Acta Pharmaceutica Sinica B 2026;16(2):746−769

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

Acta Pharmaceutica Sinica B

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REVIEW

Activating protein kinases to treat diseases: Current understanding and future challenges

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Received 10 July 2025; received in revised form 4 October 2025; accepted 23 October 2025

KEY WORDS

Protein kinase;
Activator;
Human disease;
Serine/threonine specific protein kinase;
Tyrosine protein kinase;
Small-molecule pharmacological agent;
Clinical trial;
Therapeutic strategy

Abstract Protein kinases, as one of the most important human enzymes, are signaling molecules that regulate almost all cell activities, including growth, cell division and metabolism. Dysfunction of these cellular pathways can lead to a variety of human diseases. Accumulating evidence on the down-regulation of key protein kinases in diseases has made a big progress. The down-regulation is related to cancer, heart disease, neurodegenerative diseases and other diseases. Thus, in this review, we defined the classifications of protein kinases and demonstrated the mechanisms of protein kinase activators in the treatment of human diseases, summarized the research progress of protein kinase activators, and further discussed the development progress of protein kinase activators in clinical stage. Accordingly, activation of protein kinases has become a crucial target for drug development. With the in-depth understanding of protein kinase functions and regulation mechanisms, the development of new protein kinase activators may continue to be a rapidly growing field, which will help to develop more accurate and effective targeted therapeutic strategies in the near future.

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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.2025.12.004

1. Introduction

Protein kinases, as key enzymes regulating protein phosphorylation, participate in cell proliferation, differentiation, apoptosis and metabolism through signal transduction networks[1-4]. Its dysfunction is closely related to tumors, cardiovascular disease, neurodegenerative disease and other pathological mechanisms[5-8]. Receptors are biological macromolecules composed of glycoproteins or lipoproteins that can recognize and bind bioactive molecules on the cell membrane or in cells and cause changes in cell function. Receptors can recognize and receive a specific signal by binding with ligands, amplify it accurately and transmit it to the inside of cells, so as to start a series of intracellular signal cascade reactions and produce specific biological effects. Some small molecules can bind to and excite receptors, showing corresponding physiological effects or drug effects (Fig. 1A). These small molecules are called activators of receptors. Salbutamol and clenbuterol are typical receptor activators[9-11], which can activate the β_2 receptor distributed in the airway smooth muscle to produce bronchodilation, and are used to treat asthma. Adrenaline, as a complete activator in the cardiovascular system, can strongly stimulate the heart and blood vessels, and is used for emergency treatment and treatment of cardiovascular diseases. Dopamine receptor activators are used to treat Parkinson's disease and other neurological diseases. Activators are generally divided into selective and non-selective. Selective can only promote a certain reaction, while non selective can promote a certain kind of reaction. Classic selective β 1 receptor activators currently include dobutamine. Classic selective β 2 receptor activators currently include salbutamol, terbutaline sulfate. Classic non selective beta receptor activators currently include isoproterenol (Fig. 1B).

In recent years, the development of activators or inhibitors of protein kinases has become an important strategy for disease treatment[12-14]. Among them, activators can restore dysregulated signaling pathways by enhancing the activity of specific kinases, showing unique potential in disease treatment[13]. In the field of cancer, the nonclassical functions of protein kinases (such as metabolic enzyme kinase activity) have been confirmed to directly regulate the proliferation, apoptosis and immune escape of cancer cells[15]. Activators of classical signaling pathways such as MAPK and PI3K can induce differentiation or enhance immune response in specific tumor subtypes[16,17]. AMPK activators inhibit tumor growth by regulating energy metabolism[18]. In the cardiovascular system, the activation of protein kinase G (PKG) can relax vascular smooth muscle and inhibit platelet aggregation. Its activators (such as riociguat) have been used in the treatment of pulmonary hypertension[19]. In addition, AMPK activators show protective effects in heart failure models by improving myocardial energy metabolism and inhibiting fibrosis[20,21]. In neurodegenerative diseases, dysfunction of kinases often leads to abnormal phosphorylation of tau protein or aggregation of α-synuclein. Over activation of GSK-3β is associated with Alzheimer's disease (AD), and specific activators regulating its activity may reduce neuroinflammation[22]. The activators strategy targeting the interaction of APLP1/LAG3 can inhibit the transmission of α-synuclein in Parkinson's disease[23].

The development of protein kinase activators started late compared with inhibitors, but with the in-depth study of the two-way regulation mechanism of kinase, its research has gradually accelerated. The development of protein kinase activators started late compared with inhibitors, but with the in-depth study of the two-way regulation mechanism of kinase, its research gradually accelerated. In 1875, pilocarpine, an M receptor activator, was isolated from the leaves of *Pilocarpa*. It has been used as an ophthalmic antihypertensive drug for more than a century. Ophthalmologists have done a lot of research work to prolong the efficacy and reduce side effects. Liposome as a slow-release drug

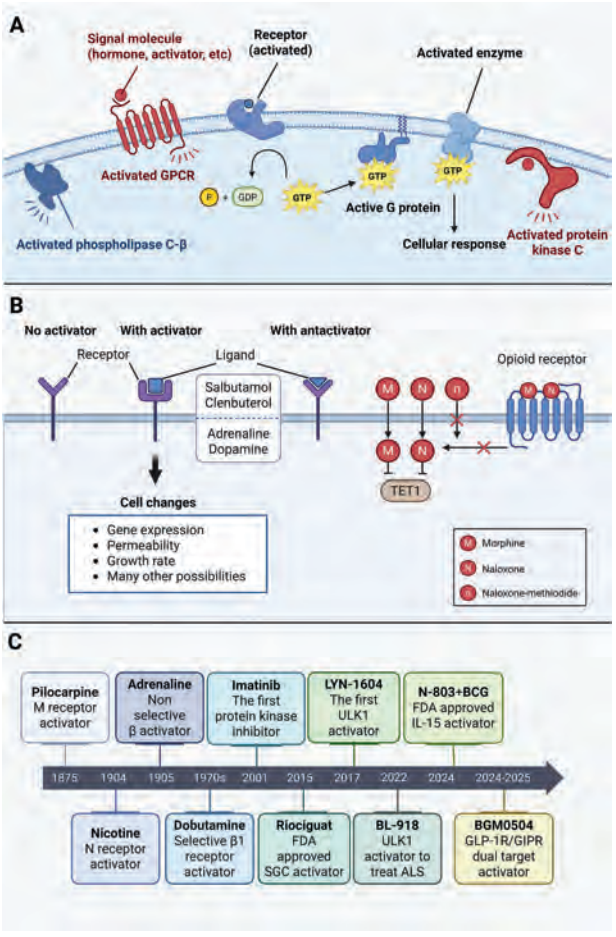

Figure 1 Kinase-specific activation mechanisms, molecular mechanisms of activator action and historical timeline of classical activators. Kinase-specific activation mechanisms, molecular mechanisms of activator action and historical timeline of classical activators. Ten-eleven translocation methylcytosine dioxygenase 1 (TET1); US Food and Drug Administration (FDA); the guanylate cyclase (SGC); unc-51 like autophagy activating kinase 1 (ULK1); amyotrophic lateral sclerosis (ALS); interleukin-15 (IL-15); glucagon-like peptide-1 receptor (GLP-1R); glucose-dependent insulinotropic polypeptide receptor (GIPR); G-protein coupled receptor (GPCR).

delivery system of pilocarpine used in the treatment of glaucoma will have a good development prospect because of its good curative effect, small side effects, convenient use and other characteristics. In 1904, the N receptor activator nicotine was successfully synthesized. Nicotine, is the main alkaloid in tobacco, accounting for about 90% of the total alkaloids. It is closely related to insect resistance, and is also an important indicator of the quality of tobacco and cigarettes. Nicotine accumulation is the result of the co-expression of structural genes encoding the nicotine biosynthesis pathway, and structural genes are usually controlled by COI1, JAZ, MYC-2 and other regulatory genes. At present, most genes involved in the biosynthesis, regulation and transport of nicotine and nornicotine have been identified. In 1905, after solving the problem of separation and purification after reduction reaction, the German chemist Friedrich Stolz finally obtained the pure product of non-selective β activator adrenaline in the laboratory and put it into production the next year, which was the first time in human history that hormone was synthesized by artificial method. Dobutamine, as a selective β_1 receptor activator, was developed in the early 1970s and approved by the U.S. Food and Drug Administration (FDA), becoming the first drug for acute myocardial infarction complicated with heart failure. In the early 2000s, the first protein kinase inhibitor, Imatinib was approved, marking the beginning of targeted kinase therapy and promoting theoretical exploration of activators research[24,25]. In 2010, AMPK activator AICAR entered clinical trials for metabolic diseases and cardiovascular protection, confirming the feasibility of the kinase activation strategy[26-28]. More recently, the AMPKα activator IMM-H007 was reported to promote hepatic cholesterol and triglyceride metabolism and attenuate hypercholesterolemia and atherosclerosis in preclinical models[29]. In 2015, the guanylate cyclase (SGC) activator riociguat was approved by FDA for the treatment of pulmonary hypertension and became the first activator drug targeting kinase[19,30]. In 2017, the team of Sichuan University first designed and found the small molecule activator LYN-1604 targeting autophagy promoter ULK1 as a new candidate drug for triple negative breast cancer[31]. Subsequently, in 2022, it was verified that BL-918 is a small molecule activator of ULK1, which can induce cytoprotective autophagy and is used for the treatment of amyotrophic lateral sclerosis[32]. In 2024, IL-15 activator Anktiva (N-803) combined with Bacillus Calmette Guerin (BCG) was approved by the FDA for the treatment of non-muscle invasive bladder cancer with carcinoma *in situ* and patients with or without papilloma[33,34]. In 2024, BGM0504 as a GLP-1R/GIPR dual target activator, through molecular dynamics optimization, its receptor activator activity was three times that of tirzepatide, and showed better hypoglycemic, weight loss and improvement effect of nonalcoholic steatohepatitis (NASH) in mouse model. Its half-life supports weekly administration[35]. The phase II clinical trial showed that the weight of patients decreased by 3.24%−8.30%, and the blood glucose control was significant. Glp-1ra and its multi-target drugs have become the core of the treatment of diabetes and obesity. In the phase III clinical trial, oral administration of small molecule glp-1ra or forglipron reduced patients' glycosylated hemoglobin by 1.3%−1.6%, and the weight of the highest dose group decreased by an average of 7.9% (about 16 pounds). It is expected to submit an application for weight loss indications by the end of 2025[36,37]. In parallel, combined activation of AdipoR1/2 and inhibition of elastin-derived peptide−EBP interaction by JT003 and V14 synergistically activated AMPK, enhanced mitochondrial function and ameliorated nonalcoholic fatty liver disease and liver fibrosis in mice[38] (Fig. 1C).

Some activators have been identified and tested in preclinical models, with a few already entering clinical trials. Despite these advances, the optimal indications for therapeutic activation and the long-term safety of these methods still need to be determined. Due to various reasons such as research paradigm deviation, complex conformational sites leading to low selectivity and off target effects, only a small number of small molecule kinase activators have been approved for clinical treatment.

Over the past two decades, a significant amount of kinase drug development resources has been focused on inhibitors[36]. In addition, kinase activation typically requires precise conformational changes, and the design of small-molecule activator requires simulating these dynamic processes, which is much more difficult than inhibitors. As discovered by UCL-TRO-1938, as a small molecule activators of the PI3K alpha subtype, 1938 conformational activation of PI3K alpha was achieved through multiple steps of enhancing the PI3K alpha catalytic cycle, resulting in local and global conformational changes in the PI3K alpha structure through different mechanisms[39]. More importantly, subtle overactivation may lead to signal cascade dysregulation, resulting in a narrow therapeutic window for kinase activators, while in complex kinase networks, single kinase activation may trigger negative feedback. Transient PKR-like endoplasmic reticulum kinase (PERK) activation has a protective effect; However, chronic ER stress and persistent PERK activation may be harmful to cellular health, and PERK overactivation is associated with many diseases[40].

Although the development of protein kinase activators still faces challenges such as low selectivity and off-target effect, its potential in disease treatment cannot be ignored. In the future, it is necessary to combine structural biology and artificial intelligence technology to design highly specific activators and explore their application in combination therapy. At the same time, in-depth analysis of the kinase "part-time" function and its interaction with epigenetic regulation will promote the development of precision treatment strategies.

2. Trends of activation of protein kinases in the treatment of human diseases

2.1. Serine/threonine specific protein kinases (ST-PKS)

2.1.1. Mitogen-activated protein kinase (MAPK)

The MAPK is a highly conserved serine/threonine protein kinase in eukaryotic cells, which plays a role in many cellular activities such as growth and proliferation, cell differentiation, cell movement or cell death[41,42]. The MAPK pathway has a three-level signal transduction process: MAPK, MAPK kinase (MEK or MKK), and MAPK kinase kinase (MEKK or MKKK), which can be activated sequentially by these three kinases[43]. The MAPK pathway has four main branches, namely: Extracellular signal-regulated protein kinase (ERK). p38 mitogen-activated protein kinase (p38 MAPK). c-Jun N-terminal kinase (JNK). Extracellular signal-regulated kinase 5 (ERK5)[44]. Ultraviolet and oxidative stress activate MAP3K (such as ASK1 and TAK1) through RAC/CDC42 and other small G proteins, and then activate p38 and JNK. Of these, JNK and p38 have similar functions and are involved in inflammation, apoptosis and growth[45]. ERK mainly regulates cell growth and differentiation, with the upstream signal being the well-known Ras/Raf protein[46]. The three kinases used in the different branches are different, and can be used as markers for

the pathway[47]. In the past two decades, the most profitable research direction worldwide has been the entangled relationship between cell signaling pathways and cancer[48]. The MAPK signaling pathway is a high-level information transmission chain in cells, involving serine/threonine protein kinases that are widely expressed in cells and involved in a range of cellular physiological activities, including growth, development, differentiation and apoptosis. It is a major hotspot for the development of cancer.

