and alleviated the progression of lupus-like disease in mice by reducing proteinuria, blood urea nitrogen, and autoantibody levels, as well as reversing renal pathology[136]. A phase I study in healthy subjects showed that R835 was well tolerated. Oral exposure was dose-dependent with rapid steady-state arrival after BID administration[137]. R835 is the initial dual IRAK1/4 inhibitor in clinical development, which emerges as a prospective drug candidate for clinical application.

R289 is a prodrug of R835. Phase Ib study of R289 (NCT05308264) is recruiting patients with lower-risk MDS who are refractory or resistant to prior therapies to date. The primary endpoint of the study is to assess the safety of R289, and the secondary endpoints are to assess efficacy and pharmacokinetic properties[83].

6.4. IRAK4 PROTAC degrader

KT-474 is the first potentially best-in-class, highly selective heterobifunctional IRAK4 degrader for the treatment of atopic dermatitis, hidradenitis suppurativa, and rheumatoid arthritis. KT-474 consists of an E3 ligase cereblon (CRBN) ligand, a linker, and an IRAK4 ligand. Upon the formation of the ternary complex of KT-474 with CRBN and IRAK4, IRAK4 is ubiquitylated for proteasomal degradation, thereby blocking IL-1R/TLRs signaling pathways. In preclinical studies, KT-474 exhibited potent anti-inflammatory activity and outperformed IRAK4 inhibitors in numerous preclinical *in vivo* models of immune inflammation. A phase I trial showed that IRAK4 degradation was observed in healthy volunteers (HVs) and patients with moderate to severe HS and AD. In addition, improved skin lesions and decreased pro-inflammatory cytokines were observed. No drug-related infections were identified in this trial, which was found to be safe and well tolerated. This trial is the first clinical trial to publish results for an IRAK4 degrader, providing a potential option for the treatment of HS and AD, which will be further confirmed in phase II clinical trial[138–140]. The structure of KT-474 was disclosed recently.

LT-002-158 is another PROTACs degrader developed by Leadingtac Biopharmaceutical Technology Co., Ltd. It is currently under phase I for the treatment of pyogenic sweating, atopic dermatitis, and autoimmune diseases. The IND for tablets of this degrader was accepted by CDE, which is the first domestic and the second global IRAK4 degrader after Kymera's KT-474. In preclinical animal models, LT-002-158 has demonstrated significant activity in improving skin inflammatory symptoms and a favorable safety profile. One clinical study is currently ongoing.

7. Limitations and challenges

Small molecule inhibitors and degraders act by blocking the active site of IRAK4 and degrading IRAK4, respectively. Therefore, it is imperative to consider potential adverse effects that could arise from excessive inhibition of IRAK4. In a study on the efficacy of PF-06650833 in treating rheumatoid arthritis in patients with inadequate response to methotrexate, it was observed that infections were the most prevalent drug-related adverse events, with no recorded fatalities[117]. One case of liver toxicity occurred in 1/39 (2.56%)[141]. In a phase I/IIa study on the combination of different doses of CA-4948 with azacitidine or venetoclax for patients with R/R AML/HR-MDS, the FDA requested a suspension of recruitment of participants due to the death of a patient who experienced rhabdomyolysis in addition to several other conditions. It is worth noting that CA-4948 acts as a dual inhibitor of IRAK4/FLT3, suggesting that the adverse events observed in the study may also be related to the FLT3[142]. KT-474, as the first milestone IRAK4 degrader, has no dose-limited toxicity or severe adverse reactions reported in clinical studies on healthy volunteers and patients with AD/HS. The most common AE is mild headache, but no significant dose correlation was observed. Atypical cardiac side effects (mild delayed QT interval) were observed, which returned to normal after a week, with no dose correlation. In subsequent studies, it was found that these phenomena were attributed to KY-474's mild inhibition of the K^+ channel subunit hERG through an unknown mechanism, which was not observed in other studies and has a suggestive effect on the development of PROTACs[139]. This may all be due to the off-target properties of the drug. Moreover, since the amino acid sequences of the KD of IRAK1 and IRAK4 are highly homologous, it is unavoidable that the IRAK4 inhibitors designed to be obtained may have inhibitory effects on IRAK1. Dual IRAK1/4 inhibitors, such as R835 and R289 developed by Rigel, have been reported, and no serious clinical side effects have been detected in clinical studies.

Although no resistance data related to IRAK4 inhibitors or degraders have been reported, as kinase inhibitors, resistance may occur in the future due to active site mutations and other reasons. Further, due to the kinase and scaffolding effects of IRAK4, traditional small molecule inhibitors cannot completely block all functions of IRAK4. Therefore, IRAK4 degradation agents have been developed in recent years, and KT-474 is the fastest degradation agent in the development stage. According to the study, the signaling pathway can be blocked completely and selectively by degrading IRAK4.

8. Conclusion and perspectives

In response to various stimuli, the body initiates inflammation as a protective defense mechanism. However, when inflammation becomes abnormal and uncontrolled, it can lead to tissue damage and contribute to the development of associated diseases. IRAK4-mediated IL-1R/TLRs signaling pathway plays an indispensable role in the occurrence and development of associated diseases. Thus, targeted inhibition of IRAK4 emerges as a promising therapeutic strategy.

