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Advances in the Investigation of the Oncological Functions and its Target Therapy of Interleukin-1 Receptor-associated Kinase 1 (IRAK1)

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Abstract:

Interleukin-1 receptor-associated kinase 1 (IRAK1) plays as a pivotal regulator within the innate immune signaling and inflammatory processes. Being a critical component in many signaling pathways, emerging evidence strongly suggests the involvement of IRAK1 in the pathophysiology of cancers, thereby rendering it an attractive target for therapeutic intervention. Notably, selective IRAK1-inhibitory molecules have been identified, opening promising avenues for the therapy of tumor. In this review, we also delve into the challenges and future prospects in this field, emphasizing the importance of gaining a deeper understanding of IRAK1 regulation in tumors and the potential of combination therapies targeting IRAK1.

Keywords:

Interleukin-1 receptor-associated kinase 1 (IRAK1)

Tumor progression

Tumor immunity

IRAK1 inhibitors

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1. Introduction

Nowadays, it is increasingly evident that immune system not only comes into play in tumor suppression, known as cancer immunosurveillance, but also contributes to tumorigenesis and tumor progression [1]. Accumulating evidence highlights the pivotal function of interleukin-1 receptor-associated kinases (IRAKs) family in immune responses as well as its altered expression in different types of cancer. Within the IRAKs, a serine/threonine kinases family, four distinct members are identifiable: IRAK1, IRAK2, IRAK3 (also recognized as IRAK-M), and IRAK4 [2]. It's important to note that among these, only IRAK1 and IRAK4 exhibit kinase activity [3,4]. This review concentrates on the latest progress made in comprehending the significance of IRAK1 in the advancement of tumors as well as potential therapeutic interventions.

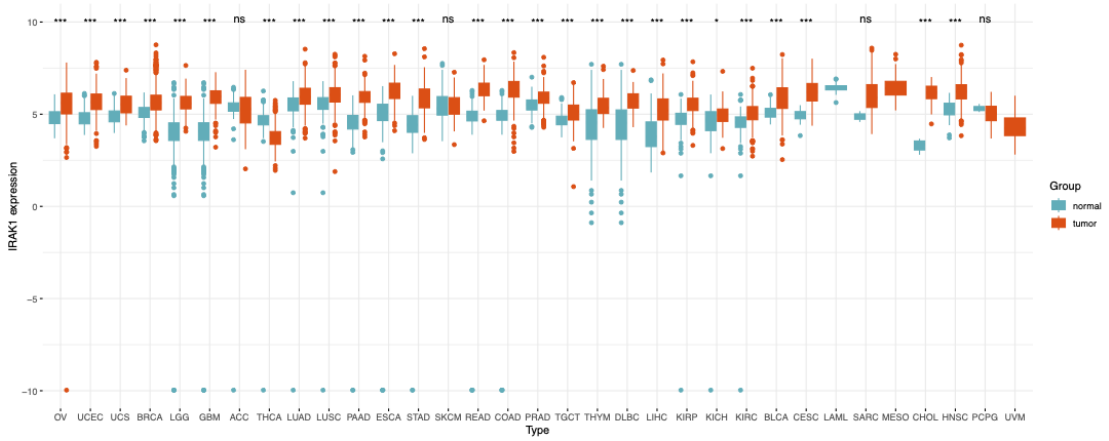

Figure 1. The expression of IRAK1 in different tumors and their paired normal tissues. The dysregulation and aberrant expression of IRAK1 have been subject to analysis across diverse cancer types. Utilizing data from the Cancer Genome Atlas (TCGA) database, it aimed to elucidate IRAK1's potential involvement in various malignancies compared with their corresponding normal tissues. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

2. The expression of IRAK1 and its effects in different cancers

Dysregulation and aberrant activation of IRAK1 have been associated with various effects on tumors (**Figure 1**). The role of IRAK1 in tumor includes promoting tumor growth, survival, inflammation, immune evasion, therapeutic resistance, angiogenesis, and metastasis. Here are some of the effects of IRAK1 in specific tumors.

2.1. Hepatocellular carcinoma

IRAK1 exhibits significant expression in hepatocellular carcinoma (HCC) cell lines and tumor tissues, indicating its feasible involvement in HCC development, which contributes to cancer cell proliferation and the inflammatory tumor microenvironment [5]. The tumor suppressor serine/threonine-protein kinase 4 (STK4) enhances TLR3/4-activated IFN-β production through IRAK1 binding and phosphorylation [6]. This leads to IRAK1 degradation and prevents the development of inflammation-related HCC. Furthermore, Cheng and colleagues pinpointed AKR1B10 as a fresh downstream target of IRAK1, and AKR1B10 is usually used as a biomarker of HCC, underscoring a previously unrecognized relationship between these molecules [7].