The MAPK pathway has a complex regulatory mechanism in cells. The activation of a single pathway may trigger feedback regulation of other pathways and affect the therapeutic effect[49]. Different pathways in the MAPK family have certain specificity. Upregulation of p38MAPK and JNK signaling pathway protein phosphorylation can promote tumor cell apoptosis, while activation of ERK can inhibit tumor cell apoptosis[50]. Stress-activated p38MAPK and JNK integrate signals from different transmission points through transcription-dependent and non-transcription-dependent mechanisms, and finally activate caspase to induce the release of mitochondrial outer membrane protein induced by mitochondrial permeability mediated by Pro-apoptotic B lymphoma 2 (Bcl-2) family proteins. Several Bcl-2 family proteins include the pro-apoptotic group and the anti-apoptotic group[51]. Two transcription factors, activator protein 1 (AP-1) and p53 tumor suppressor protein, are closely related to the expression of a variety of Pro-apoptotic target genes. P38MAPK and JNK mediated phosphorylation can activate AP-1 and p53 during and after transcription, leading to high expression of Pro-apoptotic protein and low expression of anti-apoptotic protein, and promoting programmed cell death of tumor cells. P38MAPK and JNK can also promote tumor cell apoptosis by inducing Bcl-2 related protein (Bax) phosphorylation and mitochondrial translocation to release Pro-apoptotic protein BAD (Bcl-2 cell death inhibitor)[52]. P38MAPK and JNK can regulate autophagy. Studies have shown that continuous activation of p38MAPK can induce autophagic cell death. When p38MAPK is continuously activated, the accumulation of anti-apoptotic proteins Bcl-xL and Bcl-2 in mitochondria will be weakened[52]. TNFα (tumor necrosis factor alpha) and other extrinsic pathways can also induce cleavage of caspase-8-mediated BH3 protein and BID (BH3 interaction domain death activator) protein by activating the phosphorylation of JNK, and promote apoptosis of lung cancer cells[53]. Abnormal activation of the MAPK signaling pathway is closely related to tumor growth and metastasis. Activation of p38MAPK can induce cell cycle arrest in the G2 phase of tumor cells and interfere with the growth process of tumor cells[54]. MAPK/ERK is an important node of cell signal transduction, and its downstream cell signal transduction proteins play a role in regulating the differentiation and proliferation of cancer cells by mediating extracellular signal transmembrane transmission. When the target genes *in vivo* are activated, the activation of downstream kinases promotes the transcription and expression of the body, which can transmit extracellular signals to cells, mediate the degradation of extracellular matrix, affect the movement and adhesion of cancer cells, play the role of degradation of extracellular matrix, and regulate the invasion and metastasis of tumor cells through basement membrane[55]. Tumor angiogenesis provides essential nutrients for tumor development and is one of the key steps and necessary conditions for tumor invasion, growth, invasion, metastasis and recurrence. In the absence of blood vessels, tumor tissue rarely exceeds two millimeters. Therefore, inhibiting tumor angiogenesis is of great significance for the development and prognosis of lung cancer[56]. Most of the angiogenic signals in tumor tissues cannot be regulated normally, and are often high or enhanced, leading to the overexpression of growth factors[57]. After activated by inflammatory cytokines and other extracellular substances, MAPK signaling pathway can multi effect cascade phosphorylate AP-1 and NF-κB binding sites, which are downstream targets of tumor angiogenesis initiation region, thereby up regulating the expression of vascular endothelial growth factor (VEGF), controlling the activation of recombinant activator protein and regulating the proliferation, migration and survival of endothelial cells, thus affecting the regulation of tumor angiogenesis[58]. In addition, p38MAPK activation mediates tau hyperphosphorylation and accelerates the formation of neurofibrillary tangles. Inhibition of p38 can alleviate neuronal injury, but its moderate activation may regulate the balance of inflammation under certain circumstances[59]. The activation of ERK1/2 can promote angiogenesis and nerve repair, while the overactivation of JNK/p38 aggravates the inflammatory response. Transient activation of ERK attenuates neuronal apoptosis after ischemia[60-62].

2.1.2. Cyclin-dependent kinases (CDKs)

The cell cycle is the basic process of cellular life, controlling the transition from the quiescent phase to the growth and proliferation phase[63]. CDKs and cyclins are the core molecules in the entire cell cycle regulatory mechanism[64]. Cell cycle dysregulation is a common feature of human cancer, and CDK regulators play a crucial role in cell cycle control and are one of the most promising areas of cancer therapy[65,66]. CDKs are members of the serine/threonine kinase family and are composed of a heterodimeric complex of catalytic kinase subunits and regulatory subunits[67]. Currently, 11 CDK members have been identified. Among them, CDK1, CDK2, CDK4, and CDK6 are central to cell cycle control, while others, such as CDK5 and CDK7, play roles in transcription and neuronal function. The development of CDK4/6 inhibitors (*e.g.*, palbociclib) has been a major breakthrough in cancer therapy[68,69]. The CDK regulation mechanism relies on positive phosphorylation (CDK activating kinase, CAK) and negative phosphorylation (Wee1, MYT1), as well as related CDK-cyclin complexes that assemble into highly interconnected regulatory mechanisms that drive cell cycle progression[70,71].

The activation of CDK kinase under specific conditions may have therapeutic effects on neurodegenerative diseases and autoimmune diseases[72]. In some neurodegenerative disease models, the activation of CDK5 has been proven to promote the survival of neurons and axonal regeneration. However, CDK kinase has a wide range of substrate specificity in cells. How to accurately regulate its activity to avoid side effects is the focus of current research[73]. In addition, long-term treatment may lead to drug resistance, which is also an urgent problem to be solved[74].

2.1.3. Protein kinase D (PKD)

PKD is a novel serine/threonine kinase and diacylglycerol (DAG) receptor protein family that plays a role in regulating signaling pathways of G protein-coupled receptors (GPCRs) and tyrosine kinase receptors[75]. The PKD protein family consists of three members, namely PKD1/PKCμ, PKD2, and PKD3/PKCν, which share high structural homology and all possess a carboxy-terminal domain, a PH domain, and an N-terminal DAG-rich cysteine domain (C1 domain)[76]. Deletion of the PH domain can result in sustained activation of PKD, indicating its function as an inhibitory regulatory subunit for PKD catalytic activity[77]. Each N-terminal domain of the PKD family subunits exhibits distinct characteristics leading to their diverse functions[78]. The PKD

family contains two conserved serine sites that can be phosphorylated by PKCδ to activate them[79]. This activation pathway can also be modulated by other factors or signaling pathways. For instance, DAG regulates the localization of PKDs; upon binding with DAG through their C1 domains, they localize to cell membranes and the Golgi apparatus[80]. Different signals enable shuttling between cytoplasmic and nuclear compartments; Some growth factors or hormones are capable of activating PDKs[81]. So far, reported functions related to polycystic kidney disease (PKD)[82]. Serving as downstream target molecules of protein kinase C (PKC), involved in fundamental signal regulation. Acting as a Golgi apparatus-localized kinase to regulate protein transport, such as insulin secretion function in pancreatic β cells[83]. Mediating antigen receptor signaling and regulating lymphocyte adhesion, thereby modulating immune system-related functions[84].

In recent years, kinase activation therapy for PKD has made significant progress. Pyrukynd (mitapivat), as a pioneering oral pyruvate kinase (PK) activator, it has been approved by the United States and the European Union for the treatment of hemolytic anemia in adult patients with PKD. The drug can significantly improve the hemolysis and anemia of patients by allosteric binding PK tetramer and increasing PK activity. The clinical trials of pyrukynd (activate and activate-t) provide important data for evaluating the efficacy and safety of the drug.

2.1.4. Mammalian target of rapamycin (mTOR)

MTOR, as a highly conserved serine/threonine protein kinase, plays a key role in cell growth, proliferation, survival and autophagy[85]. In recent years, as a potential therapeutic strategy, activating mTOR kinase has attracted extensive attention in the treatment of a variety of human diseases. MTOR is an important component of the PI3K/AKT/mTOR signaling pathway, and its activity disorder is closely related to a variety of diseases, including cancer, insulin resistance, arthritis, osteoporosis and neurodegenerative diseases[86]. In cancer treatment, although inhibiting the overactivated mTOR signaling pathway has become an effective treatment strategy, in some specific situations, activating mTOR kinase may also have certain therapeutic potential, such as promoting the proliferation and activation of immune cells and enhancing the body's anti-tumor immune response[87]. In addition, although mTOR kinase has shown some therapeutic effects in some disease models, its clinical application still faces many challenges, such as drug side effects, the generation of drug resistance and the determination of the treatment window.

2.1.5. Unc-51 like autophagy activating kinase 1 (ULK1)

ULK1, a serine/threonine kinase has attracted extensive attention due to its role in the initiation of autophagy. ULK1 is composed of 1050 amino acids with a molecular weight of 113 kDa, including an N-terminal kinase domain, a proline/serine region and a C-terminal domain[88]. The existing small molecule regulators targeting ULK1 regulate the kinase activity of ULK1 by acting on kinase domain. C-terminal domain contains two microtubule interaction and transport (MIT) domains, which promote the interaction of ULK1 with mATG13 and FIP200 (ULK1, mATG13, FIP200 and ATG101 form ULK complex)[89]. The PS region connecting KD and MIT is less conservative and consists of about 500 amino acids. It is mainly responsible for the interaction between ULK1 and autophagy microtubule-associated protein LC3 and the phosphorylation of ULK1 by upstream kinases (such as AMPK, mTORC1, etc.). It is worth noting that KD and MIT are highly conserved in yeast and mammals[90,91]. The biological function of ULK1 in cancer is mainly divided into two parts: autophagy function and non-autophagy function. As an autophagy promoter, ULK1 promotes the formation of autophagosomes and plays a key role in the initiation of autophagy[92]. The post-translational modification of ULK1 is regulated by the upstream pathway, which affects the downstream autophagy-related signaling pathway regulated by ULK1[90,93]. Autophagy plays a double-edged sword role in cancer of different types, stages and genetic backgrounds. In the early stage of tumorigenesis, activation of autophagy may prevent the development of cancer. On the contrary, both enhanced and inhibited autophagy have been proposed as potential therapeutic strategies in advanced cancer[94]. Because the role of autophagy in cancer is extremely complex and always depends on the specific environment, it still needs further research and discussion.

ULK1 mediated autophagy can maintain gene stability in the early stage of cancer and induce programmed cell death in specific types of cancer, thus inhibiting the occurrence and development of cancer. Especially in cancer with low expression of ULK1 or autophagy deficiency, inducing autophagy-dependent cell death by activating ULK1 mediated autophagy may be a promising therapeutic strategy. Among them, breast cancer, especially triple negative breast cancer, is a typical example. ULK1 was found to be significantly low expressed in TNBC[95], Moreover, drug intervention can induce autophagy-dependent cell death and apoptosis after targeted activation of ULK1, thus inhibiting the proliferation of TNBC *in vitro* and *in vivo*[31]. In addition, MEK inhibitor trimetinib can induce mitochondrial autophagy by upregulating the level of ULK1, thereby inhibiting TNBC bone metastasis[96]. This confirms that mitochondrial autophagy, regulated by ULK1 is involved in the therapeutic response of breast cancer to targeted drugs. At the same time, ULK1 mediated autophagy is also closely related to the regulation of tumor glycolysis and the maintenance of immunosuppression, which may be one of the important mechanisms of its tumor inhibitory effect[97].

In addition, ULK1 mediated autophagy can promote the survival of tumor cells by maintaining mitochondrial function, reducing DNA damage and enhancing the anti-stress ability of tumor cells, leading to the occurrence and development of cancer. ULK1 is highly expressed in many cancers, such as colorectal cancer, liver cancer, prostate cancer, glioblastoma and acute myeloid leukemia (AML)[91]. Silencing of eukaryotic elongation factor-2 kinase (eEF2K) in colorectal cancer can lead to the activation of AMPK−ULK1 pathway and the up regulation of autophagy, thus promoting the survival of colorectal cancer cells[98]. In the hypoxic microenvironment of pancreatic ductal adenocarcinoma (PDAC), ULK1 mediated autophagy and glycolysis can stabilize the interaction of Yap in the nucleus and promote the malignant progression and drug resistance of tumors[99,100]. It is worth noting that activating autophagy by targeting MDH1−ULK1 and LKB1−AMPK−ULK1 pathways may become a new therapeutic strategy for PDAC[101,102]. In addition, the combination of ULK1 and LC3B was found to be the main factor of poor prognosis in patients with hepatocellular carcinoma (HCC) based on tissue microarray analysis[103]. Inhibition of ULK1 by drug intervention can block autophagy and induce apoptosis, thus inhibiting the proliferation and survival of HCC cells[104]. It was found that knockdown of ULK1 could inhibit autophagy and prostate cancer cell proliferation in prostate cancer, and the high expression of ULK1 protein in primary prostate cancer was positively correlated with the recurrence rate, indicating the potential of inhibiting ULK1 in the treatment of prostate cancer[105].