Many pharmaceutical organizations have invested in the development of IRAK4 drugs. So far, more than 50 kinds of IRAK4 inhibitors or degraders have entered the clinical stage. The IRAK4 inhibitor PF-06650833 entered the clinic for the first time in 2014 for the treatment of rheumatoid arthritis; the development of degraders like KT-474 is also very promising. In addition, a large number of research articles and patents continue to work towards discovering novel IRAK4 inhibitors or degraders, contributing greatly to developing more drugs for IRAK4. Among reported IRAK4 inhibitors, we have found several phenomena: (1) The amide side chain is necessary for activity, which mainly interacts with the hinge region (Val263, Tyr264, and Met265) in the active pocket; (2) The introduction of appropriate lengths of polar side chains and fluorine atoms can improve the permeability, PK/PD properties, and druggability; (3) The presence of aromatic groups will form significant $\pi-\pi$ stacking interactions with gatekeeper Tyr262; (4) The introduction of appropriate heteroatoms can improve the solubility. Finally, based on the assistance of the molecular docking model and the others, single heterocyclic scaffolds, bicyclic heteroatom scaffolds, or tricyclic thickening scaffolds were selected to assemble the novel IRAK4 inhibitors. Although degraders can have a more complete inhibition of IRAK4-mediated signaling pathways, there are not many articles or patents in this field. Among the reported degraders, CRBN ligands are the most utilized ligands for E3 ligase, and a few use MDM2 ligands or VHL ligands. Both flexible and rigid linkers have been used in the design of degraders. Based on the above analysis, although many have been reported, no drugs against IRAK4 targets are on the market to date, hence, developing inhibitors and degraders with significant anti-inflammatory or anti-tumor activity is still challenging.

IRAK4 is a crucial component of the innate immune system, and its absence or inhibition does not result in recurrent infections in adults, highlighting its significance as a potential therapeutic target. Despite the promising therapeutic potential of IRAK4 small molecule inhibitors in various diseases, there is a need for further refinement to enhance their selectivity and minimize off-target effects. Addressing these challenges will be essential for the advancement of IRAK4 drug development in the future.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (82293684 and 82293680), the National Key R & D Program of China (2020YFA0908004), CAMS Innovation Fund for Medical Science of China (2022-I2M-1-014).

Author contributions

Yifan Feng: Writing − review & editing, Writing − original draft, Project administration, Methodology, Investigation, Data curation, Conceptualization. Chengjuan Chen: Writing − original draft, Investigation, Funding acquisition, Data curation, Conceptualization. Anqi Shao: Investigation. Lei Wu: Investigation. Haiyu Hu: Writing − review & editing, Conceptualization. Tiantai Zhang: Writing − review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Fullerton JN, Gilroy DW. Resolution of inflammation: a new therapeutic frontier. *Nat Rev Drug Discov* 2016;**15**:551−67.
2. Medzhitov R. Origin and physiological roles of inflammation. *Nature* 2008;**454**:428−35.
3. Medzhitov R. The spectrum of inflammatory responses. *Science* 2021;**374**:1070−5.
4. Varela ML, Mogildea M, Moreno I, Lopes A. Acute inflammation and metabolism. *Inflammation* 2018;**41**:1115−27.
5. Cuzzocrea S, Reiter RJ. Pharmacological actions of melatonin in acute and chronic inflammation. *Curr Top Med Chem* 2002;**2**:153−65.
6. Jogpal V, Sanduja M, Dutt R, Garg V. Tinku. Advancement of nanomedicines in chronic inflammatory disorders. *Inflammopharmacology* 2022;**30**:355−68.
7. Shi GN, Zhou Y, Liu WS, Chen CJ, Wei YZ, Yan XL, et al. Bone-derived MSCs encapsulated in alginate hydrogel prevent collagen-induced arthritis in mice through the activation of adenosine $A_{2A/2B}$ receptors in tolerogenic dendritic cells. *Acta Pharm Sin B* 2023;**13**:2778−94.
8. Suzuki K. Chronic inflammation as an immunological abnormality and effectiveness of exercise. *Biomolecules* 2019;**9**:223.
9. Cain D, Kondo M, Chen H, Kelsoe G. Effects of acute and chronic inflammation on B-cell development and differentiation. *J Invest Dermatol* 2009;**129**:266−77.
10. Shao S, Chen CJ, Shi GN, Zhou Y, Wei YZ, Wu L, et al. JAK inhibition ameliorated experimental autoimmune encephalomyelitis by blocking GM-CSF-driven inflammatory signature of monocytes. *Acta Pharm Sin B* 2023;**13**:4185−201.
11. Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002;**420**:860−7.
12. Grivennikov SI, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010;**140**:883−99.
13. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature* 2008;**454**:436−44.
14. Jin M, Fang J, Wang JJ, Shao X, Xu SW, Liu PQ, et al. Regulation of toll-like receptor (TLR) signaling pathways in atherosclerosis: from mechanisms to targeted therapeutics. *Acta Pharmacol Sin* 2023;**44**:2358−75.
15. Ospelt C, Gay S. TLRs and chronic inflammation. *Int J Biochem Cel Biol* 2010;**42**:495−505.
16. Fitzgerald KA, Kagan JC. Toll-like receptors and the control of immunity. *Cell* 2020;**180**:1044−66.
17. Duan T, Du Y, Xing C, Wang HY, Wang RF. Toll-like receptor signaling and its role in cell-mediated immunity. *Front Immunol* 2022;**13**:812774.
18. Dinarello CA. Overview of the IL-1 family in innate inflammation and acquired immunity. *Immunol Rev* 2018;**281**:8−27.
19. Boraschi D, Italiani P, Weil S, Martin MU. The family of the interleukin-1 receptors. *Immunol Rev* 2018;**281**:197−232.
20. Castelo-Soccio L, Kim H, Gadina M, Schwartzberg PL, Laurence A, O'Shea JJ. Protein kinases: drug targets for immunological disorders. *Nat Rev Immunol* 2023;**23**:787−806.
21. Ferrao R, Zhou H, Shan Y, Liu Q, Li Q, Shaw DE, et al. IRAK4 dimerization and *trans*-autophosphorylation are induced by Myddosome assembly. *Mol Cel* 2014;**55**:891−903.
22. De Nardo D, Balka KR, Cardona Gloria Y, Rao VR, Latz E, Masters SL. Interleukin-1 receptor-associated kinase 4 (IRAK4) plays a dual role in myddosome formation and Toll-like receptor signaling. *J Biol Chem* 2018;**293**:15195−207.
23. Bai YR, Yang WG, Hou XH, Shen DD, Zhang SN, Li Y, et al. The recent advance of interleukin-1 receptor associated kinase 4 inhibitors for the treatment of inflammation and related diseases. *Eur J Med Chem* 2023;**258**:115606.
24. Su LC, Xu WD, Huang AF. IRAK family in inflammatory autoimmune diseases. *Autoimmun Rev* 2020;**19**:102461.

