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EDITORIAL

Inflammatory signaling in targeted therapy resistance: focus on EGFR-targeted treatment

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Gene mutations drive oncogene addiction in tumor cells, presenting opportunities for targeted gene therapy. Currently, targeted therapy is one of the most effective cancer treatment modalities. However, tumor cells demonstrate remarkable plasticity, acquiring genetic mutations or activating alternative signaling pathways to evade targeted agents. Drug resistance frequently emerges, significantly diminishing the efficacy of targeted therapy. The precise causes of this resistance is unclear. The intricate interplay of immune and inflammatory pathways is integral to cancer development and response to treatment. Emerging evidence suggests that inflammatory pathways have pivotal roles in mediating resistance to targeted therapies across various cancer types, yet the exact mechanisms remain obscure. Herein we present an overview of the mechanisms underlying resistance to targeted therapies induced by inflammatory signaling, with a particular focus on inflammatory-driven resistance to EGFR-targeted therapies.

Targeted therapy in cancer

With advances in sequencing technologies, targeted therapy has emerged as a viable and pivotal approach in cancer treatment. One key advantage of targeted therapy is the personalized application. By identifying genetic mutations, aberrant signaling pathways, or other molecular characteristics unique to each patient's tumor, clinicians can tailor treatment regimens to target these specific vulnerabilities. Specifically, genetic mutations give rise to novel proteins distinct from the wild-type counterparts. These proteins drive tumor cell survival and reliance on mutated genes, making the proteins targetable and druggable. Currently, a variety of targetable genetic aberrations occur in genes encoding kinases (e.g., *BCR-ABL*, *EGFR*, *HER2*, *FGFR1/2/3*, *PDGFR*, *VEGFR*, *ALK*, *MET*, *NTRK*, *RET*, and *ROS1*) and downstream signaling effectors (e.g., *BRAF*, *KRAS*, *MEK1/2*, and *PI3KCA*), tumor suppressors (e.g., *BRCA1/2* and *TP53*), and chromatin modifiers (e.g., *IDH1/2* and *EZH2*)[1]. Most of these mutations have corresponding targeted therapies available for clinical use (**Table 1**). In essence, the rapid advances in targeted therapy are revolutionizing cancer treatment by exploiting specific genetic aberrations for personalized medicine and improved patient outcomes.

Challenges in targeted therapy resistance

Targeted anti-tumor therapy has revolutionized cancer treatment due to its significant efficacy and low toxicity profile. However, drug resistance remains an inevitable challenge, often emerging post-treatment. Tumor cells tend to develop acquired resistance during therapy because of new genetic mutations. For example, the development of resistance to EGFR tyrosine kinase inhibitors (TKIs) in lung cancers often involves second-site *EGFR T790M* mutations, which renders the original EGFR TKIs ineffective[2]. Similarly, resistance to BRAF inhibitors in melanoma leads to the emergence of various new mutations, such as *KRAS* mutations (20%), *BRAFV600E/K* amplifications (13%), and *MEK1/2* mutations (7%)[3]. Additionally, growing evidence suggests that non-genetic adaptive changes also contribute to tumor resistance. For example, alterations in the β-catenin-LEF1 and YAP1 signaling pathways have been implicated in melanoma resistance

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Table 1 Common genes and corresponding FDA-approved drugs for targeted therapy