The study of FLT3-ITD mutant leukemia found that ULK1 mediates protective autophagy in tumor and can promote the survival of leukemia cells[106]. The analysis based on TCGA database also found that ULK1 mRNA was highly expressed in AML, which was associated with the poor prognosis of AML[107]. Inhibition of ULK1 in chronic myeloid leukemia restores the sensitivity of leukemia stem cells to tyrosine kinase inhibitors[108]. ULK1 mediated autophagy plays a role in promoting cancer in a variety of leukemia, including drug resistance. In addition, ULK1 mediated autophagy has also been found to contribute to tumor growth and survival in glioblastoma[109].

ULK1 not only has complex functions in the occurrence and development of cancer by regulating the level of autophagy, but also plays an important role in the regulation of the non-autophagy pathway in cancer. ULK1 inhibits breast cancer metastasis by directly phosphorylating the downstream substrate Exo70[110]. ULK1/2 inhibits the activity of substrate Pxn through direct phosphorylation, impairs the assembly of actin stress fibers and focal adhesion (FA), thus hindering the contraction and migration of breast cancer cells[111]. This reveals a new function of ULK1/2 in the mechanical transduction of breast cancer cells, which has nothing to do with its autophagy function. In addition, ULK1 was found to ensure normal cell cycle progression by phosphorylation of spindle assembly checkpoint protein Mad1, and the deletion of ULK1 would enhance chromosome instability and cytotoxicity under the effect of paclitaxel, and inhibit the growth of cancer cells[112]. ULK1 plays different functions in different types and different stages of tumors of the same type. ULK1 mediated autophagy usually plays an anti-cancer role in the early stage of tumor, maintains cell growth and survival in the late stage of tumor, and plays a role in promoting cancer. And the effect of non-autophagy function of ULK1 on the tumor is also environment-dependent. However, activation of ULK1 in certain types of cancer (such as breast cancer) can inhibit the proliferation and metastasis of cancer cells in an autophagy-dependent manner or inhibit the migration and invasion of tumor cells through a non-autophagy pathway[31,96,110,111]. These findings suggest that targeted activation of ULK1 is a feasible and potential tumor treatment strategy in cancer with low expression of ULK1 or autophagy deficiency[90].

The role of the human innate immune system in eliminating invasive viruses mainly depends on type I interferon, Type I IFN). Type I IFN has been used to treat viral infections, regulate immunity, and even treat tumors[113,114]. In the presence of AKT (AKT serine/threonine kinase 1), type I IFN induced the phosphorylation and activation of serine 757 in ULK1, and in the presence of p38 MAPK, type I IFN induced the phosphorylation and activation of serine 757 in ULK1, ULK1 activation can further promote the transcriptional activation of IFN stimulated gene, such as immune related GTPase family m member 2, GTP cyclohydrolase 1, IFIT3, 2′-5′-oligoadenylatesynthase like 2, interference regulatory factor 7, IRF9 and IFIT2, thus exerting the innate immune effect of IFN[115]. ULK1 mediated MAP3K11 (mitogen-activated protein kinase kinase kinase 11) and MAPK7 activation are also essential for the antiviral effect of type I IFN[116]. In addition, ULK1 deletion can inhibit the antiviral and antiproliferative ability of type I IFN[117].

2.1.6. Eukaryotic elongation factor 2 kinase (eEF2K)

eEF2K is an atypical protein kinase that phosphorylates and inactivates eEF2, the protein that helps ribosomes move along mRNAs during the elongation stage of protein synthesis[118,119]. Phosphorylation of eEF2 on Thr56 of its mature polypeptide renders it unable to interact with ribosomes[120] and thus inactive in translation elongation. eEF2K is therefore a negative regulator of the elongation stage of protein synthesis; this is the stage that consumes almost all (>99%) of the energy (ATP and GTP) and amino acids used by protein synthesis. The addition of each amino acid requires two GTP molecules (used directly in elongation and hydrolysed to GDP) and one ATP (used in attaching amino acids to tRNAs, which is hydrolysed to AMP, *i.e.*, the equivalent of two high-energy bonds). In many cells, protein synthesis is a major part of the cellular energy economy, using up to 30%−35% of total ATP (or equivalents). Human eEF2K contains 725 amino acid residues; the catalytic domain lies towards the N-terminus. When cDNAs for eEF2K were first cloned, it was clear that the sequence of eEF2K did not resemble those of any other known kinase[121]. As more genomic data became available, it became clear that eEF2K belongs to a small family of protein kinases, which are termed 'α-kinases' on the basis of their supposed preference for phosphorylating residues in α-helices (other protein kinases prefer residues in β-turns)[122].

AMPK/eEF2K/eEF2 axis is involved in the inhibitory process of Huanglian Jiedu Decoction (HLJDD) on human hepatocellular carcinoma (HCC)[123]. HLJDD can inhibit the mTOR pathway by activating AMPK signal transduction, reducing the phosphorylation of eEF2K and activate eEF2K activity, leading to the inactivation of eEF2 and inhibiting the synthesis of new proteins[123]. In the nutrient-deficient HCC cells with inactivated eEF2, the inhibitory effect of hljdd on tumor cell expansion was interfered. mTORC1 plays an important role in the onset of chronic lymphocytic leukemia (CLL)-like disease *in vitro*, MTORC1 can promote the proliferation and metastasis of leukemia, and Raptor deficiency can increase the survival rate of CLL like disease *in vivo*. Rapamycin, as an mTORC1 inhibitor, significantly reduced p-eEF2K^{Ser366} after rapamycin treatment in secondary transplanted mice[124]. The level of p-EEF2[56] increased. Rapamycin can inhibit proliferation and reduce protein synthesis by regulating eEF2K/eEF2 signal transduction in primary CLL cells[124]. These findings suggest that eEF2K/eEF2 signaling may play a role in CLL, and indicate that targeting mTORC1−eEF2K signaling can inactivate eEF2 and may disrupt protein translation extension.

2.1.7. Sirtuin3 (SIRT3)

SIRT3, as a core deacetylase in mitochondria, plays a dual role in cancer by regulating energy metabolism, oxidative stress, and epigenetic modifications. The mechanisms underlying the tissue-specific duality of SIRT3—oncogenic in colorectal cancer (CRC) yet tumor-suppressive in breast cancer—can be attributed to fundamental differences in metabolic dependencies and microenvironmental pressures across cancer types. In colorectal cancer, which frequently exhibits a hypermetabolic state reliant on one-carbon units for nucleotide synthesis and redox homeostasis, SIRT3 plays a facilitative role. By deacetylating and stabilizing serine hydroxymethyltransferase 2, a key enzyme in the mitochondrial one-carbon pathway, SIRT3 enhances the flux of one-carbon metabolism. This augmentation provides CRC cells with the necessary precursors (purines, thymidylate) and reducing power to sustain rapid proliferation and survive metabolic stress, thereby conferring a growth advantage[125]. Conversely, in breast cancer and other solid tumors, the loss of SIRT3 is often associated with tumorigenesis. Here, SIRT3 primarily functions as a guardian of mitochondrial integrity. Its downregulation leads to hyperacetylation and inhibition of critical enzymes like superoxide dismutase 2, resulting in elevated reactive oxygen species (ROS) and a

shift toward glycolytic metabolism (the Warburg effect). This metabolic dysregulation creates a pro-tumorigenic environment characterized by genomic instability and activation of pro-survival signaling pathways[126]. In neuroblastoma models, SIRT3 activators can enhance mitochondrial antioxidant capacity, reduce DNA damage, and induce cancer cell apoptosis. In addition, SIRT3 inhibits the Warburg effect and reverses the metabolic dependence of tumor cells by regulating key glycolytic enzymes such as PFKFB3 and PKM2[127]. Research has shown that SIRT3 activates the AMPK signaling pathway, promotes autophagy to clear damaged mitochondria, and inhibits tumor cell survival. In diffuse large B-cell lymphoma, the absence of SIRT3 leads to glutamine metabolism disorders, triggering autophagy-dependent cell death, suggesting that activation of SIRT3 may enhance chemotherapy sensitivity by regulating metabolic homeostasis[128]. SIRT3 inhibits the expression of oncogenes (such as c-Myc) by deacetylating histones H3K9 and H4K16. Meanwhile, it can regulate the polarization of tumor-associated macrophages, promote M1-type anti-tumor phenotype, and enhance immune response[129].

2.1.8. p90 ribosomal protein S6 kinase 3 (RSK3)

Beyond the kinases discussed above, the p90 ribosomal S6 kinase 3, a downstream effector of the ERK/MAPK pathway, presents an intriguing target for activation despite its complex role in cellular signaling. While the RSK family is often associated with promoting cell survival and proliferation, emerging evidence suggests that targeted activation of RSK3 may confer therapeutic benefits in specific pathological contexts. For instance, RSK3 activation has been shown to exhibit a neuroprotective effect in models of oxidative stress and excitotoxicity, highlighting its potential for treating neurodegenerative diseases[130]. Furthermore, a seminal study in small cell lung cancer uncovered a novel resistance mechanism wherein RSK3 activation drives survival and confers resistance to bromodomain and extra-terminal motif (BET) inhibitors. This RSK3-mediated resistance is not overcome by direct RSK3 inhibition but is effectively reversed by targeting the upstream kinase, mTOR. Combined inhibition of mTOR and BET inhibition leads to synergistic tumor regression in RSK3-high SCLC models[131]. However, given the well-established link between the MAPK/RSK axis and oncogenesis, the development of RSK3 activators demands exceptional selectivity and strategies to minimize the risk of tumorigenesis, such as tissue-specific delivery systems.

In summary, the diverse roles of ST-PKS activators underscore their therapeutic potential beyond the traditional inhibitor paradigm. From inducing context-dependent autophagy (ULK1) to modulating cellular metabolism (AMPK, SIRT3) and the cell cycle (CDKs), targeting these kinases offers novel avenues for treating cancer, neurodegenerative, and metabolic diseases. However, the functional duality of kinases like ULK1 and SIRT3 highlights a central challenge: the critical dependence on disease context and precise biological understanding. The future of ST-PKS activators development lies in achieving exquisite selectivity and identifying patient populations most likely to benefit from pathway activation, thereby navigating the fine line between therapeutic efficacy and potential toxicity.

2.2. Tyrosine protein kinases (TKS)

2.2.1. Src family kinases (SFKs)

SFKs include Src, Yes, Fyn, Lyn, Lck, HCK, FGR, BLK and Yrk. They have similar structures and functions, and are activated by a variety of mechanisms. Src is the core regulator of the tyrosine protein kinases (TKS) family that regulates the cellular signaling network. Its targeted activation shows potential value in disease treatment. Studies have shown that moderate activation of Src can enhance the ability of tissue repair, such as accelerating mucosal barrier regeneration by promoting epithelial cell migration, or regulating immune cell metabolic reprogramming to alleviate excessive inflammatory response. In the acute inflammation model, Src activators can reduce sepsis-related organ damage by stabilizing vascular endothelial connections and inhibiting excessive neutrophil infiltration. In chronic inflammatory diseases, Src mediated cytoskeleton remodeling can improve the fibrotic microenvironment, and its regulation of macrophage polarization may break the pro-inflammatory vicious cycle. However, Src activation has the risk of promoting tumor metastasis, which requires the development of tissue-specific drug delivery systems or allosteric modifiers to achieve precise intervention. At present, the space-time specific activation strategy of Src based on nano carriers has been verified in the experimental colitis model, which provides a new idea for the treatment of inflammatory diseases[132].

Fyn, a 59 kDa member of the Src kinase family, emerges as a critical regulatory molecule within the neurovascular unit, demonstrating unique therapeutic potential through targeted activation strategies in chronic cerebral hypoperfusion and cerebral small vessel disease (CSVD)[133]. Research evidence reveals that selective Fyn activation ameliorates white matter injury induced by CCH *via* promoting oligodendrocyte maturation and myelin repair, while concurrently enhancing integrin signaling in vascular endothelial cells to stabilize blood−brain barrier integrity and mitigate cerebral microvascular leakage. In neuroinflammatory regulation, Fyn activator exhibits the capacity to reprogram microglial polarization phenotypes, suppress NLRP3 inflammasome activation, and block neurodegenerative cascades. Experimental studies demonstrate that nanoparticle-delivered Fyn allosteric activators specifically enhance neuronal synaptic plasticity and improve CSVD-associated cognitive impairment. Nevertheless, given the cell type-dependent dual effects of Fyn signaling, the development of spatiotemporal-specific regulatory tools becomes imperative to circumvent potential oncogenic risks or pathological Tau hyperphosphorylation. These findings collectively delineate novel research directions for precision neuroprotection strategies targeting Fyn signaling pathways.