25. Flannery S, Bowie AG. The interleukin-1 receptor-associated kinases: critical regulators of innate immune signalling. *Biochem Pharmacol* 2010;**80**:1981−91.
26. Patra M, Choi S. Recent progress in the molecular recognition and therapeutic importance of interleukin-1 receptor-associated kinase 4. *Molecules* 2016;**21**:1529.
27. Lasker MV, Gajjar MM, Nair SK. Cutting edge: molecular structure of the IL-1R-associated kinase-4 death domain and its implications for TLR signaling. *J Immunol* 2005;**175**:4175−9.
28. Jain A, Kaczanowska S, Davila E. IL-1 receptor-associated kinase signaling and its role in inflammation, cancer progression, and therapy resistance. *Front Immunol* 2014;**5**:553.
29. Kollewe C, Mackensen AC, Neumann D, Knop J, Cao P, Li S, et al. Sequential autophosphorylation steps in the interleukin-1 receptor-associated kinase-1 regulate its availability as an adapter in interleukin-1 signaling. *J Biol Chem* 2004;**279**:5227−36.
30. Thomas JA, Allen JL, Tsen M, Dubnicoff T, Danao J, Liao XC, et al. Impaired cytokine signaling in mice lacking the IL-1 receptor-associated kinase. *J Immunol* 1999;**163**:978−84.
31. Kawagoe T, Sato S, Matsushita K, Kato H, Matsui K, Kumagai Y, et al. Sequential control of toll-like receptor-dependent responses by IRAK1 and IRAK2. *Nat Immunol* 2008;**9**:684−91.
32. Keating SE, Maloney GM, Moran EM, Bowie AG. IRAK-2 participates in multiple toll-like receptor signaling pathways to NFκB *via* activation of TRAF6 ubiquitination. *J Biol Chem* 2007;**282**:33435−43.
33. Kobayashi K, Hernandez LD, Galán JE, Janeway CA Jr, Medzhitov R, Flavell RA. IRAK-M is a negative regulator of toll-like receptor signaling. *Cell* 2002;**110**:191−202.
34. Suzuki N, Suzuki S, Duncan GS, Millar DG, Wada T, Mirtsos C, et al. Severe impairment of interleukin-1 and toll-like receptor signalling in mice lacking IRAK-4. *Nature* 2002;**416**:750−6.
35. Motshwene PG, Moncrieffe MC, Grossmann JG, Kao C, Ayaluru M, Sandercock AM, et al. An oligomeric signaling platform formed by the toll-like receptor signal transducers MyD88 and IRAK-4. *J Biol Chem* 2009;**284**:25404−11.
36. Kawagoe T, Sato S, Jung A, Yamamoto M, Matsui K, Kato H, et al. Essential role of IRAK-4 protein and its kinase activity in Toll-like receptor-mediated immune responses but not in TCR signaling. *J Exp Med* 2007;**204**:1013−24.
37. Wesche H, Gao X, Li X, Kirschning CJ, Stark GR, Cao Z. IRAK-M is a novel member of the Pelle/interleukin-1 receptor-associated kinase (IRAK) family. *J Biol Chem* 1999;**274**:19403−10.
38. Kuglstatter A, Villasenor AG, Shaw D, Lee SW, Tsing S, Niu L, et al. Cutting edge: IL-1 receptor-associated kinase 4 structures reveal novel features and multiple conformations. *J Immunol* 2007;**178**:2641−5.
39. Li S, Strelow A, Fontana EJ, Wesche H. IRAK-4: a novel member of the IRAK family with the properties of an IRAK-kinase. *Proc Natl Acad Sci U S A* 2002;**99**:5567−72.
40. Wang Z, Liu J, Sudom A, Ayres M, Li S, Wesche H, et al. Crystal structures of IRAK-4 kinase in complex with inhibitors: a serine/threonine kinase with tyrosine as a gatekeeper. *Structure* 2006;**14**:1835−44.
41. Genung NE, Guckian KM. Small molecule inhibition of interleukin-1 receptor-associated kinase 4 (IRAK4). *Prog Med Chem* 2017;**56**:117−63.
42. Yadav H, Shirumalla RK. Emerging trends in IRAK-4 kinase research. *Mol Biol Rep* 2023;**50**:7825−37.
43. Aluri J, Cooper MA, Schuettpelz LG. Toll-like receptor signaling in the establishment and function of the immune system. *Cells* 2021;**10**:1374.
44. Cooray S, Price-Kuehne F, Hong Y, Omoyinmi E, Burleigh A, Gilmour KC, et al. Neuroinflammation, autoinflammation, splenomegaly and anemia caused by bi-allelic mutations in IRAK4. *Front Immunol* 2023;**14**:1231749.
