REVIEW
Cancer Advances 2025;8:e25002. https://doi.org/10.53388/2025825002

Abnormal activation of the Ras/MAPK signaling pathway in oncogenesis and progression

Hong Xu[1], Sen-Miao Ren[1], Yan Wang[1], Ting-Ting Zhang[1*], Jun Lu[1*]

[1]State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China.

[*]**Correspondence to:** Ting-Ting Zhang, Jun Lu. State Key Laboratory of Southwestern Chinese Medicine Resources, School of Pharmacy, Chengdu University of Traditional Chinese Medicine, No. 1166, Liutai Avenue, Wenjiang District, Chengdu 611137,Chengdu, China. E-mail: micett@126.com; ljaaa111@163.com.

Author contributions

Xu H conducted the literature review and prepared the original draft. Ren SM and Wang Y assisted in gathering literature and write the original draft. Zhang TT contributed to the project conception, reviewed and edited the final manuscript. Lu J contributed to project conception and manuscript review, and secured funding.

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This study was supported by the Sichuan Outstanding Youth Fund Project (23NSFJQ0099), and the Chengdu Science and Technology Bureau (2024-YF05-02599-SN).

Peer review information

Cancer Advances thanks all anonymous reviewers for their contribution to the peer review of this paper.

Abbreviations

MAPK, Mitogen-Activated Protein Kinase; MEK, mitogen-activated protein/extracellular signal-regulated kinase; ERK, extracellular signal-regulated kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; GAPs, GTPase-activating proteins; CDKs, cyclin-dependent kinases; p-ERK, activated ERK; MMP, matrix metalloproteinase.

Citation

Xu H, Ren SM, Wang Y, Zhang TT, Lu J. Abnormal activation of the Ras/MAPK signaling pathway in oncogenesis and progression. *Cancer Adv.* 2025;8:e25002. doi: 10.53388/2025825002.

Executive editor: Jian Jia.

Received: 22 October 2024; **Revised:** 13 December 2024; **Accepted:** 13 January 2025; **Available online:** 26 January 2025.

Abstract

The Ras/MAPK signaling cascade plays an essential role in the regulation of cellular processes, including proliferation, differentiation, and survival, serving as a pivotal intracellular communication network. Dysregulation of this pathway, frequently attributable to mutations within Ras genes, has been strongly associated with the development of a spectrum of cancers. This review underscores the pivotal role of the Ras/MAPK pathway in oncogenic transformation and tumor progression, briefing the intricate mechanisms through which the aberrant activation of this pathway leads to unbridled cell proliferation, inhibition of apoptosis, promotion of metastasis, and induction of angiogenesis, thereby providing valuable insights into the pathogenesis of malignancies. It also underscores the significance of the Ras/MAPK pathway as a therapeutic target and discusses the challenges and potential of targeted therapies, including combination treatments and personalized medicine approaches, to overcome resistance and enhance treatment efficacy in cancers driven by pathway dysregulation.

Keywords: Ras; MAPK; oncogenesis; therapeutic targets

Cancer Advances 2025;8:e25002. https://doi.org/10.53388/2025825002

Introduction

Tumorigenesis and tumor progression are multifaceted processes encompassing the dysregulation of numerous molecules and signaling cascades. Among the many signal transduction pathways, the mitogen-activated protein kinase (MAPK) signaling axis, an evolutionarily conserved cascade in eukaryotic cells, has garnered significant interest due to its pivotal role in governing cellular proliferation, differentiation, and survival [1–3]. The canonical MAPK signaling pathway typically involves Ras, Raf, mitogen-activated extracellular signal-regulated kinase (MEK), and extracellular signal-regulated kinase (ERK) cascade, also known as Ras/MAPK pathway. Aberrant activation of this pathway is closely linked to the etiology and progression of diverse malignancies, with its deregulation contributing to unchecked proliferation and the promotion of oncogenesis and tumor progression [4]. Hence, elucidating the regulatory mechanisms of the Ras/MAPK pathway is imperative for devising efficacious anti-neoplastic treatment protocols.

Abnormal activation of the Ras/MAPK signaling cascade often stems from regulatory malfunctions at various levels, including overexpression of receptor tyrosine kinases (RTKs), loss of function in GTPase-activating proteins (GAPs), and sustained activation of downstream effectors like MEK and ERK [5, 6]. These alterations not only fuel the proliferation and survival of cancer cells but also play a crucial role in reshaping the tumor microenvironment, promoting angiogenesis, and conferring drug resistance, thereby emerging as significant targets for therapeutic intervention in oncology.

Decades of research have provided an in-depth dissection of the structure and function of the Ras/MAPK signaling pathway. Notably, researchers have identified numerous molecular events associated with oncogenesis, particularly focusing on mutations in Ras or Raf proteins and the activation status of the pathway [7–9]. Concurrently, targeted therapeutic strategies against this pathway are evolving, including small molecule inhibitors and antibody-based drugs. Nonetheless, the diversity of mutations and the intricacy of pathway regulation present considerable challenges for developing effective therapeutic interventions targeting the Ras/MAPK signaling axis.

This article provides a brief overview of the role of the Raf-MAPK pathway in oncogenesis and tumor progression, detailing the transduction mechanism and implications of abnormal activation within the pathway, as well as evaluating current therapeutic approaches targeting this pathway, aiming to offer new insights and strategies for cancer management by leveraging this in-depth understanding of the regulatory mechanism.

Composition and transduction mechanism of Ras/MAPK signaling pathway

The Ras/MAPK pathway stands out as a quintessential signal transduction cascade that relays signals from upstream extracellular growth factors to a series of downstream effectors within the nucleus, thereby modulating various cellular functions [10, 11]. Activation of the Ras/MAPK pathway commences with the activation of Ras proteins [12]. Activated Ras triggers the recruitment and subsequent activation of Raf kinases, which in turn phosphorylates and activates MEK, propelling it to phosphorylate ERK, and this phosphorylated ERK then translocates to the nucleus to orchestrate gene expression changes and modulate a myriad of transcription factors [13]. This section will delve into the composition of the Ras/MAPK pathway and the mechanisms by which it transduces signals, setting the stage for understanding how dysregulation can contribute to cancer development (Figure 1).