Lyn, a member of the TKS kinase family, exhibits dual regulatory potential in oxidative stress-related pathologies and rheumatoid arthritis (RA) therapeutics. Mechanistic studies indicate that targeted Lyn activation alleviates mitochondrial dysfunction through augmentation of antioxidant signaling (*e.g.*, Nrf2 pathway), while simultaneously suppressing Syk-mediated hyperinflammatory responses to modulate aberrant proliferation of RA synovial fibroblasts. In immunomodulatory contexts, Lyn activator demonstrates the capacity to facilitate regulatory B-cell differentiation for immune tolerance restoration, alongside inhibiting neutrophil extracellular trap (NET) formation to prevent autoantigen release[134]. Experimental validation reveals that nanoparticle-encapsulated Lyn allosteric activators selectively enhance macrophage efferocytic capacity, thereby ameliorating chronic inflammatory microenvironments. Notably, Lyn activation may paradoxically promote tumor progression *via* the PI3K/AKT signaling axis, necessitating the development of cell type-selective activation strategies[135]. Current advances in Lyn signaling reprogramming-based antioxidant-anti-inflammatory synergy offer novel therapeutic frameworks for RA management and metabolic oxidative injury intervention.

2.2.2. Janus kinase (JAK) family

JAK family includes four members, Jak1, JAK2, JAK3 and Tyk2, which play an important role in signal transduction of cytokine receptor superfamily members. JAK1, functioning as a central hub in cytokine signal transduction, offers novel therapeutic perspectives for non-alcoholic fatty liver disease through targeted activation strategies[136]. Moderate JAK1 activation exerts dual hepatoprotective effects by amplifying IL-10-mediated anti-inflammatory signaling to suppress Kupffer cell hyperactivation, thereby mitigating hepatic lipid peroxidation and inflammatory microenvironment, while concurrently promoting STAT3-dependent lipolytic gene expression to accelerate hepatocyte lipid droplet catabolism[136]. Hepatocyte-targeted JAK1 activators demonstrate multi-mechanistic efficacy in improving insulin sensitivity through AMPK/mTOR pathway-mediated inhibition of de novo lipogenesis, coupled with modulation of farnesoid X receptor signaling within the gut−liver axis. During fibrogenic progression, JAK1 activation may potentially delay collagen deposition *via* induction of senescence-associated secretory phenotype in hepatic stellate cells. Nevertheless, given the tissue-specific dual effects of JAK1 signaling, the development of spatiotemporal-selective activators becomes imperative to circumvent systemic immune dysregulation risks. These mechanistic insights establish a novel paradigm for precision therapeutic interventions in metabolic liver disorders.

JAK2, functioning as a pivotal mediator in cytokine signaling and hematopoietic regulation, presents innovative therapeutic avenues for ischemic heart disease through selective activation strategies[137]. Mechanistic investigations demonstrate that targeted JAK2 agonism enhances erythropoiesis *via* EPO/JAK2/STAT5 pathway activation to ameliorate myocardial hypoxia, while concurrently boosting cardiomyocyte autophagy-mediated clearance of damaged mitochondria, thereby attenuating ischemia-reperfusion injury[138]. Within pathological microenvironments, JAK2 activators orchestrate macrophage polarization toward reparative phenotypes, suppress IL-6-driven hyperinflammatory responses, and promote collateral angiogenesis through VEGF signaling amplification. Experimental validation confirms that cardiac-specific JAK2-activating nanoparticles enhance STAT3 phosphorylation, reducing cardiomyocyte apoptosis while improving electrophysiological stability[137]. Nevertheless, the thrombotic propensity and aberrant myeloid proliferation risks associated with JAK2 hyperactivation necessitate the advancement of spatiotemporally precise modulation technologies. Current developments in JAK2 signaling reprogramming-based strategies balancing pro-repair and anti-fibrotic effects unveil novel paradigms for metabolic-immunological synergy in ischemic cardiomyopathy therapeutics.

JAK3, a critical regulator of immune cell signaling transduction, presents novel therapeutic perspectives for HIV-associated immunodeficiency through targeted activation strategies[139]. Mechanistic studies demonstrate that selective JAK3 agonism enhances $CD4^+$ T-cell survival and functional reconstitution *via* IL-7/IL-21 receptor signaling axis, while concurrently promoting thymic output of naive T cells to ameliorate immunological reconstitution failure[140]. In chronic inflammatory modulation, JAK3 activators effectively suppress NLRP3 inflammasome activation, thereby reducing viral reactivation risks associated with pyroptosis of HIV reservoir cells. Experimental evidence reveals that nanocarrier-mediated JAK3-specific agonism restores Th17/Treg balance, repairs intestinal mucosal barrier integrity, and attenuates systemic immune activation. Notably, potential adverse effects including aberrant lymphoproliferation or autoimmune activation resulting from JAK3 hyperactivation necessitate the development of spatiotemporal-specific delivery systems to circumvent off-target consequences. Current advancements in JAK3 signaling reprogramming-based dual "immune potentiation-inflammatory suppression" strategies establish innovative therapeutic avenues for achieving functional cure through combinatorial antiretroviral therapy.

2.2.3. Epidermal growth factor receptor (EGFR)

The exploration of EGFR activation represents a frontier in kinase pharmacology, challenging the oncogene-centric view by leveraging its fundamental role in epithelial homeostasis. The key to unlocking its therapeutic potential lies in exploiting the quantitative and qualitative differences between physiological regeneration and pathological proliferation. Precise, localized activation of EGFR accelerates wound healing not merely by stimulating proliferation, but by orchestrating a coordinated response: it enhances keratinocyte migration through focal adhesion kinase signaling, promotes matrix metalloproteinase (MMP)-dependent remodeling, and strengthens epithelial barrier function[141]. The paramount challenge is to avoid the ligand-induced dimerization and sustained signaling that lead to RAS−RAF−MAPK hyperactivation and oncogenesis. Sophisticated pharmacological strategies are required to achieve this. One approach involves developing "weak" or partial activators that produce a submaximal signal sufficient for migration and repair but inadequate for driving transformation. Alternatively, engineering prodrug activators activated specifically by enzymes enriched in the wound microenvironment (*e.g.*, matrix metalloproteinases) could ensure spatially restricted activity. The success of EGFR activation therapy hinges on this precise spatiotemporal control, effectively creating a "therapeutic window" for a classic oncogene.

Collectively, the exploration of TKS activators reveals a strategic shift towards harnessing kinase signaling for tissue repair and immune modulation. The potential of activating kinase signaling like JAK/STAT pathways for immune reconstitution demonstrates a move away from purely cytotoxic approaches. A key insight from this analysis is that successful activation hinges on cell-type and pathway specificity, as exemplified by the opposing roles of Src in inflammation versus cancer. Overcoming the risks of off-target activation and systemic toxicity will require advanced delivery technologies and a deeper understanding of signaling networks to ensure that TKS activation confers regenerative benefits without promoting pathological processes.

Kinase activators are increasingly being applied in disease treatment, and representative kinases together with their major disease indications are summarized in Table 1[42,65,75,85,124,130−137,141,142].

3. Progress of protein kinase activators

Activators, also known as stimulants, are drugs, enzyme activators and hormones that can enhance the activity of another molecule and promote a certain reaction. Activators are drugs, enzyme activators and hormones that can enhance the activity of another molecule and promote a certain reaction. It has both high affinity and high intrinsic activity with the receptor, and can combine with the receptor to produce the maximum effect (E_{max}), also known as complete activators. In recent years, activator drugs have made significant progress in metabolic diseases, tumor immunity, pain

Table 1 Activating protein kinases: function and disease indications in disease intervention.

Kinase	Family	Function	Disease indication	Ref.
MAPK	ST-PKS	Regulates cell growth, differentiation, apoptosis, and stress responses. Activates downstream transcription factors (*e.g.*, AP-1, p53). ERK1/2 promotes angiogenesis, while JNK/p38 mediates apoptosis and inflammation	Cancer (*e.g.*, lung cancer, breast cancer), neurodegenerative diseases, cardiovascular disorders	42
CDKs	ST-PKS	Core regulators of cell cycle progression. CDK−cyclin complexes drive transitions between cell cycle phases	Cancer, neurodegenerative diseases (*e.g.*, AD)	65
PKD	ST-PKS	Regulates GPCR and tyrosine kinase signaling. Involved in Golgi trafficking, immune response, and insulin secretion	Polycystic kidney disease (PKD), cancer, diabetes	75
mTOR	ST-PKS	Integrates nutrient and growth signals to regulate cell growth, autophagy, and metabolism	Cancer, insulin resistance, neurodegenerative diseases (*e.g.*, AD), osteoporosis	85
ULK1	ST-PKS	Initiates autophagy and regulates innate immunity. Phosphorylates downstream targets to promote autophagosome formation	Cancer, viral infections, neurodegenerative disorders	142
eEF2K	ST-PKS	Phosphorylates eEF2 to inhibit translation elongation. Regulates energy metabolism during stress	Cancer, neurodegenerative diseases	124
RSK3	ST-PKS	Downstream effector of ERK/MAPK. Promotes cancer cell survival by inhibiting pro-apoptotic signals. Potential oncogenic signaling if overactivated	Small cell lung cancer and neurodegenerative diseases	130,131
Src	TKS	Participates in cell proliferation signaling, regulates cytoskeleton reorganization, participates in cell adhesion and invasion, and regulates cell metabolism	Acute and chronic inflammatory diseases	132
Fyn	TKS	Participates in the regulation of cell growth and differentiation, cytoskeleton regulation, immune cell signaling, and regulation of nervous system function	Chronic cerebral hypoperfusion and CSVD	133
Lyn	TKS	Participates in signaling and apoptosis, regulates cell activation, and modulates the cytoskeleton	Oxidative stress-related diseases and rheumatoid arthritis	134,135
JAK1	TKS	Participates in cytokine signaling, immune regulation, hematopoietic regulation, regulation of cell growth and differentiation, and regulation of inflammatory responses	Non-alcoholic fatty liver disease	136
JAK2	TKS	Participates in cytokine signaling and immune responses, regulates hematopoietic processes and maintains intracellular homeostasis	Ischemic heart disease	137
EGFR	TKS	Orchestrates epithelial repair by enhancing cell migration and barrier function. Classic oncogene; sustained activation drives tumorigenesis	Chronic wounds and mucositis	141

management, and other fields. The development of activators is moving towards multi-target, high selectivity, long-acting, and safety optimization[143]. Structural biology and AI assisted design have accelerated drug iteration, such as the rapid clinical advancement of BGM0504. Meanwhile, the deepening of basic research, such as the CysLT2R mechanism, has laid the foundation for innovative target development. In the future, activators drugs are expected to further break through treatment bottlenecks in fields such as metabolism, oncology, and neurology.

518 kinase families (approximately 50 families) have been found in the human body, and kinase family members have highly conserved structures in the ATP binding domain, making the development of selective activators extremely difficult. Although this multi-target characteristic is beneficial in some cancer treatments, it may also lead to off target toxicity[144]. For example, diplovecim, as a multi-pathway activator, coordinates the co-activation of TLR1/TLR2 receptors while activating dendritic cell maturation and amplifying $CD8^+$ T cell-mediated immune responses. This multi-target synergistic strategy overcomes the limitations of single pathway immunotherapy and is used for the treatment of advanced or treatment-resistant melanoma[145].

3.1. Small-molecule pharmacological agents that directly or indirectly activate the MAPK signaling pathway

MAPK (mitogen activated protein kinase) signaling pathway plays a central role in cell proliferation, differentiation, apoptosis and inflammatory response. In recent years, the researches on MAPK activators have gradually become a new direction of disease treatment, especially in the fields of cancer, neurodegenerative diseases, cardiovascular diseases and so on.

Diprovocim, functioning as a multi-pathway activator targeting TLR1/TLR2 receptors with downstream engagement of p38 MAPK and NF-κB signaling axes, introduces an innovative immunotherapeutic mechanism for melanoma management[145]. Mechanistically, it orchestrates co-activation of TLR1/TLR2 receptors to potentiate p38 MAPK/NF-κB signaling, initiating phosphorylation cascades of IKKα/β, JNK, and ERK kinases. This coordinated signaling stimulates TNF-α and IL-6 cytokine secretion while accelerating IκBα degradation to enhance NF-κB nuclear translocation, thereby reprogramming the tumor microenvironment toward pro-inflammatory states[145]. Diprovocim activates dendritic cell maturation and amplifies $CD8^+$

T-cell-mediated immune responses, effectively suppressing melanoma progression. This multi-targeted synergistic strategy overcomes the limitations of single-pathway immunotherapies, establishing a novel combinatorial approach with PD-1/PD-L1 inhibitors for advanced or therapy-resistant melanomas. Future investigations necessitate dosage optimization to balance robust immune activation with mitigation of hyperinflammatory risks, while exploring temporal control of pathway engagement to maximize therapeutic index.