45. Suzuki N, Suzuki S, Yeh WC. IRAK-4 as the central TIR signaling mediator in innate immunity. *Trends Immunol* 2002;**23**:503−6.
46. Li L, Acioglu C, Heary RF, Elkabes S. Role of astroglial toll-like receptors (TLRs) in central nervous system infections, injury and neurodegenerative diseases. *Brain Behav Immun* 2021;**91**:740−55.
47. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol* 2001;**2**:675−80.
48. Tian H, Wu Z, Chen S, Ao K, Huang W, Yaghmaiean H, et al. Activation of TIR signalling boosts pattern-triggered immunity. *Nature* 2021;**598**:500−3.
49. Paracatu LC, Schuettpelz LG. Contribution of aberrant toll like receptor signaling to the pathogenesis of myelodysplastic syndromes. *Front Immunol* 2020;**11**:1236.
50. Rubartelli A, Lotze MT. Inside, outside, upside down: damage-associated molecular-pattern molecules (DAMPs) and redox. *Trends Immunol* 2007;**28**:429−36.
51. De S, Karim F, Kiessu E, Cushing L, Lin LL, Ghandil P, et al. Mechanism of dysfunction of human variants of the IRAK4 kinase and a role for its kinase activity in interleukin-1 receptor signaling. *J Biol Chem* 2018;**293**:15208−20.
52. Cai Y, Xue F, Quan C, Qu M, Liu N, Zhang Y, et al. A critical role of the IL-1β−IL-1R signaling pathway in skin inflammation and psoriasis pathogenesis. *J Invest Dermatol* 2019;**139**:146−56.
53. Blasius AL, Beutler B. Intracellular toll-like receptors. *Immunity* 2010;**32**:305−15.
54. Wang Z, Wesche H, Stevens T, Walker N, Yeh WC. IRAK-4 inhibitors for inflammation. *Curr Top Med Chem* 2009;**9**:724−37.
55. Gay NJ, Symmons MF, Gangloff M, Bryant CE. Assembly and localization of Toll-like receptor signalling complexes. *Nat Rev Immunol* 2014;**14**:546−58.
56. Lin SC, Lo YC, Wu H. Helical assembly in the MyD88−IRAK4−IRAK2 complex in TLR/IL-1R signalling. *Nature* 2010;**465**:885−90.
57. Dunne A, Carpenter S, Brikos C, Gray P, Strelow A, Wesche H, et al. IRAK1 and IRAK4 promote phosphorylation, ubiquitination, and degradation of MyD88 adaptor-like (Mal). *J Biol Chem* 2010;**285**:18276−82.
58. Li Q, Verma IM. NF-κB regulation in the immune system. *Nat Rev Immunol* 2002;**2**:725−34.
59. Li X. IRAK4 in TLR/IL-1R signaling: possible clinical applications. *Eur J Immunol* 2008;**38**:614−8.
60. Seganish WM. Inhibitors of interleukin-1 receptor-associated kinase 4 (IRAK4): a patent review (2012−2015). *Expert Opin Ther Pat* 2016;**26**:917−32.
61. Pereira M, Durso DF, Bryant CE, Kurt-Jones EA, Silverman N, Golenbock DT, et al. The IRAK4 scaffold integrates TLR4-driven TRIF and MYD88 signaling pathways. *Cell Rep* 2022;**40**:111225.
62. Bahia MS, Kaur M, Silakari P, Silakari O. Interleukin-1 receptor associated kinase inhibitors: potential therapeutic agents for inflammatory- and immune-related disorders. *Cell Signal* 2015;**27**:1039−55.
63. Kuzmich NN, Sivak KV, Chubarev VN, Porozov YB, Savateeva-Lyubimova TN, Peri F. TLR4 signaling pathway modulators as potential therapeutics in inflammation and sepsis. *Vaccines (Basel)* 2017;**5**:34.
64. Lu YC, Yeh WC, Ohashi PS. LPS/TLR4 signal transduction pathway. *Cytokine* 2008;**42**:145−51.
65. Zhou H, Yu M, Fukuda K, Im J, Yao P, Cui W, et al. IRAK-M mediates Toll-like receptor/IL-1R-induced NFkappaB activation and cytokine production. *EMBO J* 2013;**32**:583−96.
66. Liu Z, Hu M, Yang Y, Du C, Zhou H, Liu C, et al. An overview of PROTACs: a promising drug discovery paradigm. *Mol Biomed* 2022;**3**:46.
67. Zarrin AA, Bao K, Lupardus P, Vucic D. Kinase inhibition in autoimmunity and inflammation. *Nat Rev Drug Discov* 2021;**20**:39−63.
68. Lye E, Dhanji S, Calzascia T, Elford AR, Ohashi PS. IRAK-4 kinase activity is required for IRAK-4-dependent innate and adaptive immune responses. *Eur J Immunol* 2008;**38**:870−6.
69. Koziczak-Holbro M, Littlewood-Evans A, Pollinger B, Kovarik J, Dawson J, Zenke G, et al. The critical role of kinase activity of