Ras

Ras proteins, a family of small GTPases that include H-Ras, K-Ras, and N-Ras isoforms, serve as key upstream regulators of the Ras/MAPK pathway [14]. Upon binding to receptors on the cellular membrane, Ras proteins receive extracellular signals and transmit these signals by activating downstream effectors, thereby modulating cellular processes such as growth, differentiation, and survival. Ras proteins function as molecular switches in signal transduction, cycling between a GTP-bound active form and a GDP-bound inactive form within the cell. This shift is stringently regulated by guanine nucleotide exchange factors (GEFs) and GAPs: GEFs facilitate the activation of Ras by catalyzing GTP binding, whereas GAPs promote Ras inactivation through the acceleration of GTP hydrolysis.

In normal cells, the activity of Ras proteins is precisely regulated to maintain intracellular homeostasis, however, cancerous mutations in Ras proteins sustain its activation, driving unbridled cell proliferation and invasion, further exacerbating the malignancy of tumor [15, 16].

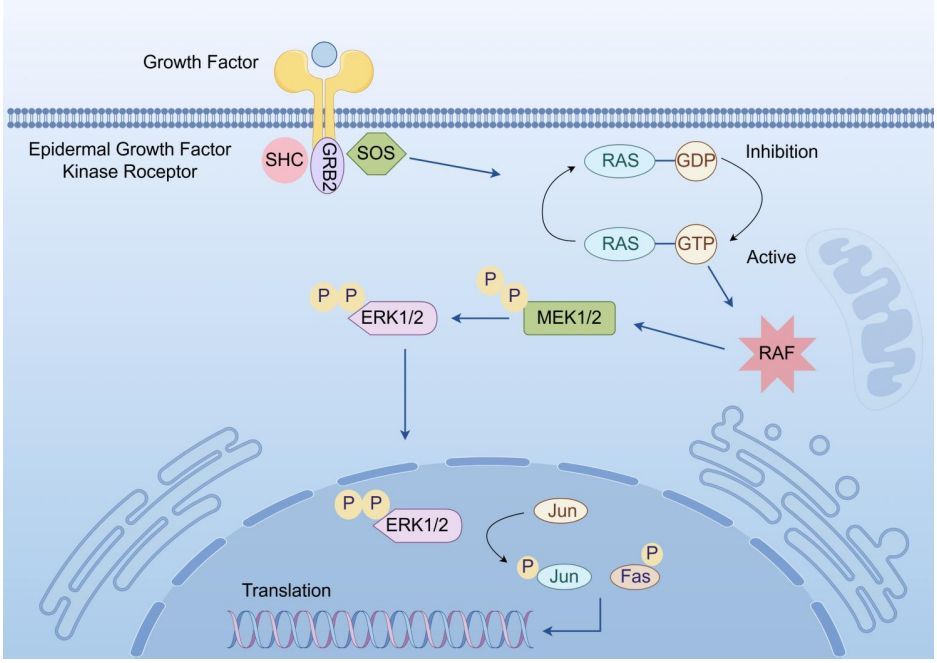

Figure 1 Composition of the Ras/MAPK pathway and the mechanism of its transduction signal

RAS is among the most prevalent genetic mutations in oncology, with a mutation rate of up to 21% across all cancer types, which differ in mutation subtypes, mutation sites, and amino acid substitutions among different cancer types [17]. Among these, *KRAS* mutations are the most prevalent, primarily involving codon 12 with G12D (glycine replaced by aspartic acid) and G12C (glycine replaced by cysteine) substitutions. *KRAS* point mutations are identified in 14.3% of all tumors, with particularly high rates in pancreatic ductal adenocarcinoma (90%), colorectal cancer (CRC) (50%), thyroid cancer (50%), and lung cancer (30%) [18–21]. *NRAS* mutations rank second, primarily observed in melanoma (23%), chronic myelomonocytic leukemia (CMML, 13.1%), and acute myeloid leukemia (AML, 13.6%) among hematological malignancies. *HRAS* mutations are less frequent, with reports of bladder cancer (4.06%) and head and neck squamous cell carcinoma (4.21%). In contrast to *KRAS*, mutations in *NRAS* and *HRAS* are predominantly localized to codon 61 [22, 23]. Such mutations abrogate the normal negative feedback of Ras proteins, leading to their persistent activation of downstream signaling cascades, thus fostering uncontrolled cellular proliferation and invasion, and propelling the initiation and progression of tumors.

Raf

As downstream kinases of Ras proteins, the Raf kinase family comprises A-Raf, B-Raf, and C-Raf, three homologous subtypes sharing highly similar structural domains [24]. The C-terminus of Raf contains a kinase-binding domain that would bind to the N-terminus in the absence of RAS-GTP, to maintain the inactive conformation of Raf. Upon activation of Ras by GTP binding, Ras-GTP binds to the kinase-binding domain of Raf, initiating Raf activation. Activation of Raf is a complex process that involves Raf recruitment to the cell membrane, the Ras-Raf complex assembly, phosphorylation and dephosphorylation of multiple regulatory sites on Raf proteins, and dimerization of Raf, including both homo- and heterodimer formation [25]. However, the precise sequence of these events and the detailed mechanisms are still under investigation [26]. Yet, the mechanism of RAF inhibitors (RAFi) has revealed that dimerization is a critical step for Raf kinase activity and the effectiveness of RAFi therapy.

The Raf family is highly conserved in mammals, with mutations implicated in numerous cancers [15]. *CRAF*, the first subtype identified for its potential oncogenic properties, is rarely mutated in human cancers, and early development of *CRAF* inhibitors functions as downstream effectors of RAS to inhibit signal transduction [27]. *BRAF* gene mutations are prevalent in several cancer types, notably in thyroid cancer (45–50.9%), melanoma (36.4%), and CRC (6.5–10.2%). The *BRAF* V600E mutation, substituting valine with glutamic acid, constitutes the majority of oncogenic *BRAF* mutations, representing over 90% of such alterations [28]. Other oncogenic *BRAF* mutations are predominantly located within the activation segment or the Gly-rich loop of the *BRAF* protein. Mutations in ARAF are relatively rare in cancer, occasionally observed in lung and melanoma, and may influence the modulation of RAS activity [29]. Hyperactivation of *CRAF* is a frequent hallmark of oncogenic signaling by upstream proteins, including RAS and growth factor receptors, whereas *BRAF* mutation can lead to sustained activation of the Raf/MAPK pathway, promoting tumorigenesis.