Fulvestrant, functioning as a selective estrogen receptor degrader, demonstrates a unique therapeutic mechanism in pituitary adenoma (PA) management[146]. Its pharmacological action involves concurrent activation of the PTEN/MAPK signaling pathway and suppression of PI3K/AKT pro-survival signaling, thereby inducing tumor cell apoptosis while downregulating estrogen receptor expression to block hormone-dependent proliferation. Preclinical investigations reveal that fulvestrant significantly inhibits PA progreson, particularly exhibiting therapeutic potential against invasive or recurrent tumors refractory to conventional interventions[146]. This dual-action mechanism combining estrogen receptor degradation with PTEN/MAPK axis activation provides a novel targeted strategy for PAs with limited responsiveness to standard surgical or dopamine activators therapies. Future research directions should focus on elucidating synergistic effects with existing treatment modalities and characterizing resistance mechanisms to optimize therapeutic protocols for endocrine-resistant pituitary neoplasms.

Activation of JNK and p38 isoforms in the MAPK pathway can induce apoptosis and autophagy in lung cancer cells. Traditional Chinese medicine compounds such as "Fufang Tuixiao" induce apoptosis of lung adenocarcinoma cells by activating p38MAPK, upregulating Pro-apoptotic protein Bax and down regulating anti apoptotic protein Bcl-2[147]. Baiqiuli alcohol in Mufangji Decoction promotes apoptosis and autophagy of A549 lung cancer cells by activating the JNK pathway[147]. The activation of the JNK pathway plays an important role in promoting cancer cell apoptosis. Studies have shown that arsenic trioxide and other chemotherapeutic drugs can treat leukemia by activating the JNK pathway[148]. Arsenic trioxide modulates Heat Shock Protein 70 expression through the ROS/JNK/HSF1 signaling axis, a process characterized by elevated reactive oxygen species (ROS) levels and phosphorylation-dependent JNK activation[146]. Mechanistically, JNK drives Hsp70 transcriptional activation *via* phosphorylation-mediated HSF1 modification, thereby establishing a cytoprotective pathway that sustains cellular survival through enhanced oxidative stress tolerance[149]. This regulatory cascade underscores the critical role of redox-sensitive kinase signaling in maintaining proteostatic adaptation under arsenic-induced stress conditions.

Ursolic acid (UA), a naturally occurring pentacyclic triterpenoid compound, demonstrates multi-target therapeutic potential in bladder cancer management[150]. Mechanistically, UA activates the JNK signaling pathway to upregulate pro-apoptotic protein expression, while concurrently suppressing the mTORC1 pathway to inhibit tumor cell proliferation, thereby synergistically inducing growth arrest and programmed cell death[150]. Experimental evidence reveals that UA exhibits selective cytotoxicity against bladder cancer cells by inducing apoptosis while demonstrating minimal toxicity toward normal cell lines[150]. This dual-mechanism action overcomes the limitations of conventional single-target therapies, offering a novel strategy for drug-resistant bladder cancer treatment. Future research should focus on elucidating its target specificity and exploring synergistic effects with immune checkpoint inhibitors to facilitate clinical translation.

Endometriosis is characterized by the growth of endometrial-like tissue outside the uterus, leading to chronic inflammation and pelvic pain. Pathological hyperplasia, angiogenesis, and related inflammation are the hallmark features of EM lesions. WIN 55 reduces proliferation and angiogenesis *in vitro* through MAPK/AKT mediated cell apoptosis. TRPV1 expression was reduced in the dorsal root ganglia of the EM mouse model exposed to WIN 55, leading to decreased signal transduction of pain stimuli[151].

In addition, the activation of the p38 pathway has also been proven to have the effect of inhibiting tumor growth and metastasis. Some chemotherapeutic drugs such as nocodazole and paclitaxel play a therapeutic role by activating p38 pathway[152]. Stilbene compounds (resveratrol/pterostilbene) exert cardiovascular protective effects through activating AMPK−ERK5/HDAC5−KLF2 signal axis and multi-target synergy of antioxidant and anti-aging. However, the treatment of activated MAPK kinase also faces challenges[153].

The concept of therapeutic ERK pathway activators has been proposed, which exhibit selective activity against cancer cell lines associated with ERK compared to normal cells[154]. It is noteworthy that the ERK signaling pathway is abnormally activated in many cancers, and traditional research has focused on developing inhibitors to block this pathway. However, the hyperactivation susceptibility of cancer cells to ERK provides a possibility for the development of activators, which may be a new therapeutic strategy. The key to this strategy is to find small-molecule compounds that can selectively activate the ERK signaling pathway in cancer cells without affecting normal cells. the activation of ERK1/2 may be beneficial for cancer treatment in certain cases. For instance, certain ERK1/2 variants have been identified in human cancers and are associated with resistance to RAF inhibitors and MEK inhibitors. Research has shown that intermittent dosing in combination with ERK1/2−MITF pathway activators can inhibit the proliferation of drug-resistant melanoma cells. In this study, the use of ERK1/2 activator TBHQ and MITF inhibitor ML329, following the withdrawal of BRAF inhibitor vemurafenib, further activates the ERK1/2−MITF pathway, aiming to achieve better inhibition of drug-resistant melanoma proliferation. The results showed that ERK1/2 activator TBHQ and MITF inhibitor ML329 can produce a synergistic effect with drug withdrawal, enhancing the inhibition of drug-resistant melanoma cell proliferation. Dikafosson promotes corneal epithelial healing through intracellular calcium-mediated activation of ERK, effectively promoting corneal epithelial wound healing. This effect may be due to the upregulation of Ca^{2+} mediated by ERK through P2Y2R, which stimulates cell proliferation and migration[155]. By targeting effectors such as EGFR with ligand-mimetic molecules, ERK can be activated. Although these therapeutic agents are not selective for their direct targets, they may have selective detrimental effects on cancer cells. Existing ERK activators may all be ERK pathway activators, not directly acting on ERK itself.

Nr4a1, a member of the NR4A subfamily of nuclear receptors, is a ligand-activated transcription factor. NR4A1 may promote renal fibrosis by activating p38 MAPK kinase, and renal interstitial fibrosis (RIF) is a common cause of end-stage renal disease[156]. Octanol glucoside can promote osteoblast activity and correct bone loss in osteoporosis mice by directly binding to p38 protein, and is a p38 activator to improve downstream signaling, which has great potential in targeting p38 for osteoporosis treatment[157]. Anisomycin (an activator of p38MAPK) eliminates the positive effects of glutamate on ethanol-induced oxidative stress and inflammation. Overall, the photosynthetic isoflavones extracted

from licorice can alleviate alcoholic liver injury through the p38 MAPK/Nrf2/NF-κB pathway, and can potentially serve as a new health product or drug to alleviate alcoholic liver disease[158].

For the MAPK signaling system in PA, the activation of ERK signaling is generally believed to promote cell proliferation and growth. The activation of p38 and JNK signaling is generally believed to promote cell apoptosis. The role of MAPK in the treatment of PA is demonstrated by the current use of drugs such as somatostatin analogs such as SOM230 and OCT, dopamine activators such as cabergoline and bromocriptine, and the inhibitory effect of retinoic acid on the MAPK pathway. In addition, putative molecular targets based on the MAPK pathway include 18β-glycyrrhetinic acid, dopamine somatostatin chimeric compound (BIM-23A760), UA, fluconazole, Raf kinase inhibitor protein, epidermal growth factor pathway substrate 8, with EGF like and two follicle stimulating factor like domains, cold inducible RNA binding protein, miR-16, and mammalian infertility like kinase. The combination of ERK inhibitors (such as SOM230, OCT, or dopamine) with p38 activators (such as cabergoline, bromocriptine, and fluvoxetine) and/or JNK activators (such as UA), or the development of a single drug (such as BIM-23A760) to target the ERK and p38 or JNK pathways, may produce better anti-tumor effects on PA[159].

3.2. Small-molecule pharmacological agents that directly or indirectly activate the mTOR signaling pathway

It is worth noting that the activation of mTOR kinase is a complex biological process involving the interaction of a variety of upstream signaling molecules and downstream effectors. Therefore, when developing the therapeutic strategy of activating mTOR kinase, we must fully consider its complex signal network and influence on different cell types[160].

NV-5138, a novel dual activator of mammalian target of rapamycin complex 1 (mTORC1) and brain-derived neurotrophic factor (BDNF) signaling pathways, represents an innovative neural plasticity-targeting strategy for depression therapeutics[161]. Mechanistically, it orchestrates mTORC1 activation to enhance synaptic protein synthesis while potentiating BDNF expression, thereby promoting hippocampal neurogenesis and synaptic remodeling to reverse chronic stress-induced neural circuit impairments[161]. NV-5138 rapidly ameliorates behavioral deficits in depression models, with sustained therapeutic efficacy achieved through single-dose administration, overcoming the therapeutic latency characteristic of conventional antidepressants[161]. This dual-pathway synergy establishes a precision intervention paradigm for treatment-resistant depression, warranting further investigation into clinical translatability and potential synergistic interactions with serotonergic pharmacotherapies to optimize therapeutic outcomes.

Docosahexaenoic acid (DHA) attenuates palmitate-induced apoptosis by autophagy upregulation *via* GPR120/mTOR axis in insulin-secreting cells. DHA specifically induces phosphorylation of S2448 in mTOR, while phosphorylation of S2481 decreases. DHA-induced autophagy activation with protection against palmitic acid-induced apoptosis mediated by the GPR120/mTOR axis. DHA has therapeutic effects on pancreatic beta cells induced by PA[162].

Ipastatin combined with sorafenib inhibits HepG2 cell proliferation *in vitro*, blocks the cell cycle at G0/G1, promotes cell apoptosis, and induces autophagy. Treatment with the specific mTOR activator MHY-1485 can increase mTOR phosphorylation while inhibiting cell apoptosis and autophagy[163].

Tanshinone IIA is a well-known small molecule that has significant cardioprotective effects on heart failure. Tanshinone IIA can significantly improve cardiac function, reverse pathological changes in the body, and restore autophagic flux by promoting autolysosome degradation and autophagosome formation. mTOR activator MHY1485 eliminates TSA through the ULK1−Beclin1/TFEB−LAMP1 signaling pathway *in vitro*[164].

3.3. Small-molecule pharmacological agents that directly or indirectly activate the ULK1 signaling pathway

Unc-51-like kinase 1 (ULK1) is well-known to initiate autophagy, and the downregulation of ULK1 has been found in most breast cancer tissues. So far, only two small molecules, LYN-1604 and BL-918, have been found to directly activate ULK1, and only LYN-1604 has been reported to inhibit the proliferation of triple negative breast cancer, while BL-918 has not been studied for its anti-tumor activity[31,165]. LYN-1604 is a potent ULK1 activator with potential therapeutic effects on breast cancer. According to the results of TCGA and tissue microarray analysis, ULK1 is significantly underexpressed in breast cancer, especially triple negative breast cancer, and is considered as a potential therapeutic target for TNBC[31]. Through three rounds of structure-based virtual screening, the lead compound DB01127 was obtained. Subsequently, the structure−activity relationship of the lead compound was analyzed and the structure was optimized. Firstly, the chlorophenyl and imidazole rings of DB01127 were replaced with 2-naphthyl and *n*-boc-piperazinyl, respectively, to obtain compound UA1-03. It is worth noting that the nitrogen atom of *n*-boc-piperazinyl interacts with the amino group of lys50 side chain through hydrogen bond, while the naphthyl group is regarded as a pharmacodynamic group. Subsequently, several methylene-containing compounds were obtained by introducing substituents on acyl piperazine-1-yl. The kinase activity of ULK1 at 100 nm was 141.37%−160.29%, indicating that methylene enhanced the activation effect. Finally, LYN-1604 was obtained by introducing diisobutylamine into acyl piperazine-1-yl. The last step may improve the activity by increasing the volume of N-substituents and enhancing the hydrophobic interaction with leu53. In addition, tyr89 has been proven to be the key amino acid residue of ULK1 binding to LYN-1604. As the best candidate compound, LYN-1604 (ULK1 EC_{50} = 18.94 nmol/L, MDA-MB-231 IC_{50} = 1.66 μmol/L) showed the best ULK1 activation and antiproliferative activity, which was nearly 10 times higher than that of UA1-03. Further studies showed that LYN-1604 could induce apoptosis and autophagy-dependent death by activating ULK1 complex *in vitro* and *in vivo*, thus exerting good TNBC proliferation inhibitory activity[166]. BL-918, a novel ULK1 activator, may be a candidate drug for the treatment of Parkinson's disease (PD)[165]. By comparing the structure of ULK1 kinase domain and AMPK, the ULK1 activation pocket for virtual screening was determined. Under the guidance of *in vitro* activity results (ULK1 kinase activity and MDC positive rate), the lead compound was subjected to multiple rounds of structural modification, and finally BL-918 (EC_{50} = 24.14 nmol/L) was obtained. From the perspective of structure−activity relationship, the interaction between BL-918 and the key amino acid residues of ULK1 was enhanced in the process of structural optimization. Among them, the trifluoromethyl group of BL-918 forms three halogen bonds with Ala85 and Asn86, which helps to enhance the

binding conformation, while the phenolic hydroxyl group of Tyr89 forms a hydrogen bond with the carbonyl group of the scaffold. In addition, the $\pi-$cation interaction between the nitrogen cation of lys50 and the parent nucleus and difluorophenyl, as well as the $\pi-$sulfur bond between the phenyl group and thiourea group of Tyr89, are important for improving the interaction of ULK1−BL-918[165].