interleukin-1 receptor-associated kinase 4 in animal models of joint inflammation. *Arthritis Rheum* 2009;**60**:1661−71.
70. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol* 2015;**12**:584−96.
71. Smith MA, Choudhary GS, Pellagatti A, Choi K, Bolanos LC, Bhagat TD, et al. U2AF1 mutations induce oncogenic IRAK4 isoforms and activate innate immune pathways in myeloid malignancies. *Nat Cel Biol* 2019;**21**:640−50.
72. Rhyasen GW, Starczynowski DT. IRAK signalling in cancer. *Br J Cancer* 2015;**112**:232−7.
73. Bennett J, Starczynowski DT. IRAK1 and IRAK4 as emerging therapeutic targets in hematologic malignancies. *Curr Opin Hematol* 2022;**29**:8−19.
74. Smolen JS, Aletaha D, McInnes IB. Rheumatoid arthritis. *Lancet* 2016;**388**:2023−38.
75. Smolen JS, Aletaha D, Barton A, Burmester GR, Emery P, Firestein GS, et al. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;**4**:18001.
76. Nejatbakhsh Samimi L, Farhadi E, Tahmasebi MN, Jamshidi A, Sharafat Vaziri A, Mahmoudi M. NF-κB signaling in rheumatoid arthritis with focus on fibroblast-like synoviocytes. *Autoimmun Highlights* 2020;**11**:11.
77. Sacre SM, Andreakos E, Kiriakidis S, Amjadi P, Lundberg A, Giddins G, et al. The toll-like receptor adaptor proteins MyD88 and Mal/TIRAP contribute to the inflammatory and destructive processes in a human model of rheumatoid arthritis. *Am J Pathol* 2007;**170**:518−25.
78. Samarpita S, Kim JY, Rasool MK, Kim KS. Investigation of toll-like receptor (TLR) 4 inhibitor TAK-242 as a new potential anti-rheumatoid arthritis drug. *Arthritis Res Ther* 2020;**22**:16.
79. Liu T, Zhang L, Joo D, Sun SC. NF-κB signaling in inflammation. *Sig Transduct Target Ther* 2017;**2**:17023.
80. Ferraccioli G, Bracci-Laudiero L, Alivernini S, Gremese E, Tolusso B, De Benedetti F. Interleukin-1β and interleukin-6 in arthritis animal models: roles in the early phase of transition from acute to chronic inflammation and relevance for human rheumatoid arthritis. *Mol Med* 2010;**16**:552−7.
81. Goh FG, Midwood KS. Intrinsic danger: activation of Toll-like receptors in rheumatoid arthritis. *Rheumatol* 2012;**51**:7−23.
82. Abdollahi-Roodsaz S, Joosten LA, Roelofs MF, Radstake TR, Matera G, Popa C, et al. Inhibition of Toll-like receptor 4 breaks the inflammatory loop in autoimmune destructive arthritis. *Arthritis Rheum* 2007;**56**:2957−67.
83. Wiese MD, Manning-Bennett AT, Abuhelwa AY. Investigational IRAK-4 inhibitors for the treatment of rheumatoid arthritis. *Expert Opin Investig Drugs* 2020;**29**:475−82.
84. Huang J, Fu X, Chen X, Li Z, Huang Y, Liang C. Promising therapeutic targets for treatment of rheumatoid arthritis. *Front Immunol* 2021;**12**:686155.
85. Radu AF, Bungau SG. Management of rheumatoid arthritis: an overview. *Cells* 2021;**10**:2857.
86. Chiang EY, Yu X, Grogan JL. Immune complex-mediated cell activation from systemic lupus erythematosus and rheumatoid arthritis patients elaborate different requirements for IRAK1/4 kinase activity across human cell types. *J Immunol* 2011;**186**:1279−88.
87. Lartigue A, Colliou N, Calbo S, Francois A, Jacquot S, Arnoult C, et al. Critical role of TLR2 and TLR4 in autoantibody production and glomerulonephritis in lpr mutation-induced mouse lupus. *J Immunol* 2009;**183**:6207−16.
88. Fillatreau S, Manfroi B, Dörner T. Toll-like receptor signalling in B cells during systemic lupus erythematosus. *Nat Rev Rheumatol* 2021;**17**:98−108.
89. Cohen JI, Chen X, Nagy LE. Redox signaling and the innate immune system in alcoholic liver disease. *Antioxid Redox Signal* 2011;**15**:523−34.
90. Wang H, Zhou H, Zhang Q, Poulsen KL, Taylor V, McMullen MR, et al. Inhibition of IRAK4 kinase activity improves ethanol-induced liver injury in mice. *J Hepatol* 2020;**73**:1470−81.