MEK

MEK, a pivotal intermediate node in the Ras/MAPK signaling pathway, serves as a bridge connecting upstream RAS and RAF proteins with downstream ERK proteins, thereby executing its biological function [30]. Upon activation, the C-terminal catalytic domain of Raf engages with MEK, phosphorylating two Ser residues in the VIII subdomain of MEK's catalytic domain, which activates MEK. MEK as a rare dual-specificity kinase, phosphorylates specific threonine and tyrosine residues on ERK, leading to a spectrum of biological outcomes such as cell proliferation, differentiation, migration, and survival [31, 32].

Mutations in *MEK1* and *MEK2*, such as Q56P-MEK1, K57N-MEK1, and D67N-MEK1, have been detected in lung, gastric, and ovarian cancers [33]. These alterations augment the intrinsic activity of MEK, resulting in the persistent activation of ERK, thereby promoting cell proliferation and oncogenic development. Despite the lower mutation frequency of *MEK1/2* compared to *BRAF* and RAS, their position downstream of these commonly mutated genes makes *MEK1/2* a highly promising therapeutic target.

ERK

ERK kinases, predominantly ERK1 and ERK2, are the exclusive downstream effectors of MEK widely distributed in the cytoplasm [34, 35]. Upon MEK activation, it directly interacts with ERKs through its N-terminal domain, specifically phosphorylating the Tyr and Thr residues within the "TEY motif" of ERK, leading to its activation. Activated ERK translocate to the nucleus, modulating the activity of transcription factors to regulate gene expression, influencing the cell cycle, and promoting cell proliferation, differentiation, and apoptosis [36].

ERK1/2 is implicated in diverse physiological processes, including meiosis and mitosis, and is activated by a spectrum of stimuli, such as growth factors, cytokines, and viral agents. Dysregulated ERK activation acts as a signaling intermediary and amplifier in tumor invasion and metastasis, influencing the proliferation and survival of cancer cells by impacting nuclear transcription factors such as AP-1 and NF-κB. ERK has been observed to be overactive in various human cancers, including oral, melanoma, and breast [37, 38]. Studies have indicated that ERK inhibitors (ERKi) can effectively block the Ras-Raf-MEK-ERK signaling cascade, overcoming resistance induced by upstream *BRAF* and MEK mutations [39–42]. Currently, primary ERK inhibitors such as AZD0364, KO-947, Ulixertinib, and HH2710 are being evaluated in clinical trials for their efficacy.

In brief, the Ras/MAPK signaling pathway orchestrates a series of phosphorylation events, amplifying initial signals to elicit an appropriate cellular response. Under normal conditions, this process is stringently regulated to preserve cellular homeostasis. In cancer, however, this balance is perturbed, resulting in pathological outcomes. Gaining insight into the regulatory mechanisms of this pathway is essential for devising targeted therapies to restore cellular equilibrium and curb tumorigenesis.

Implication of Ras/MAPK pathway in oncogenesis and progression

Aberrant activation of the Ras/MAPK signaling pathway can drive tumorigenesis by promoting cellular proliferation, survival, invasion, and metastasis through multiple mechanisms. Approximately one-third of cancers exhibit abnormal activation of the Ras/MAPK signaling pathway, particularly *KRAS* mutations in pancreatic, CRC, and lung cancers, as well as *BRAF* mutations in melanoma and hypermutated CRCs [43, 44]. Notably, despite RAS being recognized as an proto-oncogene, a single RAS mutant alone is insufficient to trigger cancer; instead, the combination of mutant RAS with hyperactivated downstream effectors in the MAPK pathway is more likely to contribute to cancer progression [45]. This section will dissect how the dysregulation of this pathway contributes to the hallmarks of cancer, including uncontrolled cell proliferation, inhibition of apoptosis, the acquisition of invasive properties, and tumor angiogenesis.

Cell proliferation

A hallmark of cancerization is uncontrolled cell proliferation, characterized by disruptions in cell cycle regulation, hyperactivation of growth factor signaling, and resistance to apoptosis [46]. Mutations in Ras genes are a major driving force behind the initiation and progression of various cancers, typically identifiable in the early phases of oncogenesis (Figure 2). Such mutations confer Ras proteins with insensitivity to GAPs, perpetuating their active state and triggering stimuli-free, unrestrained signal transduction, resulting in unchecked cell growth and proliferation. Extensive experimental data

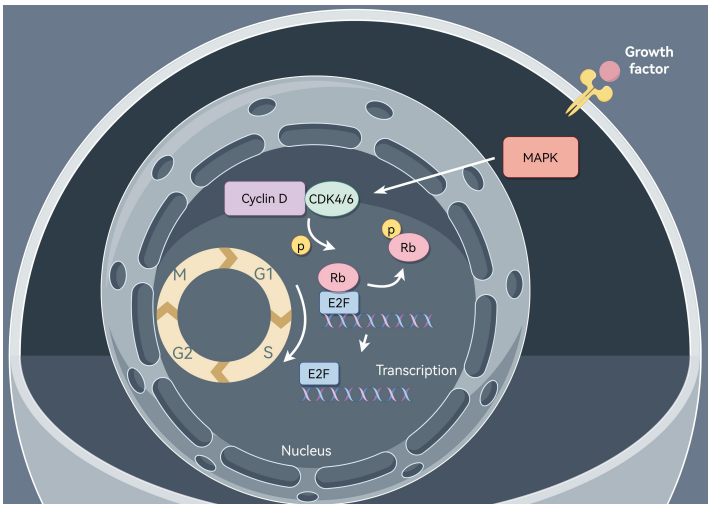

Figure 2 Regulation of Ras/MAPK signaling pathway on tumor cell cycle

demonstrated that the Raf-MEK-ERK signaling cascade, triggered by the activation of Ras proteins, is one of the primary pathways in tumorigenesis, promoting a variety of cellular processes, including cell proliferation and survival [47–49]. Activated ERK, for instance, can stimulate transcription factors such as Fos and Jun to form AP-1 complexes, or bind to specific DNA sequences adjacent to genes such as Myc, thereby initiating the transcription of these genes and further activating other gene expressions [50].