Gene	Drug name	FDA-approved indications	Approval date
EGFR	Gefitinib	First-line, second-line, or beyond for EGFR-mutant locally advanced or metastatic non-small cell lung cancer (mNSCLC)	2003 (US), 2004 (China)
	Erlotinib	First-line, second-line, or beyond for EGFR-mutant mNSCLC; with gemcitabine for locally advanced, unresectable, or metastatic pancreatic cancer; first- or second-line treatment for metastatic renal cell carcinoma	2004 (US), 2012 (China)
	Icotinib	First-line, second-line, or beyond for EGFR-mutant mNSCLC	2011 (China)
	Afatinib	First-line treatment for EGFR-mutant mNSCLC; first- or second-line for locally advanced or mNSCLC with T790M mutations after EGFR-TKI failure; HER-2 positive metastatic breast cancer (mBC)	2013 (US), 2014 (China)
	Osimertinib	First-line, second-line, or beyond for EGFR-mutant mNSCLC	2015 (US), 2016 (China)
	Dacomitinib	First-line, second-line, or beyond for EGFR-mutant mNSCLC	2018 (US), 2019 (China)
	Necitumumab	In combination with gemcitabine and cisplatin for first-line treatment of metastatic squamous NSCLC	2015 (US)
	Neratinib	For patients with high-risk breast cancer (BC) who have completed adjuvant trastuzumab-based therapy without disease progression	2017 (US)
	Panitumumab	As monotherapy or after failure of 5-FU, oxaliplatin, and irinotecan-based chemotherapy in RAS wild-type metastatic colorectal cancer (mCRC)	2006 (US)
	Cetuximab	As monotherapy or combined with irinotecan for EGFR-expressing, irinotecan-refractory, RAS wild-type mCRC; combined with chemotherapy for advanced (metastatic) squamous cell carcinoma of the head and neck	2004 (US), 2013 (China)
	Nimotuzumab	Combined with radiotherapy for EGFR-positive stage III/IV nasopharyngeal carcinoma	2008 (China)
HER-2	Trastuzumab	Monotherapy for HER-2 overexpressing mBC after one or more chemotherapy regimens; combined with paclitaxel or docetaxel for HER-2 overexpressing mBC with no prior chemotherapy; adjuvant monotherapy for HER-2 overexpressing breast cancer after surgery, anthracycline-based chemotherapy, and radiotherapy	1998 (US), 2001 (China)
	Trastuzumab emtansine (T-DM1)	Monotherapy for HER-2 overexpressing mBC previously treated with trastuzumab and taxanes, alone or in combination	2013 (US)
	Trastuzumab-DKST	Adjuvant monotherapy for HER-2 overexpressing BC post-surgery, anthracycline-based chemotherapy, and radiotherapy; monotherapy for HER-2 overexpressing mBC after one or more chemotherapy regimens; combined with paclitaxel or docetaxel for HER-2 overexpressing mBC with no prior chemotherapy	2017 (US)
	Trastuzumab-PKRB	Adjuvant monotherapy for HER-2 overexpressing BC post-surgery, anthracycline-based chemotherapy, and radiotherapy; monotherapy for HER-2 overexpressing mBC after one or more chemotherapy regimens; combined with paclitaxel or docetaxel for HER-3 overexpressing mBC with no prior chemotherapy	2019 (US)
ALK	Crizotinib	First-line treatment for ALK-positive locally advanced or mNSCLC; first-line for ROS1-positive NSCLC	2011 (US), 2017 (China)
	Alectinib	First-line treatment for ALK-positive locally advanced or mNSCLC; second-line for ALK-positive NSCLC resistant to crizotinib	2015 (US), 2018 (China)
	Ceritinib	First-line treatment for ALK-positive locally advanced or mNSCLC; second-line for ALK-positive NSCLC resistant to crizotinib	2014 (US), 2018 (China)