91. Uesugi T, Froh M, Arteel GE, Bradford BU, Thurman RG. Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice. *Hepatology* 2001;**34**:101−8.
92. Kesar V, Odin JA. Toll-like receptors and liver disease. *Liver Int* 2014;**34**:184−96.
93. Coccia M, Harrison OJ, Schiering C, Asquith MJ, Becher B, Powrie F, et al. IL-1β mediates chronic intestinal inflammation by promoting the accumulation of IL-17A secreting innate lymphoid cells and CD4$^+$ Th17 cells. *J Exp Med* 2012;**209**:1595−609.
94. Chen JQ, Szodoray P, Zeher M. Toll-like receptor pathways in autoimmune diseases. *Clin Rev Allergy Immunol* 2016;**50**:1−17.
95. Low HZ, Witte T. Aspects of innate immunity in Sjögren's syndrome. *Arthritis Res Ther* 2011;**13**:218.
96. Spaner DE, Masellis A. Toll-like receptor agonists in the treatment of chronic lymphocytic leukemia. *Leukemia* 2007;**21**:53−60.
97. Giménez N, Schulz R, Higashi M, Aymerich M, Villamor N, Delgado J, et al. Targeting IRAK4 disrupts inflammatory pathways and delays tumor development in chronic lymphocytic leukemia. *Leukemia* 2020;**34**:100−14.
98. Srivastava R, Geng D, Liu Y, Zheng L, Li Z, Joseph MA, et al. Augmentation of therapeutic responses in melanoma by inhibition of IRAK-1, -4. *Cancer Res* 2012;**72**:6209−16.
99. Zhan C, Qi R, Wei G, Guven-Maiorov E, Nussinov R, Ma B. Conformational dynamics of cancer-associated MyD88-TIR domain mutant L252P (L265P) allosterically tilts the landscape toward homo-dimerization. *Protein Eng Des Sel* 2016;**29**:347−54.
100. Shuai W, Lin P, Strati P, Patel KP, Routbort MJ, Hu S, et al. Clinicopathological characterization of chronic lymphocytic leukemia with MYD88 mutations: L265P and non-L265P mutations are associated with different features. *Blood Cancer J* 2020;**10**:86.
101. Yoon SB, Hong H, Lim HJ, Choi JH, Choi YP, Seo SW, et al. A novel IRAK4/PIM1 inhibitor ameliorates rheumatoid arthritis and lymphoid malignancy by blocking the TLR/MYD88-mediated NF-κB pathway. *Acta Pharm Sin B* 2023;**13**:1093−109.
102. Chaudhary D, Wood N, Romero DL, Robinson SD, Greenwood JR, Shelley M, et al. Synergistic blockade of activated B cell-like DLBCL proliferation with a selective inhibitor of IRAK4 in combination with inhibition of the B-cell receptor signaling network. *Blood* 2013;**122**:3833.
103. Nagel D, Vincendeau M, Eitelhuber AC, Krappmann D. Mechanisms and consequences of constitutive NF-κB activation in B-cell lymphoid malignancies. *Oncogene* 2014;**33**:5655−65.
104. Maratheftis CI, Andreakos E, Moutsopoulos HM, Voulgarelis M. Toll-like receptor-4 is up-regulated in hematopoietic progenitor cells and contributes to increased apoptosis in myelodysplastic syndromes. *Clin Cancer Res* 2007;**13**:1154−60.
105. Wei Y, Dimicoli S, Bueso-Ramos C, Chen R, Yang H, Neuberg D, et al. Toll-like receptor alterations in myelodysplastic syndrome. *Leukemia* 2013;**27**:1832−40.
106. Barreyro L, Chlon TM, Starczynowski DT. Chronic immune response dysregulation in MDS pathogenesis. *Blood* 2018;**132**:1553−60.
107. Ganan-Gomez I, Wei Y, Starczynowski DT, Colla S, Yang H, Cabrero-Calvo M, et al. Deregulation of innate immune and inflammatory signaling in myelodysplastic syndromes. *Leukemia* 2015;**29**:1458−69.
108. Varney ME, Niederkorn M, Konno H, Matsumura T, Gohda J, Yoshida N, et al. Loss of *Tifab*, a del(5q) MDS gene, alters hematopoiesis through derepression of Toll-like receptor−TRAF6 signaling. *J Exp Med* 2015;**212**:1967−85.
109. Ferguson FM, Gray NS. Kinase inhibitors: the road ahead. *Nat Rev Drug Discov* 2018;**17**:353−77.
110. O'Brien Laramy MN, Luthra S, Brown MF, Bartlett DW. Delivering on the promise of protein degraders. *Nat Rev Drug Discov* 2023;**22**:410−27.
111. Chirnomas D, Hornberger KR, Crews CM. Protein degraders enter the clinic—a new approach to cancer therapy. *Nat Rev Clin Oncol* 2023;**20**:265−78.