2.2. Nasopharyngeal carcinoma

In the context of Nasopharyngeal carcinoma (NPC) metastasis, S100 calcium-binding protein A14 (S100A14) exhibits a suppressive effect on metastasis by facilitating the ubiquitin-mediated degradation of IRAK1, which blocks cellular migration in NPC [8]. Additionally, Liu *et al.* discovered that IRAK1 has potential function in drug resistance and poor prognosis in NPC. Specifically, IRAK1 is essential to the expression of S100A9, and the IRAK1/S100A9 axis contributes to drug resistance and unfavorable outcomes in NPC [9].

2.3. Low-grade glioma

Notably, comprehensive studies have substantiated that the high level of IRAK1 in LGG exerts an oncogenic function by inhibiting cell apoptosis and promoting LGG malignancy [10]. IRAK1 is warranted to enhance the prognosis and treatment outcomes for LGG patients.

2.4. Colorectal cancer

Aberrant expression of IRAK1 in colorectal cancer (CRC) is linked to malignant phenotypes, and targeting its expression could mitigate the inflammatory process and modulate the downregulation of epithelial-mesenchymal transition (EMT) in mice [11,12]. Furthermore, scientists have discovered that the loss of heterogeneous nuclear ribonucleoprotein I (hnRNRI) within the intestinal epithelial cells undermines the immune adaption process in newborns, ultimately leading to colitis and colorectal cancer [13].

2.5. Breast cancer

Research has revealed a substantial decrease in the expression of IRAK1 following neoadjuvant chemotherapy, which aligns with a noticeable reduction in tumor size [13]. In the context of triple-negative breast cancer (TNBC), IRAK1 upregulation confers a growth advantage and contributes to acquired resistance to paclitaxel treatment [14]. Restraining the phosphorylation of IRAK1 has demonstrated increased apoptosis and reduced migration in TNBC [15].

2.6. Prostate cancer

IRAK1 exhibits significant overexpression specifically in prostate cancer (PCa) compared to normal tissues. This overexpression is particularly observed in luminal epithelial cells of Pca [16]. Moreover, IRAK1 is found to exhibit varying expression levels between benign and malignant samples within a patient cohort [17].

2.7. Non-small cell lung cancer

IRAK1 is highly expressed in non-small cell lung cancer (NSCLC) and is considered a new inflammation-related marker [18]. In NSCLC with epidermal growth factor receptor (EGFR) mutation, the IRAK1/NF-κB axis demonstrates a significant role in standing up to EGFR tyrosine kinase inhibitors(TKIs) [19]. Additionally, the expression of IRAK1 in non-tumor cells, such as tumor-associated macrophages (TAMs), can negatively impact the anti-tumor activity against tumor cells [20].

2.8. Endometrial carcinoma

The reduction of IRAK1 expression in endometrial carcinoma (EC) cells led to distinct outcomes: it prompted cell cycle arrest and apoptosis while concurrently restraining cell migration and invasion [21]. Another study uncovered that the transfer of miR-192-5p via specific exosomes derived from TAMs could inhibit the IRAK1/NF-κB signaling pathway, leading to the suppression of tumor formation, inhibition of EMT in EC cells, and promotion of EC cell apoptosis [22].

2.9. Squamous cell carcinomas

Within squamous cell carcinoma (SCC), the pro-oncogenic impact and tumorigenic properties of Desmoglein 2 (Dsg2) are achieved through the alteration of IRAK1 and its downstream target IL-8 [23]. Furthermore, in Oral SCC, miR-146 is up-regulated and acts as an oncogenic molecule [24]. Another significant finding reveals that IRAK1 is transcriptionally upregulated by the chromatin-binding DEK protein, promoting cell survival [25]. In an effort to heighten the sensitivity of chemotherapy-resistant cells to chemotherapy, inhibiting IRAK1 pharmacologically can consider as a potentially effective cytostatic method [26].

2.10. Melanoma

Within melanoma cells, the expression of chemokines and cytokines associated with cancer cell survival, division, and the promotion of angiogenesis strongly correlates with the activation of IRAK1/IRAK4 signaling [27]. Melanoma and its stem cells could respond to the aurora kinase inhibitor CCT137690 because of its effect on a significant decrease in the expression of IRAK1 [28].

2.11. Activated B-cell-like diffuse large B-cell lymphoma

In activated B-cell-like diffuse large B-cell lymphoma (ABC DLBCL) with MyD88 mutation, IRAK1 functions as a scaffold protein, facilitating tumor cell proliferation and apoptosis [29].

2.12. Stem cell leukemia/lymphoma syndrome

IRAK1 regulates the activity of interferon-gamma (IFN-γ), which facilitates the accumulation of myeloid-derived suppressor cells. These cells inhibit the T-cell response to leukemic cells, contributing to the progression of stem cell leukemia/lymphoma syndrome (SCLL) [30].