Table 1 Continued

Gene	Drug name	FDA-approved indications	Approval date
	Brigatinib	Second-line treatment for ALK-positive NSCLC resistant to crizotinib; second-line for NSCLC resistant to osimertinib after T790M mutation failure	2017 (US)
	Lorlatinib	For mNSCLC resistant to crizotinib or at least one other ALK inhibitor	2018 (US)
VEGFR	Bevacizumab	Combined with carboplatin and paclitaxel for first-line treatment of locally advanced, metastatic, or recurrent non-squamous NSCLC; combined with erlotinib for first-line treatment of EGFR-positive mNSCLC; combined with 5-FU-based chemotherapy for mCRC; combined with interferon-α for metastatic renal cell carcinoma	2004 (US), 2017 (China)
	Ramucirumab	Combined with docetaxel for mNSCLC resistant to platinum-based chemotherapy; combined with paclitaxel for mGC or gastroesophageal junction adenocarcinoma resistant to fluoropyrimidine or platinum; combined with FOLFIRI for mCRC after progression with bevacizumab, oxaliplatin, and 5-FU; for hepatocellular carcinoma after sorafenib with AFP ≥400 ng/mL	2014 (US)
	Anlotinib	Third-line treatment for locally advanced or mNSCLC; third-line treatment for locally advanced or metastatic small-cell lung cancer (mSCLC)	2018 (China)
	Recombinant Human Endostatin	Combined with NP chemotherapy for first-line or recurrent stage Ⅲ/Ⅳ NSCLC	2005 (China)
	Apatinib	For mGC or gastroesophageal junction adenocarcinoma after at least two prior lines of chemotherapy	2015 (China)
	Sunitinib	For unresectable or metastatic pancreatic neuroendocrine tumors; unresectable renal cell carcinoma; for gastrointestinal stromal tumor (GIST) after imatinib failure or intolerance	2006 (US), 2007 (China)
	Regorafenib	For mCRC progression after 5-FU, oxaliplatin, irinotecan, or EGFR/VEGF-targeted therapy (RAS wild-type); for advanced hepatocellular carcinoma after sorafenib	2014 (US), 2012 (China)
	Sorafenib	For unresectable or distant metastatic hepatocellular carcinoma; unresectable renal cell carcinoma; for locally recurrent or metastatic differentiated thyroid carcinoma resistant to radioactive iodine therapy	2005 (US), 2006 (China)
	Lenvatinib	First-line treatment for unresectable hepatocellular carcinoma; combined with everolimus for advanced or metastatic renal cell carcinoma; for progressive differentiated thyroid carcinoma after radioactive iodine therapy	2015 (US), 2018 (China)
	Cabozantinib	Second-line treatment for hepatocellular carcinoma; first-line treatment for advanced renal cell carcinoma	2012 (US)
	Pazopanib	First-line treatment for advanced renal cell carcinoma; for advanced renal cell carcinoma after cytokine therapy	2009 (US), 2017 (China)
BRAF	Dabrafenib	Combined with trametinib for BRAF V600E-mutant mNSCLC; combined with trametinib for BRAF V600E-mutant unresectable or metastatic melanoma	2013 (US)
	Trametinib	Combined with dabrafenib for BRAF V600E-mutant mNSCLC; combined with dabrafenib for BRAF V600E-mutant unresectable or metastatic melanoma	2013 (US)
	Sorafenib	For unresectable or distant metastatic hepatocellular carcinoma; unresectable renal cell carcinoma; for locally recurrent or metastatic differentiated thyroid carcinoma resistant to radioactive iodine therapy	2005 (US), 2006 (China)
	Vemurafenib	For advanced metastatic or unresectable melanoma with BRAF mutations	2011 (US), 2017 (China)

Table 1 Continued

Gene	Drug name	FDA-approved indications	Approval date
	Cobimetinib	Combined with vemurafenib for BRAF V600E or V600K-mutant unresectable or metastatic melanoma	2015 (US)
	Encorafenib	Combined with binimetinib for BRAF V600E-mutant unresectable or metastatic melanoma	2018 (US)
	Binimetinib	Combined with encorafenib for BRAF V600E-mutant unresectable or metastatic melanoma	2018 (US)
CDK4/6	Palbociclib	Combined with letrozole for postmenopausal women with ER^+/HER-2–advanced or metastatic BC as initial endocrine therapy	2015 (US), 2018 (China)
	Ribociclib	Combined with letrozole for ER^+/HER-2–advanced or metastatic BC in postmenopausal women	2017 (US)
	Abemaciclib	Combined with fulvestrant for ER^+/HER-2–advanced or metastatic BC resistant to endocrine therapy; monotherapy for ER^+/HER-2–advanced or metastatic BC after endocrine therapy and prior chemotherapy	2017 (US)
KRAS	Sotorasib	For KRAS G12C-mutant locally advanced or mNSCLC after at least one prior systemic therapy	2021 (US)
	Adagrasib	For adult patients with KRAS G12C-mutated locally advanced or mNSCLC who have previously received at least one prior systemic therapy	2022 (US)

to MAPKi, resulting in reduced apoptosis and enhanced resistance[4]. Moreover, the tumor microenvironment (TME) assumes a critical role in nurturing resistance mechanisms. Various growth factors and cytokines originating from the neighboring TME contribute to drug resistance. Indeed, drug resistance creates a protective barrier against therapeutic interventions[5]. Consequently, dissecting the intricate crosstalk within the TME reveals latent vulnerabilities ripe for exploitation to augment treatment efficacy. Typically, targeted therapy triggers activation of bypass pathways, circumventing the original pathway targeted for cancer cell death. The mechanisms underlying this resistance are unclear and warrant further exploration in corollary studies.