112. Yao T, Xiao H, Wang H, Xu X. Recent advances in PROTACs for drug targeted protein research. *Int J Mol Sci* 2022;**23**:10328.
113. Lee KL, Ambler CM, Anderson DR, Boscoe BP, Bree AG, Brodfuehrer JI, et al. Discovery of clinical candidate 1-[(2*S*,3*S*,4*S*)-3-Ethyl-4-fluoro-5-oxopyrrolidin-2-yl]methoxy-7-methoxyisoquinoline-6-carboxamide (PF-06650833), a potent, selective inhibitor of interleukin-1 receptor associated kinase 4 (IRAK4), by fragment-based drug design. *J Med Chem* 2017;**60**:5521−42.
114. Winkler A, Sun W, De S, Jiao A, Sharif MN, Symanowicz PT, et al. The interleukin-1 receptor-associated kinase 4 inhibitor PF-06650833 blocks inflammation in preclinical models of rheumatic disease and in humans enrolled in a randomized clinical trial. *Arthritis Rheumatol* 2021;**73**:2206−18.
115. Danto SI, Shojaee N, Singh RSP, Li C, Gilbert SA, Manukyan Z, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of PF-06650833, a selective interleukin-1 receptor-associated kinase 4 (IRAK4) inhibitor, in single and multiple ascending dose randomized phase 1 studies in healthy subjects. *Arthritis Res Ther* 2019;**21**:269.
116. Singh RSP, Dowty ME, Salganik M, Brodfuehrer JI, Walker GS, Sharma R, et al. A phase 1 study to assess mass balance and absolute bioavailability of zimlovisertib in healthy male participants using a ^{14}C-microtracer approach. *Clin Pharmacol Drug Dev* 2022;**11**:815−25.
117. Danto S, Shojaee N, Singh RSP, Manukyan Z, Mancuso J, Peeva E, et al. Efficacy and safety of the selective interleukin-1 receptor associated kinase 4 inhibitor, PF-06650833, in patients with active rheumatoid arthritis and inadequate response to methotrexate. *Arthritis Rheumatol* 2019;**71**(S10):2909.
118. Anderson K, Hsueh CH, Gurtovaya O, Mathur A, Taylor J, Serone A, et al. First-in-human study of GS-5718, an oral IRAK-4 inhibitor, in healthy subjects: pharmacokinetics, safety, tolerability, and assessment of effect of food and acid reducing agents on exposure. *Ann Rheum Dis* 2021;**80**(Suppl):581.
119. Dudhgaonkar S, Ranade S, Nagar J, Subramani S, Prasad DS, Karunanithi P, et al. Selective IRAK4 inhibition attenuates disease in murine lupus models and demonstrates steroid sparing activity. *J Immunol* 2017;**198**:1308−19.
120. Bothe U, Günther J, Nubbemeyer R, Siebeneicher H, Ring S, Bömer U, et al. Discovery of IRAK4 inhibitors BAY1834845 (Zabedosertib) and BAY1830839. *J Med Chem* 2024;**67**:1225−42.
121. Inami H, Mizutani T, Watanabe J, Hayashida H, Ito T, Terasawa T, et al. Design, synthesis, and pharmacological evaluation of *N*-(3-carbamoyl-1*H*-pyrazol-4-yl)-1,3-oxazole-4-carboxamide derivatives as interleukin-1 receptor-associated kinase 4 inhibitors with reduced potential for cytochrome P450 1A2 induction. *Bioorg Med Chem* 2023;**87**:117302.
122. Kondo M, Tahara A, Hayashi K, Abe M, Inami H, Ishikawa T, et al. Renoprotective effects of novel interleukin-1 receptor-associated kinase 4 inhibitor AS2444697 through anti-inflammatory action in 5/6 nephrectomized rats. *Naunyn Schmiedebergs Arch Pharmacol* 2014;**387**:909−19.
123. Booher RN, Samson ME, Xu GX, Cheng H, Tuck DP. Efficacy of the IRAK4 inhibitor CA-4948 in patient-derived xenograft models of diffuse large B cell lymphoma. *Cancer Res* 2017;**77**(S13):1168.
124. Gummadi VR, Boruah A, Ainan BR, Vare BR, Manda S, Gondle HP, et al. Discovery of CA-4948, an orally bioavailable IRAK4 inhibitor for treatment of hematologic malignancies. *ACS Med Chem Lett* 2020;**11**:2374−81.
125. Garcia-Manero G, Winer ES, DeAngelo DJ, Tarantolo SR, Sallman DA, Dugan J, et al. Phase 1/2a study of the IRAK4 inhibitor CA-4948 as monotherapy or in combination with azacitidine or venetoclax in patients with relapsed/refractory (R/R) acute myeloid leukemia or lyelodysplastic syndrome. *J Clin Oncol* 2022;**40**(S16):7016.