Ultimately, the activation of these signaling pathways results in increased Cyclin D expression, which forms complexes with cyclin-dependent kinases (CDKs) such as CDK4 and CDK6, driving the cell from the G1 phase into the S phase to initiate DNA replication, thereby facilitating cell cycle progression [51]. In short, the seamless progression of the cell cycle is essential for cell proliferation, which is crucially stimulated by the Ras/MAPK pathway.

Apoptosis inhibition

In cancer cells, the Ras/MAPK signaling pathway dually promotes cell proliferation and inhibits apoptosis under specific conditions, modulating an array of apoptosis-related proteins to influence cellular survival and demise (Figure 3). The modulation of apoptosis by the Ras/MAPK pathway is highly intricate. It has been confirmed that blocking the Ras/Raf/MEK/ERK cascade can activate the expression of PARP and Caspase-3, thereby inducing apoptosis [52]. Moreover, ERK1/2, acting as upstream regulatory kinases, can activate NF-κB, which then regulates the expression of anti-apoptotic genes Bcl-2 and Bcl-xL, while concurrently reducing the phosphorylation levels of the pro-apoptotic protein Bad, promoting the degradation of Bad, Bax, and Bim [53, 54]. The activated ERK1/2 signaling pathway can also preserve mitochondrial function, inhibiting the release of cytochrome C from mitochondria that would otherwise trigger the caspase cascade, further dampening downstream effector molecules, and consequently reducing cell apoptosis [55]. These studies collectively underscore the pivotal role of the Ras/Raf/MEK/ERK signaling pathway in the induction of apoptosis.

Metastasis and invasion

Tumor metastasis, as a major contributor to cancer-related mortality, involves the Ras/MAPK signaling pathway, which plays a crucial role in tumor cell migration and invasion by regulating the gene expressions associated with cell migration (Figure 4) [56]. For one thing, the Ras/MAPK signaling pathway facilitates cell migration by modulating the expression and activity of integrins, enhancing cell adhesion to the extracellular matrix [57]. For another, activated ERK (p-ERK) fosters the degradation of the extracellular matrix by enhancing the expression of MMP-2 and MMP-9, members of the calcium-dependent matrix metalloproteinases (MMPs) that are involved in tissue remodeling and extracellular matrix degradation, facilitating the invasion of cancer cells through the basement membrane, thus enabling them to enter the circulatory or lymphatic systems and initiate distant metastasis [58]. The natural product Bruceine A has recently been proven to inhibit the proliferation, migration, and invasion of triple-negative breast cancer, correlating with the downregulation of MMP-2/9 proteins and the suppression of the ERK signaling pathway [59].

Furthermore, ERK activation enhances actomyosin contractility and cell motility, inducing master regulators of the epithelial-mesenchymal transition (EMT) to bolster cell migration capabilities [60]. Studies have shown that in a xenograft mouse model of CRC, ERK2 activation mediates liver metastasis [61]. ERK1 and ERK2 with an 84% sequence homology, are recognized for their overlapping roles, yet recent findings underscore the unique function of ERK2 in mediating EMT in breast and colon cancers, suggesting that inhibiting the ERK pathway could curtail the promotional effects of HGF and similar extracellular signals on cell motility, potentially suppressing tumor invasion and metastasis [62–64]. Additionally, oncogenic *KRAS* effectors were reported to capable of activating CREB1 for physical interactions with mutant p53, thus hyperactivating multiple prometastatic transcriptional networks, contributing to pancreatic ductal adenocarcinoma [65]. Pharmacologic CREB1 inhibition can disrupt cooperation between oncogenic *KRAS* and mutant p53 to mitigate metastasis, offering a new strategy to dampen pancreatic ductal adenocarcinoma.

Tumor angiogenesis

Angiogenesis refers to the process of forming new blood vessels from pre-existing vascular systems, typically induced by hypoxia, inflammation, or tumor growth [66–68]. This process is crucial for tumor growth and metastasis, as tumor cells require the supply of adequate oxygen and nutrients provided by neovasculature. VEGF is a highly specific angiogenic factor that stimulates blood vessel formation within the body. Studies have shown that the Ras/MAPK pathway acts as a promoter of angiogenesis, capable of activating transcription factors to boost VEGF gene transcription and upregulate VEGF expression in tumor cells, thus fostering the development of new blood vessels (Figure 5) [69]. The Ras/MAPK pathway can also suppress the expression of thrombospondin-1 (TSP-1), a negative regulator of angiogenesis with anti-angiogenic properties. By inhibiting TSP-1 gene expression, activated Ras promotes angiogenesis, thereby facilitating tumor growth, invasion, and metastasis [70].

Overall, mutations within the Ras/MAPK signaling cascade are pivotal in instigating oncogenic processes, including enhanced cell proliferation, impeded apoptosis, and the facilitation of metastasis and angiogenesis. The dysregulation of Ras/MAPK pathway is a pervasive