Inflammatory pathways in targeted therapy resistance

The TME is comprised a complex network of immune cells, stromal cells, and signaling molecules that influence cancer progression and treatment response. Targeted therapies aimed at impeding cancer cell survival induce polarization and dysfunction of immune cells within the TME, fostering therapeutic resistance. Recent studies highlight the dynamic interplay between immune and cancer cells in the context of targeted therapy resistance. BRAF inhibition recruits and reprograms macrophages into an M2 phenotype in melanoma mouse models, which enhances macrophage-derived secretion of VEGF. This secretion subsequently reactivates ERK in melanoma cells, leading to therapeutic resistance[6]. Additionally, the multi-RTK inhibitor sorafenib impairs dendritic cell function and the induction of antigen-specific T cells in mouse models[7]. Moreover, inflammatory cytokines and chemokines released by immune cells activate survival pathways in cancer cells, thereby enhancing the resistance to targeted agents[8]. In addition to immune cell-mediated mechanisms, aberrant activation of inflammatory signaling pathways within tumor cells has been linked to resistance against targeted therapies. Our previous investigations showed that targeting EGFR with inhibitors in glioblastoma and lung cancer upregulates tumor necrosis factor (TNF) signaling. This upregulation precipitates a TNF-driven adaptive response that confers resistance to EGFR inhibition. Moreover, the nuclear factor-kappa B (NF-κB) pathway, a pivotal regulator of inflammation, is upregulated in a TNF-dependent manner, which contributes to the development of EGFR inhibition resistance. Similarly,