126. Younes A, Nowakowski G, Rosenthal A, Leslie L, Tun H, Lunning M, et al. Phase 1 study of CA-4948, a novel inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4) in patients with R/R non-hodgkin lymphoma (NHL). *Cl Lymph Myelom Leuk* 2019;**19**:S256−7.
127. Joffe E, Nowakowski GS, Tun HW, Rosenthal AC, Lunning MA, Ramchandren R, et al. Open-label, dose-escalation, and expansion trial of CA-4948 in combination with ibrutinib in patients with relapsed or refractory hematologic malignancies. *J Clin Oncol* 2022;**40**(S16):7575.
128. Parrondo RD, Iqbal M, Von Roemeling R, Von Roemeling C, Tun HW. IRAK-4 inhibition: emavusertib for the treatment of lymphoid and myeloid malignancies. *Front Immunol* 2023;**14**:1239082.
129. Doonan BP, Roemeling CV, Klippel K, Hoang-Minh L, Mitchell DA. CA-4948 for the treatment of melanoma brain metastasis. *J Clin Oncol* 2022;**40**(S16):2011.
130. Von Roemeling CA, Doonan BP, Klippel K, Schultz D, Hoang-Minh L, Trivedi V, et al. Oral IRAK-4 inhibitor CA-4948 is blood−brain barrier penetrant and has single-agent activity against CNS lymphoma and melanoma brain metastases. *Clin Cancer Res* 2023;**29**:1751−62.
131. Park H, Iglesia M, Pedersen KS, Grierson P, Hu ZI, Suresh R, et al. Phase I trial of CA-4948, an IRAK4 inhibitor, in combination with FOLFOX/PD-1 inhibitor +/− trastuzumab for untreated unresectable gastric and esophageal cancer. *J Clin Oncol* 2022;**40**(S16):TPS4168.
132. Küppers R. IRAK4 inhibition to shut down TLR signaling in autoimmunity and MyD88-dependent lymphomas. *J Exp Med* 2015;**212**:2184.
133. Kelly PN, Romero DL, Yang Y, Shaffer AL 3rd, Chaudhary D, Robinson S, et al. Selective interleukin-1 receptor-associated kinase 4 inhibitors for the treatment of autoimmune disorders and lymphoid malignancy. *J Exp Med* 2015;**212**:2189−201.
134. Lamagna C, Chan M, Tai E, Siu S, Frances R, Yi S, et al. Preclinical efficacy of R835, a novel IRAK1/4 dual inhibitor, in rodent models of joint inflammation. *Ann Rheum Dis* 2020;**79**(Suppl):86.
135. Lamagna C, Gundel C, Chan M, Young C, Braselmann S, Frances R, et al. FRI0016 R835, a novel IRAK1/4 dual inhibitor in clinical development, blocks toll-like receptor 4 (TLR4) signaling in human and mouse. *Ann Rheum Dis* 2020;**79**(Suppl):579.
136. Lamagna C, Chan M, Bagos A, Tai E, Young C, Chen Y, et al. Targeting IRAK1 and 4 signaling with R835, a novel oral small molecule inhibitor: a potential new treatment for systemic lupus erythematosus. *Ann Rheum Dis* 2020;**79**(Suppl):30.
137. Yan L, Tong S, Absalom A, Daas ID, Park G, Taylor V, et al. First-inhuman study of safety, pharmacokinetics and pharmacodynamics of IRAK1/4 inhibitor R835 in healthy subjects. *Ann Rheum Dis* 2020;**79**(Suppl):336.
138. Ackerman L, Acloque G, Bacchelli S, Schwartz H, Feinstein BJ, La Stella P, et al. IRAK4 degrader in hidradenitis suppurativa and atopic dermatitis: a phase 1 trial. *Nat Med* 2023;**29**:3127−36.
139. Ferguson FM. PROTACs reach clinical development in inflammatory skin disease. *Nat Med* 2023;**29**:3006−7.
140. Eccleston A. PROTAC in clinic for autoimmune skin disease. *Nat Rev Drug Discov* 2024;**23**:18.
141. ClinicalTrial.gov. Safety and efficacy of Pf-06650833 in rheumatoid arthritis subjects with inadequate response to methotrexate. Available from: https://clinicaltrials.gov/study/NCT02996500?tab=results#adverse-events, 2020. [Accessed 18 June 2024]. Published: February 27.
142. Garcia-Manero G, Winer ES, DeAngelo DJ, Tarantolo S, Sallman DA, Dugan J, et al. A phase 1/2a study of the IRAK4 inhibitor emavusertib (CA-4948) as monotherapy or combination with azacitidine or venetoclax in relapsed/refractory AML or MDS. *HemaSphere* 2022;**6**:30−1.