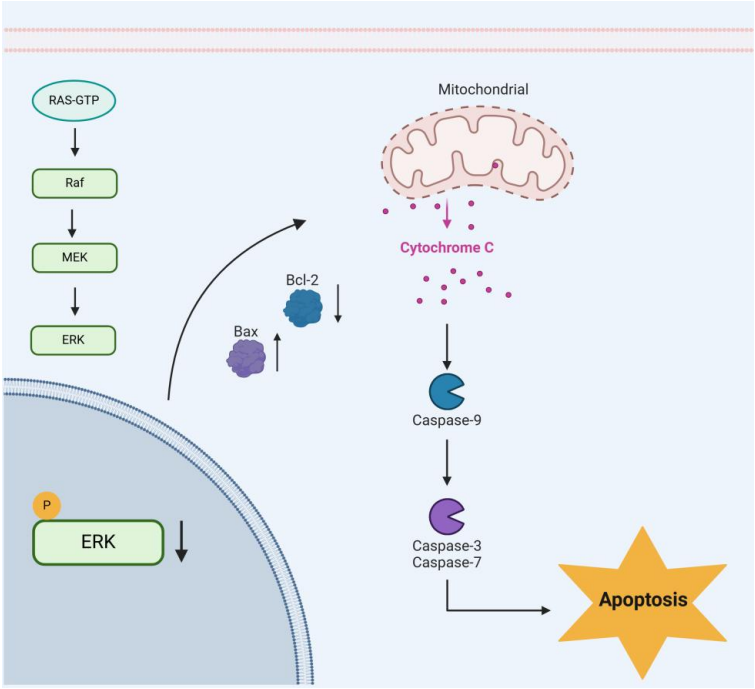

Figure 3 The Ras/MAPK signaling pathway is involved in tumor cell apoptosis

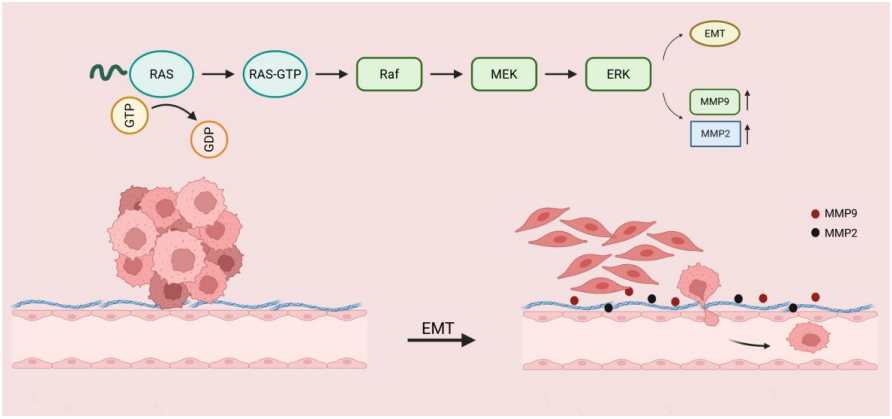

Figure 4 The Ras/MAPK signaling pathway is involved in tumor cell migration

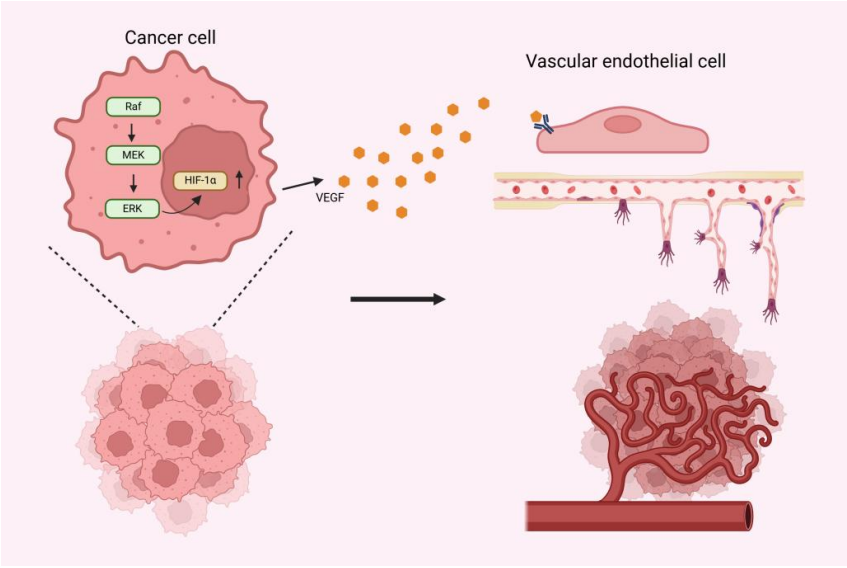

Figure 5 Effect of Ras/MAPK on tumor angiogenesis

feature across various malignances, highlighting its significance as a therapeutic target. Understanding these mechanisms is crucial for developing effective cancer treatments.

Progress and challenges in anti-tumor research targeting the Ras/MAPK signaling pathway

The widespread dysregulation of the Ras/MAPK signaling pathway across multiple cancer types has spurred significant research into targeted therapeutics. Current treatment approaches are directed either at the mutated Ras proteins themselves or at their downstream effectors. Nonetheless, the propensity for resistance with single-agent therapies underscores the importance of combination drug regimens in pharmaceutical development.

Targeting Ras mutant

RAS inhibitors suppress the activity of Ras protein either by locking its GDP-bound state or covalently binding to the GTP-bound state of RAS. Although Ras proteins were once considered "undruggable" due to the absence of allosteric inhibitor binding pockets and their high affinity for GTP, recent research has surmounted these challenges, especially with significant progress in the development of *KRAS* inhibitors [71–73]. These inhibitors can occupy the newly discovered "Switch-II pocket" on *KRAS* G12C, locking the *KRAS* G12C protein in its GDP-bound inactive state and thereby inhibiting downstream signaling. Sotorasib and adagrasib, as the first approved *KRAS* G12C inhibitors, offer new hope for the treatment of tumors with RAS mutations.

Targeting downstream effectors of Ras

Beyond direct RAS targeting, efforts are underway to develop inhibitors against RAS downstream effectors. RAF kinases, the immediate downstream targets of RAS, have inhibitors like Vemurafenib and Dabrafenib that have been approved for treating melanoma with *BRAF* V600 mutations [74, 75]. However, the application of these drugs in RAS-mutant tumors is constrained, as they may intensify MAPK pathway activation. Next-generation RAF inhibitors, particularly type II RAF inhibitors that target RAF dimers, have demonstrated therapeutic efficacy against RAS-mutant tumors, offering novel strategies for clinical treatment [76]. Advancements in MEK inhibitor research have led to the approval of multiple MEK inhibitors for market use, with further candidates in various stages of clinical investigation [77]. While ERK, being the exclusive substrate of MEK, lacks approved inhibitors, small molecule compounds targeting ERK1/2 are under assessment in preclinical and clinical studies for cancer treatment [42, 78].