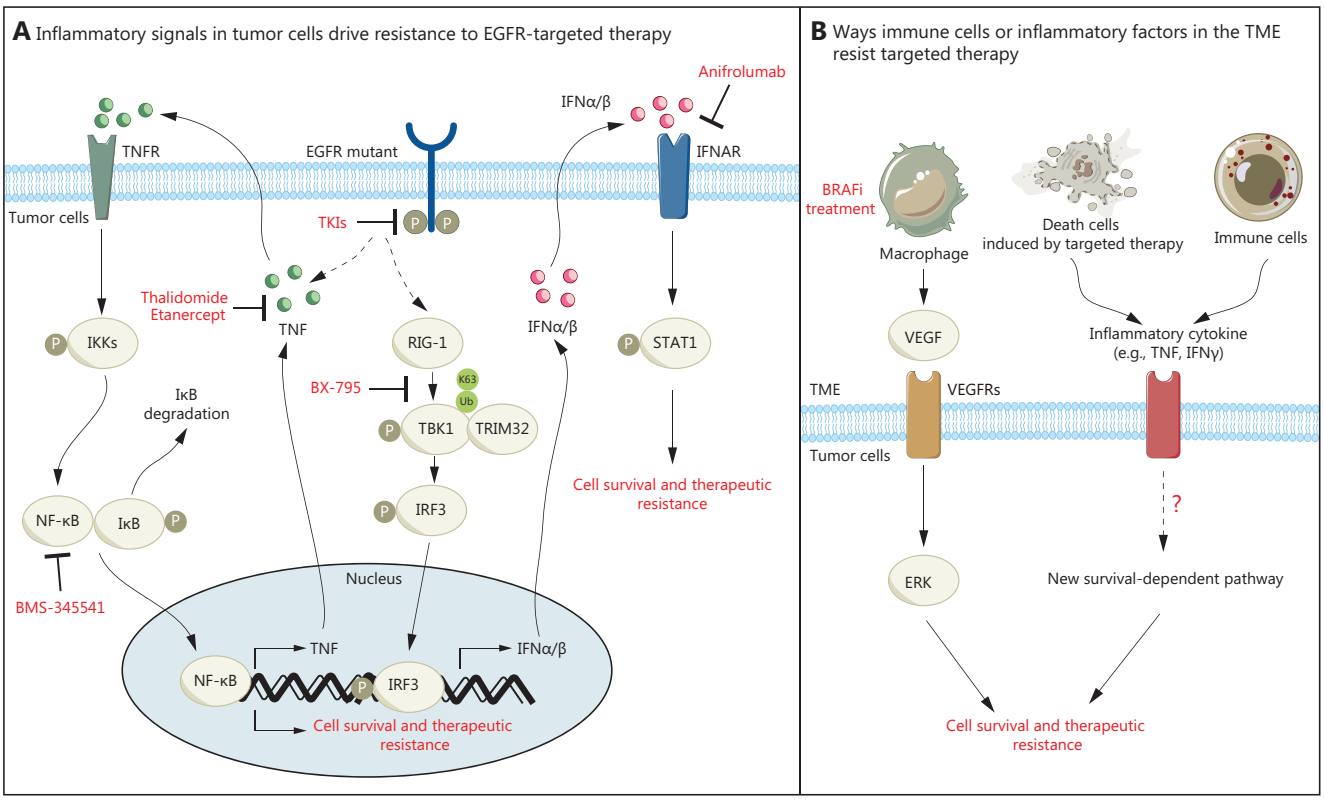

Figure 1 Mechanisms of resistance to targeted therapy mediated by inflammatory signals and immune cells. (A) Resistance mechanism induced by upregulation of TNF and IFN in EGFR-targeted therapy. TNF is rapidly activated in response to EGFR inhibition and plays a crucial role in resistance to EGFR-targeted treatments. Upon TNF binding to TNFR1, IKK is recruited and activated by the TNFR1 complex. The activated IKK phosphorylates IκB, which is then rapidly degraded by polyubiquitination. The degradation of IκB releases NF-κB, allowing NF-κB to translocate into the nucleus and promote the transcription of numerous NF-κB target genes. Nuclear NF-κB binds to the promoter of TNF, increasing TNF expression in a feed-forward loop. Many of these NF-κB target genes have anti-apoptotic and pro-survival functions. Additionally, type I interferon (IFN-I) is upregulated in response to EGFR inhibition. RIG-I is strongly induced by EGFR inhibition, leading to the ubiquitous expression and activation of TBK1. The ubiquitin ligase, TRIM32, associates with TBK1 upon EGFR inhibition and is necessary for K63-linked ubiquitination and TBK1 activation. Inhibiting mutant EGFR triggers IFN-I upregulation *via* the RIG-I-TBK1-IRF3 pathway. STAT1 activation by IFN-I promotes cell survival and therapeutic resistance in the context of EGFR inhibition. (B) Immune cells or inflammatory factors in the TME resist targeted therapy in various ways. BRAF inhibitors (BRAFi) paradoxically activate the mitogen-activated protein kinase (MAPK) pathway in macrophages in BRAF-mutant melanomas, leading to the production of VEGF, which reactivates the MAPK pathway in melanoma cells and promotes cell growth. Additionally, inflammatory factors released from dying tumor and immune cells during targeted therapy may activate novel survival pathways in tumor cells, contributing to resistance to targeted therapy. TKIs, tyrosine kinase inhibitors; TNF, tumor necrosis factor; EGFR, epidermal growth factor receptor; TNFR1, tumor necrosis factor receptor 1; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; IκB, inhibitor of NF-κB alpha; IKK, IκB kinase; IFN, interferon; RIG-I, retinoic acid-inducible gene I; TBK1, TANK-binding kinase 1; TRIM32; tripartite motif-containing 32; IRF3, interferon regulatory factor 3; STAT1, signal transducer and activator of transcription 1; VEGF, vascular endothelial growth factor; TME, tumor microenvironment.

our group reported that activation of the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, which is induced by interferon type I (IFN-I), is associated with resistance to EGFR TKIs (**Figure 1A**). These findings highlight the critical role of targeting inflammatory signaling pathways to overcome therapeutic resistance[9-12].

Targeted therapies, by inhibiting pathways vital for cancer cell proliferation and survival, reduce tumor growth but may also induce inflammatory cell death. For example, inhibition of MEK, EGFR, or ALK pathways in lung cancer cell lines driven by these pathways results in pyroptotic cell death, which is characterized by GSDME cleavage[13]. The occurrence

of inflammatory cell death often coincides with an escalation in pro-inflammatory cytokines, profoundly affecting both tumor cells and the immune microenvironment. This phenomenon fosters targeted drug resistance by circumventing oncogene addiction and rendering conventional targeted therapies ineffective (**Figure 1B**). Consequently, a comprehensive understanding of the regulatory mechanisms governing these pathways may offer novel insights and strategies to overcome targeted therapy resistance. This knowledge provides a crucial theoretical foundation for the further optimization and personalization of cancer treatment.