2.13. Acute myeloid leukemia

IRAK1 is implicated as an oncotarget in acute myeloid leukemia (AML). Targeting IRAK1 has shown promising results in reducing AML progenitors in vitro and decreasing the leukemia burden in xenograft model [31]. Moreover, IRAK1 has been identified as a viable target to overcome adaptive resistance in the FLT3-mutant subtype [32].

2.14. T-cell acute lymphoblastic leukemia

IRAK1 plays a critical role in T-cell acute lymphoblastic leukemia (T-ALL) cell proliferation and survival through

the stabilization of the antiapoptotic protein MCL1 [33]. Additionally, the DNA methylation of miR-204 has been shown to promote cell proliferation and enhance apoptosis through IRAK1 [34].

2.15. Mixed lineage leukemias

In mixed lineage leukemias (MLL), the inhibition of IRAK1/4 has been shown to delay leukemia progression and improve survival in murine models by stabilizing the normal MLL protein [35].

2.16. Waldenström macroglobulinemia

Waldenström macroglobulinemia (WM) typically manifests with the presence of a MYD88 mutation. In WM cells, inhibiting the kinase activity of IRAK1/4 leads to apoptosis in WM cells [37].

3. Application of irak1 inhibitor in tumor therapy

3.1. IRAK1/4 inhibitor

The IRAK1/4 inhibitor shows potential in weakening the stability of the antiapoptotic protein MCL1, demonstrating promising potency in combination treatment for T-ALL with ABT-737 or vincristine [36]. In the context of anaplastic thyroid cancer (ATC), inhibition of IRAK1 exhibits anti-proliferation and anti-tumor effects its cell lines [37]. Moreover, combining IRAK-1/4 Inhibitor with ABT-737 proves more effective in restoring white blood cell count in peripheral blood and reducing mortality in a T-ALL mouse model [38]. Additionally, this inhibitor sensitizes the curative effect of methotrexate chemotherapy in breast cancer cell lines [39]. In TNBC, the IRAK1/4 inhibitor induces massive apoptosis to reverse paclitaxel resistance [16]. To address MDS and eliminate MDS-initiating clones, an IRAK1/4 inhibitor is employed to impair MDS cells while preserving normal CD34 positive cells [40]. Furthermore, the IRAK1/4 inhibitor decreases the expression of inflammatory cytokines and prevents tumor growth in colorectal cancer. Notably, it also inhibits EMT, effectively slowing down colitis-induced tumorigenesis [12].

3.2. NCGC1481

NCGC1481 demonstrates a novel strategy to overcome adaptive resistance via inhibiting IRAK1 and its associated signaling [34]. This approach holds great promise in enhancing treatment outcomes and addressing the challenge of adaptive resistance in AML.

3.3. JH-X-119-01

JH-X-119-01 has been published as a highly potent and selective covalent inhibitor of IRAK1. In the MYD88-mutated B-cell lymphomas, JH-X-119-01 acts as a potent antiproliferative effector, offering a potential therapeutic approach [41]. Moreover, JH-X-119-01 shows favorable outcomes in LPS-induced septic mice. It not only improves the survival of septic mice but also protects macrophages with reduced toxicity when compared to non-selective IRAK1/4 inhibitors [42].

3.4. Pacritinib

Recent evidence has shown that pacritinib also acts as a specific inhibitor of IRAK1. Building on this, pacritinib exerts a dual effect on the immune system and tumors by restraining IRAK1. It attenuates leukemogenesis through the suppression of CD4+/CD8+ T-cells and myeloid-derived suppressor cells. Furthermore, pacritinib demonstrates potential as an anti-pan cancer inhibitor by effectively inhibiting tumor proliferation via impacting the PD-1/PD-L1 axis and mediating immunosuppression [33,43].

3.5. HS-243

HS-243, a takinib analog, is used to suppress IRAK1 in human rheumatoid arthritis, it exhibits a notable responsiveness to cytokine/chemokine signaling in fibroblast-like synoviocytes [44].

3.6. Takinib

Takinib was developed as a selective inhibitor of TAK1, but because of the similar ATP-binding pocket, takinib could also be used as the inhibitor of IRAK1 [45,46].

3.7. JNJ-1013

Recognizing the significance of IRAK1's scaffolding function, which is crucial for tumor cell survival and distinct from its kinase activity, an IRAK1 degrader Degrader-3 (JNJ-1013) specifically aims to disrupt this function. JNJ-1013 displays valid anti-proliferative

properties in ABC DLBCL cells possessing MyD88 mutation [30].

4. Conclusion

Amid its functions, IRAK1's involvement in cancer emerges especially. This association emphasizes the potential of IRAK1 as a valuable target for therapeutic intervention, with selective IRAK1 inhibitors garnering attention. In the broader context, our comprehensive review unveils IRAK1's multifaceted contributions to tumorigenesis, tumor immunity, and progression.

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Disclosure statement

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