Drug resistance and combination therapy

Tumor resistance to Ras/MAPK pathway inhibitors represents a considerable challenge, potentially attributable to negative feedback mechanisms, sustained activation of upstream receptors, emergence of new mutations at drug-binding sites, redundant activation within the MAPK pathway, and engagement of parallel pathways like PI3K/AKT/mTOR [79]. These resistance mechanisms curtail the effectiveness of monotherapy, thereby driving the exploration of combination therapy strategies to augment therapeutic efficacy.

The essence of combination therapy strategies lies in targeting multiple nodes within the Ras/MAPK pathway simultaneously, as well as integrating immunotherapy and inhibiting parallel pathways. For instance, co-targeting both upstream and downstream nodes of the Ras/MAPK pathway can reduce signal escape, while the integration of immunotherapy may activate the innate immune system to attack tumor cells. Research has demonstrated that MEK inhibitors, such as trametinib and cobimetinib, yield synergistic effects when combined with RAF inhibitors in oncological therapy, an good example is the The Fast Track designation for the combination therapy granted by the U.S. FDA On December 11, 2023, which combines RAF dimer inhibitor naporafenib with MEK inhibitor trametinib for the treatment of adult patients with *NRAS*-mutated unresectable or metastatic melanoma [80, 81]. Additionally, an increase in autophagy activity is observed in numerous RAFi-resistant cells, potentially aiding cancer cells in circumventing RAFi. Consequently, the concurrent targeting of RAF and autophagy genes may constitute a novel and potent therapeutic approach for treating *BRAF* and *KRAS*-mutated cancers.

To date, a variety of drugs targeting the Ras/MAPK signaling pathway have been successfully approved and commercialized (Table 1), with numerous candidates in preclinical or clinical studies. Despite the challenges inherent in therapeutic strategies aimed at the Ras/MAPK signaling pathway, including the emergence of tumor resistance and the intricacies of signal transduction networks, future research promises a field replete with both opportunities and challenges.

Table 1 Overview of approved drugs targeting Ras/MAPK pathway

General name	Trade name	First approval	Targets/biomarkers	Indications
Vemurafenib [82]	Zelboraf	2011	BRAF	*BRAF*-mutated metastatic melanoma
Dabrafenib [83]	Tafinlar®	2013	BRAF	Unresectable or metastatic melanoma in patients with the $BRAF^{V600E}$ mutation
Trametinib [84]	–	2013	MEK1/2	Unresectable or metastatic malignant melanoma with $BRAF^{V600E}$ or $^{-V600K}$ mutations
Cobimetinib [74]	Cotellic®	2015	MEK	Unresectable or metastatic $BRAF^{V600}$ mutation-positive melanoma
Selumetinib [85]	Koselugo®	2017	MEK1/2	Adjuvant treatment for thyroid cancer, neurofibromatosis type 1 (NF1)
Binimetinib [86]	Mektovi®	2018	MEK	Unresectable or metastatic melanoma with a $BRAF^{V600E}$ or $^{-V600K}$ mutation
Encorafenib [86]	Braftov™	2018	BRAF	Unresectable or metastatic melanoma with a $BRAF^{V600E}$ or $^{-V600K}$ mutation
Sotorasib [87]	Lumakras™	2021	RAS	Non-small cell lung cancer (NSCLC) and CRC with *KRAS* mutations
Tunlametinib [88]	Keluping®	2024	MEK1/2	Solid tumors with *RAS* and *RAF* mutations, including melanoma, NSCLC, CRC and NF1 plexiform neurofibromas
Adagrasib [89]	KRAZATI™	2023	KRAS G12C	NSCLC and CRC harboring *KRAS* G12C oncogenic driver mutation

Perspective and Conclusion

The Ras/MAPK signaling pathway, with its intricate network of kinases and transcription factors, stands at the forefront of oncogenic research due to its pivotal role in tumorigenesis and cancer progression. Dysregulation of this pathway has been implicated in a multitude of cancers, positioning it a promising target for therapeutic intervention.

The advent of therapies specifically targeting the Ras/MAPK pathway has yielded promising results in both preclinical and clinical studies [90–93]. Nonetheless, the intricate nature of the pathway, coupled with the multiplicity of signaling mechanisms, has presented considerable hurdles in the development and application of effective treatments. For instance, the engagement of alternative pathways can lead to resistance against MEK or ERK inhibitors [94, 95]. In light of this, multi-target intervention strategies that simultaneously disrupts various nodes within the pathway may be crucial for achieving robust tumor suppression. Considering the complexity of resistance mechanisms and the intricate interactions within signaling pathways, combination therapy has emerged as a feasible alternative. Research is ongoing to evaluate the synergistic effects of combining MEK inhibitors with other targeted therapeutices, including PI3K inhibitors and immunotherapies, aiming to overcome drug resistance mechanism and enhance treatment efficacy [96–98]. This multi-targeted therapeutic approach is designed to engage multiple key nodes within the Ras/MAPK pathway, leveraging the synergistic action of disparate mechanisms to potentiate treatment outcomes and diminish the incidence of resistance. Moreover, this multifaceted approach may attenuate the adverse effects associated with single-agent therapies, potentially elevating patient quality of life.

Moreover, the rise of personalized medicine has ushered in an era where treatment is tailored to the molecular profile of an individual's tumor [99, 100]. Given the site-specific nature of oncogenic mutations in key components of the Ras/MAPK signaling pathway, such as RAS, RAF, and MEK, genomic sequencing to pinpoint these mutations is essential for the precision development of targeted therapeutics, thereby optimizing treatment efficacy and minimizing unwanted adverse effects. Inhibitors specifically targeting the *KRAS* G12C mutation, such as sotorasib and adagrasib, as well as those targeting the *BRAF* V600E mutation, such as encorafenib, have exhibited therapeutic efficacy in clinical trials for tumors harboring these specific mutations [101–103]. The advancement of these targeted inhibitors offers novel therapeutic avenues for patients with such mutations, signifying a substantial advancement in treatment strategies. The etiology and progression of tumors are intricate and dynamic processes, with malignancy levels leading to significant disparities in tumor biomarkers. Consequently, the precise detection of biomarkers is crucial for devising personalized treatment plans. In addition to chemotherapy, it is imperative to consider a range of therapeutic modalities, including radiotherapy and surgical resection, tailored to the specific conditions of each patient, in order to maximize patients' outcomes.