3.4. Small-molecule pharmacological agents that directly or indirectly activate the eEF2K signaling pathway

The activation of eEF2K leads to phosphorylation and inhibition of eEF2, thereby reducing the mRNA translation rate. Emerging evidence indicates that exacerbated activation of eEF2K is detrimental to tumor survival. Nelfinavir, an inhibitor of HIV aspartate proteases, triggers strong activation of eEF2K, leading to the phosphorylation of eEF2. Nelfinavir is a well-known anticancer medication that overactivates eEF2K to reduce tumor viability. It has a generally safe profile and is bioavailable orally[167]. NFR signals eEF2K activation independently of eEF2K-activating pathways such as mTORC1 inhibition or AMPK. Everolimus sensitizes nasopharyngeal cancer cells to lapatinib by activating eEF2K, providing a possible framework for combination treatment[168]. The mTOR inhibitor everolimus enhances lapatinib-induced autophagy and potentiates the cytocidal effect of lapatinib in nasopharyngeal.

3.5. Small-molecule pharmacological agents that directly or indirectly activate the SIRT3 signaling pathway

In recent years, structure-based high-throughput screening techniques have driven the development of SIRT3 activators. By targeting autophagy-related pathways, small molecule compounds with drug properties can be screened, which can specifically activate SIRT3 and induce tumor cell apoptosis[129]. In addition, natural products such as resveratrol derivatives can activate SIRT3 through allosteric activation, which shows a significant anti-tumor effect in breast cancer models[169,170]. Current SIRT3 activators face issues such as low selectivity and off-target effects. YC8-02 is effective as a SIRT3 inhibitor in the treatment of lymphoma, but its activators may have varying therapeutic effects due to tissue-specific expression differences[128]. In addition, the dual role of SIRT3 in promoting and inhibiting cancer requires stratification of patient populations through biomarkers to achieve precise treatment. Combining SIRT3 activators with immune checkpoint inhibitors (such as PD-1/PD-L1 antibodies) can synergistically enhance anti-tumor immunity. In colorectal cancer, activation of SIRT3 may reverse the immunosuppressive microenvironment and increase the response rate to immunotherapy Developing mitochondrial-targeted nanocarriers can increase the enrichment of activators in tumor tissues and reduce toxicity to normal tissues[125]. The *SIRT3* gene expression level of SIRT3 activators encapsulated in liposomes significantly increased, which may be a potential anti-cancer strategy in the future[171]. Using deep learning to predict the conformational sites of SIRT3 and design highly selective activators. Based on AlphaFold's three-dimensional structural simulation of SIRT3, multiple candidate molecules have been screened for preclinical evaluation[129]. SIRT3, as a key node in metabolic and epigenetic regulation, has shown potential as an activator in cancer treatment. However, its dual role requires treatment strategies to be based on tumor type and molecular typing. Future research needs to focus on developing highly selective activator, optimizing combination therapies, and deeply analyzing their mechanism heterogeneity in different cancers to promote clinical translation.

3.6. Other signaling pathways

The hepatocyte growth factor (HGF) is the primary endogenous ligand for the c-MET receptor tyrosine kinase. Therefore, activation of the HGF/c-MET pathway represents a strategy for indirectly activating the kinase function of c-MET. This signaling axis is a critical regulator of neuronal survival and synaptic plasticity. Emerging evidence suggests pharmacological activation of this pathway may counteract neurodegenerative progression. The active metabolite derived from a novel HGF/MET positive modulator demonstrates significant neuroprotection by reducing Aβ-induced neuronal mortality[147]. Functioning as a first-in-class small-molecule activator specifically targeting the HGF/MET pathway, HGF/MET positive modulator exerts dual mechanisms of action combining neurotrophic support and anti-inflammatory modulation to remodel the neural microenvironment[172]. Currently undergoing phase II clinical evaluation, this therapeutic candidate represents a novel intervention strategy for dementia management that marks a paradigm shift from single-target approaches to systemic neuromodulation strategies in neurodegenerative disease therapeutics. Amyotrophic lateral sclerosis, a fatal neurodegenerative disorder of motor neurons, remains inadequately addressed by current therapeutic strategies that fail to substantially modify disease progression. The MET receptor tyrosine kinase, a critical regulator of motor neuron survival with dual neurotrophic and immunomodulatory functions, presents therapeutic potential though limited by the pharmacokinetic deficiencies (short half-life, poor bioavailability) of its endogenous ligand HGF/SF. Novel MET-specific activators demonstrate enhanced neuroprotective efficacy compared to HGF/SF, significantly delaying disease progression in murine ALS models[173]. However, emerging drug tolerance during chronic administration manifests as diminished therapeutic effects, suggesting compensatory mechanisms involving epigenetic reprogramming or receptor desensitization pathways. These MET activators operate through dual neuroprotective-immunomodulatory mechanisms to attenuate ALS pathogenesis, with their pronounced short-term efficacy providing a rationale for developing sequential therapeutic regimens[173]. Although drug tolerance remains a critical challenge requiring mechanistic resolution, this pharmacological strategy establishes a proof-of-concept framework for combinatorial treatment approaches in motor neuron disease management. Patients with cirrhosis and other hepatic disorders exhibit significant plasma accumulation of HGF precursor, yet suffer from active HGF deficiency due to enzyme zymogen conversion-impaired activation, severely compromising hepatic regenerative capacity[174]. In partial hepatectomy rat models, experimental studies demonstrated that portal vein administration of recombinant human HGF agonist elicited rapid conversion of proHGF to mature HGF *via* activation of STAT3/MAPK signaling pathways[174]. These findings validate that exogenous HGF activators can overcome hepatic regenerative failure through a dual-action mechanism ("zymogen instant activation-receptor sustained activation"), providing a novel therapeutic strategy to bypass zymogen conversion defects in liver regeneration. Furthermore, Cordycepin exerts its anti-renal fibrotic therapeutic effects through dual modulation of the pro-fibrotic TGF-β/Smad signaling axis and the anti-fibrotic HGF/c-MET pathway, demonstrating a

bidirectional pharmacological mechanism to counteract renal fibrogenesis[175]. Cilostazol facilitates ischemic repair *via* the "PPARγ/cAMP−HGF" signaling axis, thereby establishing a mechanistic foundation for optimizing combinatorial therapeutic strategies that concurrently target HGF signaling pathways[176] (Fig. 2).

This survey of kinase activators in development underscores the translation of mechanistic understanding into therapeutic candidates. The progression from natural product-inspired compounds (*e.g.*, ursolic acid) to rationally designed agents (*e.g.*, LYN-1604) reflects a maturing field. However, the predominance of preclinical studies and the scarcity of approved classic kinase activators reveal a significant translational gap. This gap is not due to a lack of candidate molecules, but rather to the formidable pharmacological hurdles of achieving safe and selective kinase activation in humans, setting the stage for the discussion of challenges in the following section (Table 2[31,125,128,129,145−159,161-172]).

4. Trends for clinical trials and approved protein kinase activators

In recent years, with the in-depth understanding of the mechanism of disease signaling pathways, activators have shown important therapeutic potential in the fields of tumor, immune disease, metabolic disease and so on. IL-15 activator N-803 (anktiva), as the first approved IL-15 activator, has successfully verified the potential of cytokine activators in tumor immunotherapy. Through the fusion of mutant IL-15 (N72D) and IL-15R α/FC, N-803 can prolong the half-life and enhance the activity, selectively activate $CD8^+$ T cells and NK cells, avoid stimulating Treg cells, and

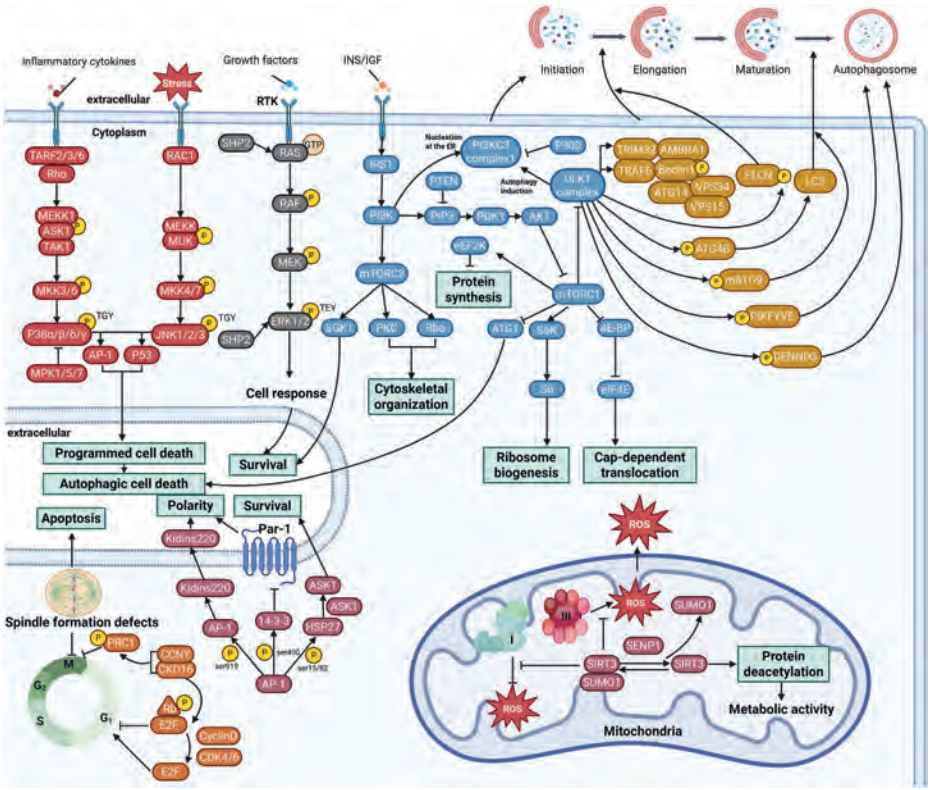

Figure 2 Activating protein kinases: biological processes and molecular mechanisms in human disease intervention. 4E-BP, eukaryotic initiation factor 4e-binding protein; Akt, protein kinase B; AMBRA1, activating molecule in BECN1-regulated autophagy; AP-1, activator protein 1; ASK1, apoptosis signal-regulating kinase 1; ATG14, autophagy-related 14; ATG4B, autophagy-related 4B; CCNY, cyclin Y; DENND3, differentially expressed in normal and neoplastic domains 3; E2F, E2F transcription factor; eEF2K, eukaryotic elongation factor 2 kinase; eIF4E, eukaryotic initiation factor 4E; ERK1/2, extracellular signal-regulated protein kinase 1/2; FLCN, Folliculin; Hsp27, heat shock protein 27; IGF, insulin-like growth factor; INS, insulin; IRS1, insulin receptor substrate 1; JNK1/2/3, c-Jun N-terminal kinase 1/2/3; kidins220, kinase D-interacting substrate 220; LC3, microtubule-associated protein 1A/1B-light chain 3; mATG9, mammalian autophagy-related 9; MEK or MKK, MAPK kinase; MEKK, mitogen-activated protein kinase kinase kinase; MEKK1, mitogen-activated protein kinase kinase kinase 1; MKK3/4/6/7, mitogen-activated protein kinase kinase 3/4/6/7; MPK1/5/7, mitogen-activated protein kinase 1/5/7; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; P300, E1A-binding protein p300; PDK1, 3-phosphoinositide-dependent protein kinase-1; PI3K, phosphatidylinositol 3-kinase; PI3KC3, class III phosphoinositide 3-kinase; PIP3, phosphatidylinositol-3,4,5-trisphosphate; PIKFYVE, phosphoinositide kinase, FYVE-type zinc finger-containing; PKC, protein kinase C; PRC1, protein regulator of cytokinesis 1; PTEN, phosphatase and tensin homolog; RAC1, ras-related C3 botulinum toxin substrate 1; Raf, rapidly accelerated fibrosarcoma; RAS, rat sarcoma virus; Rho, Ras-homologous; ROS, reduces reactive oxygen species; RTK, receptor tyrosine kinase; S6, ribosomal protein S6; S6K, ribosomal protein S6 kinase; SENP1, SUMO-specific peptidase 1; SGK1, serum/glucocorticoid-regulated kinase 1; SIRT3, Sirtuin3; SUMO1, small ubiquitin-like modifier 1; TAK1, transforming growth factor-β-activated kinase 1; TRAF2, TNF receptor associated factor 2; TRAF3, TNF receptor associated factor 3; TRAF6, TNF receptor associated factor 6; TRIM32, tripartite motif-containing protein 32; ULK1, unc-51 like autophagy activating kinase 1; VPS15, vacuolar protein sorting 15; VPS34, vacuolar protein sorting 34.

Table 2 Pharmacological small-molecule compounds that directly or indirectly activate the protein kinase to treat diseases.