Overcoming inflammation-driven resistance to targeted therapy

The multifaceted targeting in cancer therapy presents significant potential for combination approaches. Currently, overcoming resistance originating from immune and inflammatory pathways within the tumor or its microenvironment presents a promising avenue through combination therapies. These approaches hold the potential for disrupting pro-survival signaling pathways and eliciting robust antitumor immune responses.

EGFR-activating mutations frequently occur in tumors. Our previous studies have revealed that the combined use of EGFR TKIs and TNF inhibitors significantly suppresses the growth of secondary resistant tumors. Furthermore, this combination therapy exhibits similar inhibitory effects on *EGFR* wild-type (*EGFRwt*) tumors, which are non-responsive to EGFR TKIs[11,12]. Mechanistically, inhibition of EGFR signaling prompts tumor cells to activate the TNF pathway for cell survival and concurrent inhibition of the TNF pathway can eliminate the formation of this new dependency. Furthermore, tumor cells upregulate inflammatory signals, recruiting and hijacking immune cells within the TME, thereby fostering an inflammatory immune milieu. This process not only shapes the tumor cells to develop novel dependency pathways to bypass oncogene addiction but also hampers immune surveillance, rendering immune-cell-dependent targeted therapies ineffective. As the mechanisms of the TME unfold, the emergence of resistance to targeted therapies increasingly intertwines with immunotherapy. With successful trials of combined targeted therapies and immune checkpoint inhibitors (ICBs), numerous studies investigating combination therapies are underway. Clinical trials combining PD-1/PD-L1/CTLA-4 blockades with MAPK inhibitors, EGFR inhibitors, or BRAF and MEK inhibitors are being conducted in BRAF-mutant and wild-type melanoma[14-18]. Targeted therapy combined with immunomodulatory or anti-inflammatory approaches appears to hold promise in overcoming resistance to targeted therapy in cancer. However, substantial research efforts are still required to elucidate the mechanisms underlying this phenomenon. The identification of predictive biomarkers associated with inflammation-induced resistance is imperative for accurate patient stratification and the development of personalized treatment strategies.

Discussion and perspectives

Targeted therapy has evolved rapidly, offering personalized treatment options for various malignancies. Recent advances, especially the approval of AMG510 (sotorasib) targeting KRAS (G12C)[19], underscore the progress being achieved in targeted therapy. However, the critical challenge now is addressing acquired resistance to these therapies.

A key mechanism underlying resistance involves upregulation of alternative survival pathways that bypass the targeted mutations. Understanding how targeted therapies induce these compensatory pathways is crucial for overcoming resistance. While immune and inflammatory pathways have traditionally been associated with tumor suppression, the pathways also contribute to resistance. Inhibitors often trigger inflammatory responses that foster tumor cell survival by activating new dependency pathways. Furthermore, immune cells in the TME have a role in resistance formation, altering the immune landscape to support tumor cell evasion of targeted therapies. Thus, targeting inflammatory and immune signals presents a promising strategy for addressing resistance. Fortunately, antagonists targeting major inflammatory cytokines, such as TNF, IL-6, and IL-1, as well as chemokines or chemokine receptors, can be administered safely to patients with advanced-stage cancers[8]. These valuable preliminary studies may offer promising solutions to the issue of drug resistance in targeted therapy.

Addressing inflammation-driven resistance represents a formidable challenge in precision medicine, necessitating collaborative efforts across disciplines. Future research endeavors should focus on elucidating the dynamic interplay between inflammation, immune response, and therapy resistance at single-cell resolution. Integration of multi-omics data and computational modeling holds promise for identifying novel therapeutic targets and predictive biomarkers. Moreover,

clinical trials should incorporate comprehensive molecular profiling to facilitate patient stratification and optimize treatment outcomes. Ultimately, a deeper understanding of the molecular mechanisms driving inflammation-mediated resistance will pave the way for the development of more effective therapeutic strategies and improve patient outcomes in diverse disease settings.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Zhihong Luo, Ke Gong. Wrote the paper: Zhihong Luo, Ke Gong.

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