In conclusion, the Ras/MAPK signaling pathway is a critical mediator of cellular processes that, when dysregulated, contributes significantly to cancer development and progression. An in-depth investigation of the Ras/MAPK signaling pathway not only offers novel insights into the molecular mechanisms underlying tumorigenesis but also provides a scientific rationale for the development of innovative therapeutic strategies and pharmaceuticals. Future research endeavors should delve into the mechanisms of these pathway constituents across diverse tumors and explore how to surmount therapeutic challenges through combinatorial treatments and personalized medicine approaches.

References

1. Jiang X, Yang X, Shi Y, et al. Maackiain inhibits proliferation and promotes apoptosis of nasopharyngeal carcinoma cells by inhibiting the MAPK/Ras signaling pathway. *Chin J Nat Med.* 2023;21(3):185–196. Available at: http://doi.org/10.1016/S1875-5364(23)60420-0
2. Dong T, Jiang J, Zhang H, et al. PFP@PLGA/Cu12Sb4S13-mediated PTT ablates hepatocellular carcinoma by inhibiting the RAS/MAPK/MT-CO1 signaling pathway. *Nano Converg.* 2021;8(1):29. Available at: http://doi.org/10.1186/s40580-021-00279-2
3. Benmokhtar S, Laraqui A, El Boukhrissi F, et al. Clinical Significance of Somatic Mutations in RAS/RAF/MAPK Signaling Pathway in Moroccan and North African Colorectal Cancer Patients. *Asian Pac J Cancer Prev.* 2022;23(11):3725–3733. Available at: http://doi.org/10.31557/apjcp.2022.23.11.3725
4. Dillon M, Lopez A, Lin E, Sales D, Perets R, Jain P. Progress on Ras/MAPK Signaling Research and Targeting in Blood and Solid Cancers. *Cancers.* 2021;13(20):5059. Available at: http://doi.org/10.3390/cancers13205059
5. Rezatabar S, Karimian A, Rameshknia V, et al. RAS/MAPK signaling functions in oxidative stress, DNA damage response and cancer progression. *J Cell Physiol.* 2019;234(9):14951–14965. Available at: http://doi.org/10.1002/jcp.28334
6. Mlakar V, Morel E, Mlakar SJ, Ansari M, Gumy-Pause F. A review of the biological and clinical implications of RAS-MAPK pathway alterations in neuroblastoma. *J Exp Clin Cancer Res.* 2021;40(1):189. Available at: http://doi.org/10.1186/s13046-021-01967-x
7. Khan AQ, Kuttikrishnan S, Siveen KS, et al. RAS-mediated oncogenic signaling pathways in human malignancies. *Semin Cancer Biol.* 2019;54:1–13. Available at: http://doi.org/10.1016/j.semcancer.2018.03.001
8. Gimple RC, Wang X. RAS: Striking at the Core of the Oncogenic Circuitry. *Front Oncol.* 2019;9:965. Available at: http://doi.org/10.3389/fonc.2019.00965
9. Nolan AA, Aboud NK, Kolch W, Matallanas D. Hidden Targets in RAF Signalling Pathways to Block Oncogenic RAS Signalling. *Genes.* 2021;12(4):553. Available at: http://doi.org/10.3390/genes12040553
10. Yuan S, Stewart KS, Yang Y, et al. Ras drives malignancy through stem cell crosstalk with the microenvironment. *Nature.* 2022;612(7940):555–563. Available at: http://doi.org/10.1038/s41586-022-05475-6
11. Deng J, Qin J, Lin N. 583P RHBDL2 promotes non-small cell lung cancer metastasis and osimertinib resistance by activating the RAS/MEK/ERK signaling pathway through interaction with FGFR. *Ann Oncol.* 2023;34:S1698. Available at: http://doi.org/10.1016/j.annonc.2023.10.661
12. Della Rocca GJ, van Biesen T, Daaka Y, Luttrell DK, Luttrell LM, Lefkowitz RJ. Ras-dependent Mitogen-activated Protein Kinase Activation by G Protein-coupled Receptors. *J Biol Chem.* 1997;272(31):19125–19132. Available at: http://doi.org/10.1074/jbc.272.31.19125
13. Jeon H, Tkacik E, Eck MJ. Signaling from RAS to RAF: The Molecules and Their Mechanisms. *Annu Rev Biochem.* 2024;93(1):289–316. Available at: http://doi.org/10.1146/annurev-biochem-052521-040754
14. Hancock JF. Ras proteins: different signals from different locations. *Nat Rev Mol Cell Biol.* 2003;4(5):373–384. Available at: http://doi.org/10.1038/nrm1105
15. Hobbs GA, Der CJ, Rossman KL. RAS isoforms and mutations in cancer at a glance. *J Cell Sci.* 2016;129(7):1287–1292. Available at: http://doi.org/10.1242/jcs.182873
16. Pikoulis E, Papaconstantinou D, Pikouli A, Wang J, Theodoridis C, Margonis GA. Reevaluating the prognostic value of RAS mutation status in patients with resected liver metastases from colorectal cancer: A systematic review and meta-analysis. *J*