Drug/brand name	Disease	Target	Mechanism	Model	Clinical trial identifier	Ref.
Diprovocim	Melanoma	TLR1/TLR2/p38 MAPK/NF-κB	Induces phosphorylation of IKKα, IKKβ, p38, JNK, and ERK, production of TNF and IL-6, and degradation of IκBα	THP-1 (EC_{50} = 110 pmol/L) PBMC (EC_{50} = 875 pmol/L) BMDC (EC_{50} = 6.7 nmol/L) peritoneal macrophages (EC_{50} = 1.3 nmol/L) Intramuscular injection 10 mg/kg	N/A	145
Flvestrant	Pituitary adenomas (PAs)	Selective estrogen receptor	Activation of PTEN/MAPK signaling pathways and inducing apoptosis	GH3 (20 mg); Animal model (0.5, 3, 20, 40 mg significant decreases the mean weight of tumors)	N/A	146
Fufang Tuixiao	Lung cncer	−	Activates p38MAPK, upregulates Bax, downregulates Bcl-2	Lung adenocarcinoma cells	N/A	147
Baiqiuli alcohol	Lung cancer	−	Activates JNK pathway	A549 lung cancer cells	N/A	147
Arsenic trioxide	Leukemia	−	Activates JNK pathway	MDA231 (8 μmol/L)	NCT01471279	148,149
Ursolic acid (UA)	Hman bladder cancer, pituitary adenoma (PA)	−	Pomoted c-Jun N-terminal kinase (JNK) activation, but inhibited mTOR complex 1 (mTORC1) signaling, contributes to growth inhibition and apoptosis, JNK pathway activation	T24 (25−400 μg/mL)	NCT02938403	150,159
NV-5138 hydrochloride	Depression	mTORC1	*Via* activation of the mTORC1 pathway and BDNF signaling	Animal model (PO, single dose (160 mg/kg) or daily for a total of 7 days (40, 80 mg/kg))	NCT05066672 NCT03606395	161
WIN 55	Endometriosis (EM)	−	Reduces proliferation/angiogenesis *via* MAPK/Akt-mediated apoptosis	*In vitro* models	NCT04581824	151
Nocodazole, paclitaxel	Breast cancer	−	Activates p38 pathway	MCF-7 breast cancer cells	NCT00002560	152
Resveratrol/pterostilbene	Cardiovascular diseases	−	AMPK−ERK5/HDAC5−KLF2 axis; antioxidant synergy	Mouse atherosclerosis model	NCT02261844	153
TBHQ	Drug-resistant melanoma, sepsis-induced cardiomyopathy	ERK1/2	Selective ERK1/2-MITF pathway activation	HeLa (EC_{50} = 12 μmol/L)	NCT05123482 (hypothetical)	154
Dikafosson	Corneal epithelial injury	−	ERK activation *via* P2Y2R-mediated $[Ca^{2+}]_i$	Corneal epithelial cells	N/A	155
Nr4a1 transcription factor	Renal interstitial fibrosis (RIF)	−	Activates p38 MAPK	Mouse renal fibrosis model	N/A	156
Octanol glucoside (OG)	Osteoporosis (GIOP)	−	Binds p38 protein, enhances downstream signaling	p38 (EC_{50} = 45.34 μmol/L); Osteoblast cells (OB) treated with OG at different concentrations of 10, 50, 100 nmol/L for 72 h; Animal model (5 mg/kg)	NCT03817905	157
Glycyrrhiza isoflavones (Gla)	Alcoholic liver injury (ALD)	−	p38 MAPK/Nrf2/NF-κB pathway	Rat hepatocytes	N/A	158
Docosahexaenoic acid (DHA)	Pancreatic β-cell injury		GPR120/mTOR axis-mediated autophagy	Insulin-secreting β-cells	NCT03510871	162
Ipastatin + sorafenib	Liver cancer		Inhibits mTOR phosphorylation	HepG2 cells	NCT00117663	163

(*continued on next page*)

Table 2 (*continued*)

Drug/brand name	Disease	Target	Mechanism	Model	Clinical trial identifier	Ref.
Tanshinone IIA (TSA)	Heart failure	VEGF/VEGFR2	ULK1-Beclin1/TFEB-LAMP1 pathway	Cardiomyocytes	NCT03739554	164
LYN-1604	Triple-negative breast cancer (TNBC)	ULK1	ULK1 complex-mediated autophagy-related cell death, activate the ULK1 and ULK complexes, rigger cell death *via* ATG5 involvement, as well as ATF3, RAD21 and caspase3	MDA-MB-231 (2.0 μmol/L) intragastric administration for 14 days (low dose, 25 mg/kg; median dose, 50 mg/kg; high dose, 100 mg/kg)	NCT04187552	31
Nelfinavir	Nasopharyngeal cancer	eEF2K	Trigger a robust activation of eEF2K leading to the phosphorylation of eEF2, leading to decreased rates of translation elongation	HeLa (EC_{50} = 10 μmol/L); injected intraperitoneally daily 100 mg/kg NFR	NCT03033199 NCT02188537	167,168
YC8-02	Lymphoma	–	SIRT3 inhibitor (tissue-specific effects)	Mouse lymphoma model	NCT04282044	128,129
Resveratrol	Breast cancer	mTOR, JAK, β-amyloid, adenylyl cyclase, IKKβ, DNA polymerase, SIRT1, PXR, Nrf2	Allosteric SIRT3 activation	A549 (IC_{50} 16 mmol/L)	NCT01240457	169,170
Liposome-delivered	Colorectal cancer	SIRT3	Reverses immunosuppressive microenvironment	Mouse colorectal cancer model	NCT04850560	125,171
HGF	Neurodegenerative diseases	MET	MET activators	Mouse AD model	N/A	172

ivate Jak-Stat5, PI3K/AKT and MAPK pathways. N-803 combined with BCG in the treatment of non-muscle invasive bladder cancer without response to BCG. In the phase II/III trial, 62% patients achieved complete remission, and 58% achieved remission for more than 12 months. Mwn105 injection (Class 1 new drug) has been implicitly licensed for clinical trials. Its indications are type 2 diabetes and obesity. It can regulate blood glucose and reduce weight by simultaneously activating GIP, GLP-1 and FGF21 receptors. The multi-target activators represented by GLP-1/GIP dual activators (such as tilpoteptide) achieve synergy by activating multiple metabolism related receptors. In the phase II clinical trial of metabolic dysfunction associated steatohepatitis (MASH), tilpotide alleviated MASH in 62% of patients without worsening fibrosis[177]. The mechanism involved weight loss, liver fat reduction and anti-inflammatory effect[177]. In the future, the combined application of GLP-1, FGF21 and PPAR activators may further improve the effect of fibrosis improvement. Regrettably, currently no small-molecule classic kinase activators have been clinically approved. The main reason might be that the activation of classic kinases such as EGFR and ERK usually involves ligand binding, dimerization, and conformational changes, which are complex processes difficult for small-molecule activators to precisely simulate or induce. For example, the activation process of EGFR involves the precise binding of extracellular ligands (such as EGF) and the dimerization of receptors, which is hard for small-molecule activators to simulate simultaneously[178]. In addition to this, the functions of kinases targeted by the approved small molecule activators are relatively simple, mainly focusing on metabolic diseases. For example, dorzagliatin, a glucokinase activator approved by the FDA, is mainly used for the treatment of type 2 diabetes[179]. In contrast, the activation of classic signaling pathway kinases may trigger a cascade of reactions, leading to unintended physiological effects. For example, the PKC activator phorbol ester may trigger a cascade of reactions, promote the generation of ROS, induce the activation of immune cells, and thus over-activate the immune system, leading to inflammation[180]. In addition to the cascade of reactions, compensatory signaling pathways are also a major challenge. EGFR activators may induce the expression of negative feedback proteins, such as suppressor of cytokine signaling 3, to inhibit the phosphorylation of EGFR itself, resulting in a transient activation effect[181]. Another crucial point is that the structural similarity of the kinase family can lead to off-target effects and overactivation of a single kinase, which may trigger the development of other diseases. For instance, overactivation of JAK3 may result in abnormal lymphoproliferation or autoimmune activation. Therefore, it is of great significance to develop small-molecule kinase activators in conjunction with specific drug delivery systems (Fig. 3).

5. Novel emerging therapeutic strategies for activating protein kinases

As a core tool for regulating specific signaling pathways, activators have been emerging as innovative strategies in the field of disease treatment in recent years. Beyond the continuous optimization of small-molecule activators, novel dimensions of intervention are being explored. First, gene therapy and protein overexpression strategies represent a direct approach to enhance kinase activity by increasing intracellular kinase abundance. This paradigm is particularly relevant for diseases driven by haploinsufficiency or pathological underexpression of beneficial

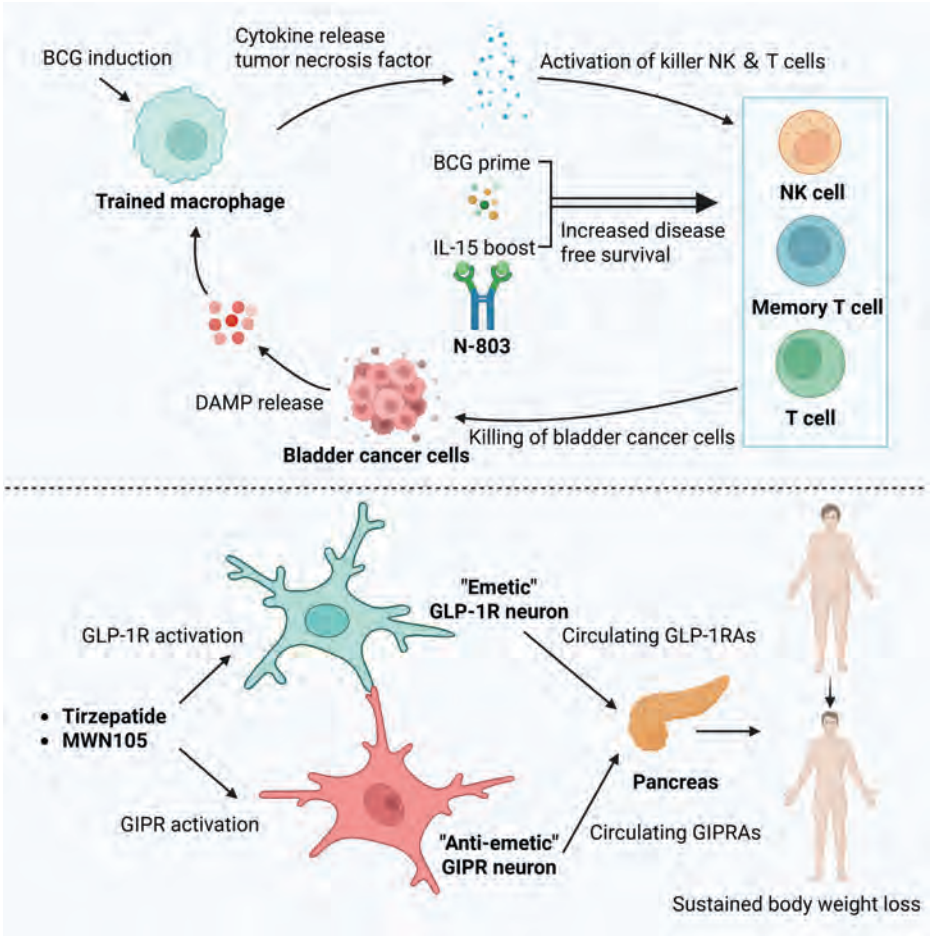

Figure 3 Trends for clinical trials and approved kinase activators. BCG, bacillus calmette guerin; DAMP, damage-associated molecular patterns; GIPR, glucose-dependent insulinotropic polypeptide receptor; GIPRAs, glucose-dependent insulinotropic polypeptide receptor agonists. GLP-1R, glucagon-like peptide-1 receptor; Glp-1ra, glucagon-like peptide-1 receptor agonist; IL-15, interleukin-15.

kinases. For instance, adeno-associated virus-mediated delivery of an AMPKα1 expression construct in the liver of diabetic mice results in sustained kinase activation, ameliorating steatosis and insulin resistance[182]. Similarly, modified mRNA encoding VEGFR2 can be administered to transiently boost receptor tyrosine kinase levels in ischemic tissues, promoting robust therapeutic angiogenesis[183]. These approaches bypass the complex chemistry of allosteric activators design and instead directly augment the kinase pool to drive signaling, offering a powerful complement to pharmacological strategies for conditions requiring profound and sustained pathway activation. The combination of IL-15 activator and PD-1 inhibitor can enhance the anti-tumor immune response, and the related clinical trials are being explored. The pharmacokinetic characteristics were improved by Fc fusion, prodrug design (such as ASKG315) or mutation optimization (such as N-803). Nano carriers or cell therapies (such as IPSC-derived cells) enhance the targeting and persistence of activator. Innate immune pathway activators (such as TLR activator) reprogram immunosuppressive cells to anti-tumor phenotypes by reshaping the tumor microenvironment (TME)[184]. Activating innate immunity can enhance the function of antigen-presenting cells, promote T cell infiltration, and improve the response of "cold tumor" to immunotherapy. The combination of targeted metabolic pathways (such as PD-1 inhibitors) can overcome single-drug resistance[184]. At present, many clinical trials are exploring such combinations. In addition, using the enhanced macropinocytosis of tumor cells, albumin bound drugs can target the delivery of activators to the lesions, improve the curative effect and reduce the systemic toxicity[185]. For example, askg315 can reduce the off-target effect through the specific activation of the tumor microenvironment[177]. Interestingly, machine learning is used to predict activator target interactions and accelerate the screening of lead compounds. Collect long-term efficacy and safety data through expanded access programs to optimize clinical medication programs. The key genes or allosteric sites regulating kinase activity were identified by CRISPR-Cas9 library screening. Using gene editing technology to design constitutive active mutants of kinase, which provides the structural basis for the design of small molecule activators. "Liposome-based split-and-mix proteolysis-targeting chimera" is a novel liposome-based delivery system for bifunctional molecules designed to recruit activators. It is worth noting that although the LipoSM-PROTAC system was originally used for protein degradation, its "split mix" design can be transformed into an activator platform[186,187]. Bifunctional molecules are delivered through liposomes, one end of which binds to a kinase, and the other end recruits activators, forming multivalent complexes to enhance kinase activity[188,189]. It is worth noting that the team from the

Shanghai Institute of Materia Medica, Chinese Academy of Sciences, has for the first time analyzed the complex structure of the cysteine leukotriene receptor CysLT2R and its endogenous ligand LTD4, revealing the key mechanism of receptor activation. This study provides a structural basis for designing highly selective activator, which is expected to promote targeted therapy for inflammatory diseases such as allergic asthma and chronic obstructive pulmonary disease[190]. STING activators enhance antitumor effects by activating immune responses. We are exploring the use of STING activator as an effective payload for ADCs to enhance immune activation in the tumor microenvironment. This type of drug has shown potential in preclinical studies and may overcome the resistance issues of existing ADCs[191]. In addition to small-molecule activators, there are also many non-small-molecule therapeutic approaches that have made significant contributions to disease treatment by activating kinases. First and foremost are antibody-based drugs. Monoclonal antibodies can target receptors or ligands on the cell surface and modulate signaling pathways by binding to them, thereby indirectly affecting the activity of kinases. For instance, trastuzumab is a monoclonal antibody that targets HER2, a receptor tyrosine kinase. By binding to HER2, this antibody blocks the HER2-mediated signaling pathway, thus inhibiting the proliferation of tumor cells[192]. In addition to this, gene-editing technologies like CRISPR-Cas9 can be employed for gene therapy in cells to alter the expression levels or activity of kinases.

In perspective, the novel strategies outlined here represent a paradigm shift from merely finding activator molecules to engineering precision interventions. The convergence of proteolysis-targeting chimeras, nanomedicine, and gene therapy with kinase activator design holds the promise of overcoming the historical challenges of selectivity and therapeutic window. The ultimate goal is no longer just to turn on a kinase, but to deliver the right activator to the right cell at the right time and for the right duration (Fig. 4).

6. Challenges and prospects

Protein kinase activators provide a new paradigm for the treatment of a variety of diseases by specifically activating targeted kinase activity. In the field of cancer, activator targeting metabolic kinases (*e.g.*, CKB) or apoptosis-related kinases (*e.g.*, AMPK) can inhibit tumor progression by regulating iron death and energy metabolism reprogramming. Their mode of action breaks through the limitation that traditional inhibitors only block proliferation signals. In the treatment of cardiovascular diseases, PKG activators (such as riociguat) have successfully verified the feasibility of the kinase activation strategy, which can improve vascular

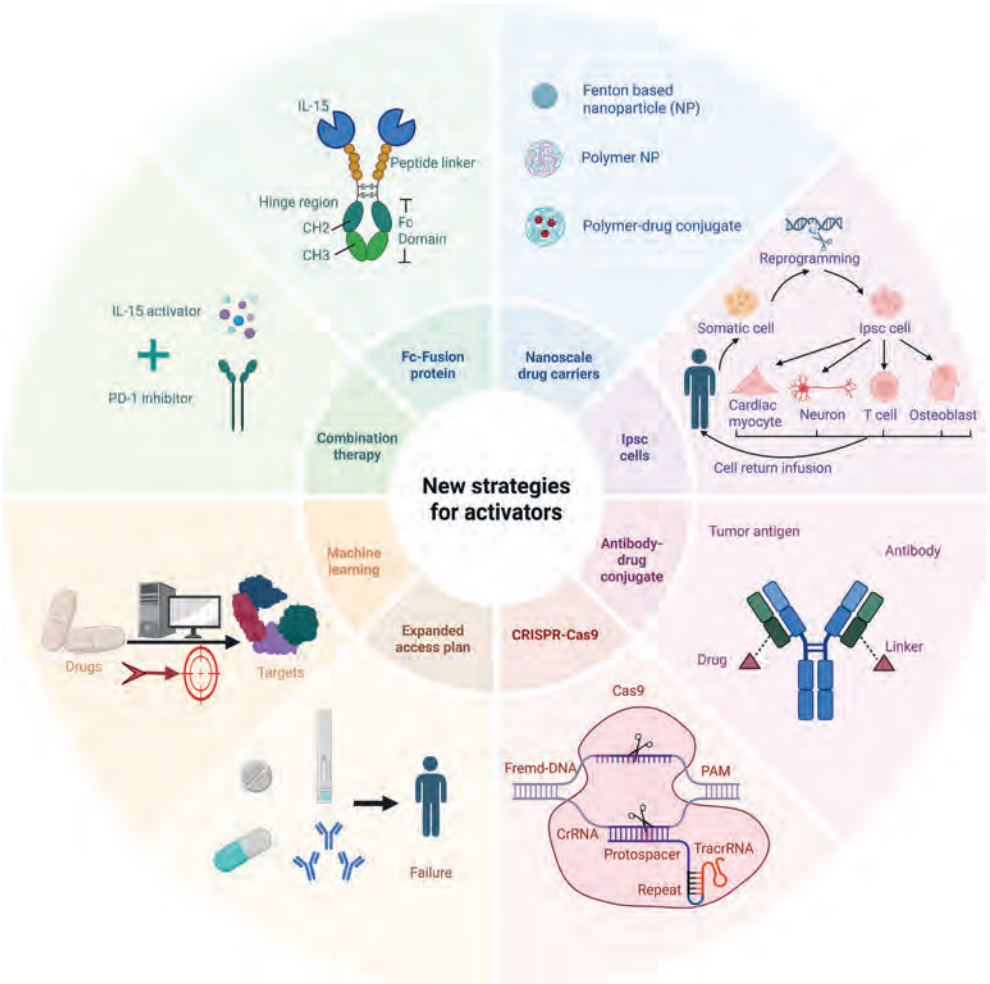

Figure 4 Novel therapeutic strategies for activating protein kinases. CrRNA, CRISPR RNA; NP, nanoparticle; PD-1, programmed death-1; PD-1, programmed death-1; TracrRNA, *trans*-activating CRISPR RNA.

function by enhancing the activity of the NO−SGC−cGMP pathway, and provide precise intervention for pulmonary hypertension and other diseases. In neurodegenerative diseases, activators targeting GSK-3β and APLP1/Lag3 have revealed new ways to regulate tau phosphorylation or α-synuclein transmission. It is worth noting that the discovery of "part-time" functions of kinases (such as non-catalytic regulation) has further expanded the theoretical framework of activator design.

While the therapeutic potential of protein kinase activators is compelling, as detailed throughout this review, their path to clinical translation is fraught with unique challenges that distinguish them from the more established paradigm of kinase inhibition. A critical discussion of these limitations is essential to guide future research and maximize the chances of success. We summarize the major hurdles, their underlying causes, and promising strategies to address them. Several key areas warrant further emphasis: A primary concern in developing kinase activators is the risk of oncogenic transformation or other pathologies due to overactivation. Many kinases targeted for activation (*e.g.*, Src, mTOR) are well-known oncogenes when mutated or overexpressed. This underscores the imperative for tissue-specific targeting and controllable activation mechanisms. To overcome the critical challenge of a narrow therapeutic window, innovative pharmacological and technological strategies are being developed. Prodrug approaches involve designing inactive precursors of kinase activators that are selectively converted to their active form within the target disease

Table 3 Major challenges in developing protein kinase activators and potential strategies.

Challenge	Underlying cause	Potential consequence	Promising mitigation strategy	Ref.
Narrow therapeutic window	High conservation of kinase ATP-binding sites; risk of overactivation leading to oncogenic signaling or toxicity.	Off-target effects, dose-limiting toxicity, limited clinical efficacy.	Development of allosteric activators targeting unique regulatory sites. Prodrug designs activated specifically in diseased tissue (*e.g.*, by tumor-specific enzymes). Use of targeted delivery systems (*e.g.*, antibody−drug conjugates, ligand-conjugated nanoparticles).	39
Signaling complexity and feedback loops	Kinases operate in highly interconnected networks; activation of one node may trigger compensatory feedback mechanisms.	Kinases operate in highly interconnected networks; activation of one node may trigger compensatory feedback mechanisms.	Systems biology approaches to model network responses. Rational combination therapies (*e.g.*, pairing an activator with an inhibitor of a feedback node). Intermittent dosing schedules to preempt adaptive resistance.	193
Context-dependent biological effects	The same kinase can play opposing roles (*e.g.*, pro-survival *vs*. pro-death) in different tissues, disease stages, or genetic backgrounds.	Unpredictable efficacy and potential for harm in unselected patient populations. (*e.g.*, ULK1 in early *vs*. late-stage cancer).	Development of companion biomarkers for patient stratification. Detailed understanding of kinase function in specific disease microenvironments. Exploration of tissue-specific delivery platforms.	91
Pharmacological hurdles in activator design	Structurally mimicking the complex process of kinase activation (*e.g.*, inducing conformational changes) is more challenging than designing inhibitors.	Low success rate in identifying high-potency, selective small-molecule activators.	Advanced techniques: Fragment-based screening, DNA-encoded libraries. AI and machine learning for predicting activator binding and efficacy. Focusing on natural products as sources of novel activator scaffolds.	37
Limited clinical validation	The field is younger than kinase inhibitor research; most candidates are in preclinical or early clinical stages.	Uncertainty regarding long-term safety, optimal dosing, and true therapeutic potential in humans.	Expansion of clinical trials with sophisticated pharmacodynamic biomarkers. Utilizing adaptive trial designs to efficiently test hypotheses. Learning from the safety profiles of approved kinase inhibitors.	37

microenvironment. This activation can be triggered by disease-specific factors, such as elevated levels of specific enzymes (*e.g.*, matrix metalloproteinases in tumors or inflammatory zones), or a characteristic pH, ensuring that kinase activation is spatially confined to pathological tissues. Concurrently, nanocarrier-based delivery systems offer a powerful solution for systemic administration. Nanoparticles, liposomes, or ADCs can be engineered to encapsulate kinase activators and functionalized with targeting ligands (*e.g.*, peptides, antibodies) that recognize receptors abundant on specific cell types (*e.g.*, vascular endothelial cells in ischemic tissues or cancer cells). This targeted delivery minimizes off-target exposure, maximizes the drug concentration at the site of action, and significantly reduces the risk of systemic toxicity, thereby effectively widening the therapeutic window. Most kinases have highly conserved ATP-binding domains, and traditional n-activators are prone to trigger off-target effects. In the future, it is necessary to combine allosteric site mining (such as the analysis of non-classical functions of CKB by the team of Zhejiang University) and AI-driven molecular design to develop highly selective activators. Single kinase activation may not be able to reverse the disease network with multi-channel interaction. Exploring multi-target synergistic activation strategies (such as AMPK/PGC-1α activation to improve mitochondrial dysfunction) or space-time specific delivery systems (such as nano carriers targeting pathological tissues) is expected to improve the curative effect. The existing studies mostly focus on the catalytic function of kinases, and the lack of understanding of their non-enzymatic activity (such as the role of scaffold protein) restricts the development of new activators. It is necessary to systematically analyze the functional polymorphism of the kinase and its pathological correlation by combining with freezing electron microscopy, single-cell sequencing and other technologies.

An individualized activator screening model was constructed based on patient genotypes (such as kinase mutation spectrum) and epigenetic characteristics. Develop light-controlled or pH-responsive intelligent activator to achieve precise spatio-temporal control of kinase activity. Integrating synthetic biology and systemic pharmacology, we designed and synthesized artificial kinases or engineered activator antibody conjugates to break through the functional limitations of natural kinases. To sum up, protein kinase activator therapy has entered the clinical transformation stage from concept verification, but its full application still needs to break through the technical bottleneck and deepen the mechanism cognition. With the integration and development of multi-omics technology and new drug models, this field is expected to open a more breakthrough era of precise treatment in human diseases (Table 3[37,39,91,193]).

Acknowledgements

This work was supported in part by the National Natural Science Foundation of China (Grant No. 82473230), Sichuan Science and Technology Program (Grant No. 2024NSFSC0632) and the Fundamental Research Funds for the Central Universities (Grant No. 2682025ZTPY043). We also thank BioRender (https://biorender.com) for assistance in the creation of the figures.

Author contributions

Xin Jin, Leilei Fu and Kun Huang conceived the project and supervised the project. Peng Jin and Minru Liao drafted the tables and manuscript. Huidi Liu draw the figures. Kun Huang proofread the structure and figures. Xin Jin and Leilei Fu polished the manuscript. All the authors read and approved the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest.

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