Hepatobiliary Pancreat Sci. 2021; 28: 637–647. Available at: https://doi.org/10.1002/jhbp.1007
17. Wittinghofer A, Vetter IR. Structure-Function Relationships of the G Domain, a Canonical Switch Motif. *Annu Rev Biochem.* 2011;80(1):943–971. Available at: http://doi.org/10.1146/annurev-biochem-062708-134043
18. Liu ZM, Liu LN, Li M, Zhang QP, Cheng SH, Lu S. Mutation detection of KRAS by high-resolution melting analysis in Chinese with gastric cancer. *Oncol Rep.* 2009;22(3):515–520. Available at: http://doi.org/10.3892/or_00000465
19. Bannoura SF, Uddin MdH, Nagasaka M, et al. Targeting *KRAS* in pancreatic cancer: new drugs on the horizon. *Cancer Metastasis Rev.* 2021;40(3):819–835. Available at: http://doi.org/10.1007/s10555-021-09990-2
20. Modest DP, Ricard I, Heinemann V, et al. Outcome according to KRAS-, NRAS- and BRAF-mutation as well as KRAS mutation variants: pooled analysis of five randomized trials in metastatic colorectal cancer by the AIO colorectal cancer study group. *Ann Oncol.* 2016;27(9):1746–1753. Available at: http://doi.org/10.1093/annonc/mdw261
21. Uras IZ, Moll HP, Casanova E. Targeting KRAS Mutant Non-Small-Cell Lung Cancer: Past, Present and Future. *Int J Mol Sci.* 2020;21(12):4325. Available at: http://doi.org/10.3390/ijms21124325
22. Dehem A, Mazieres J, Chour A, et al. Characterization of 164 patients with NRAS mutated non-small cell lung cancer (NSCLC). *Lung Cancer.* 2023;186:107393. Available at: http://doi.org/10.1016/j.lungcan.2023.107393
23. Muñoz-Maldonado C, Zimmer Y, Medová M. A Comparative Analysis of Individual RAS Mutations in Cancer Biology. *Front Oncol.* 2019;9:1088. Available at: http://doi.org/10.3389/fonc.2019.01088
24. Wellbrock C, Karasarides M, Marais R. The RAF proteins take centre stage. *Nat Rev Mol Cell Biol.* 2004;5(11):875–885. Available at: http://doi.org/10.1038/nrm1498
25. Mott HR, Carpenter JW, Zhong S, Ghosh S, Bell RM, Campbell SL. The solution structure of the Raf-1 cysteine-rich domain: a novel ras and phospholipid binding site. *Proc Natl Acad Sci USA.* 1996;93(16):8312–8317. Available at: http://doi.org/doi:10.1073/pnas.93.16.8312
26. Kano Y, Gebregiworgis T, Marshall CB, et al. Tyrosyl phosphorylation of KRAS stalls GTPase cycle via alteration of switch I and II conformation. *Nat Commun.* 2019;10(1):224. Available at: http://doi.org/10.1038/s41467-018-08115-8
27. Riaud M, Maxwell J, Soria-Bretones I, Dankner M, Li M, Rose AAN. The role of CRAF in cancer progression: from molecular mechanisms to precision therapies. *Nat Rev Cancer.* 2024;24(2):105–122. Available at: http://doi.org/10.1038/s41568-023-00650-x
28. Andrews LJ, Thornton ZA, Saincher SS, et al. Prevalence of BRAFV600 in glioma and use of BRAF Inhibitors in patients with BRAFV600 mutation-positive glioma: systematic review. *Neuro Oncol.* 2021;24(4):528–540. Available at: http://doi.org/10.1093/neuonc/noab247
29. Su W, Mukherjee R, Yaeger R, et al. ARAF protein kinase activates RAS by antagonizing its binding to RASGAP NF1.. *Molecular Cell..* 2022;82(13):2443–2457. Available at: http://doi.org/10.1016/j.molcel.2022.04.034
30. Barbosa R, Acevedo LA, Marmorstein R. The MEK/ERK Network as a Therapeutic Target in Human Cancer. *Mol Cancer Res.* 2021;19(3):361–374. Available at: http://doi.org/10.1158/1541-7786.Mcr-20-0687
31. Caunt CJ, Sale MJ, Smith PD, Cook SJ. MEK1 and MEK2 inhibitors and cancer therapy: the long and winding road. *Nat Rev Cancer.* 2015;15(10):577–592. Available at: http://doi.org/10.1038/nrc4000
32. Yuan J, Dong X, Yap J, Hu J. The MAPK and AMPK signalings: interplay and implication in targeted cancer therapy. *J Hematol Oncol.* 2020;13(1):113. Available at: http://doi.org/10.1186/s13045-020-00949-4
33. Ordan M, Pallara C, Maik-Rachline G, et al. Intrinsically active MEK variants are differentially regulated by proteinases and phosphatases. *Sci Rep.* 2018;8(1):11830. Available at: http://doi.org/10.1038/s41598-018-30202-5
34. Miller DC, Harnor SJ, Martin MP, Noble RA, Wedge SR, Cano C. Modulation of ERK5 Activity as a Therapeutic Anti-Cancer Strategy. *J Med Chem.* 2023;66(7):4491–4502. Available at: http://doi.org/10.1021/acs.jmedchem.3c00072
35. Lavoie H, Gagnon J, Therrien M. ERK signalling: a master regulator of cell behaviour, life and fate. *Nat Rev Mol Cell Biol.* 2020;21(10):607–632. Available at: http://doi.org/10.1038/s41580-020-0255-7
36. Hirashima T, Hino N, Aoki K, Matsuda M. Stretching the limits of extracellular signal-related kinase (ERK) signaling — Cell mechanosensing to ERK activation. *Curr Opin Cell Biol.* 2023;84:102217. Available at: http://doi.org/10.1016/j.ceb.2023.102217
37. Ten Bosch GJA, Bolk J, 't Hart BA, Laman JD. Multiple sclerosis is linked to MAPKERK overactivity in microglia. *J Mol Med.* 2021;99(8):1033–1042. Available at: http://doi.org/10.1007/s00109-021-02080-4
38. Liu F, Yang X, Geng M, Huang M. Targeting ERK, an Achilles' Heel of the MAPK pathway, in cancer therapy. *Acta Pharm Sin B.* 2018;8(4):552–562. Available at: http://doi.org/10.1016/j.apsb.2018.01.008
39. Pan X, Pei J, Wang A, et al. Development of small molecule extracellular signal-regulated kinases (ERKs) inhibitors for cancer therapy. *Acta Pharm Sin B.* 2022;12(5):2171–2192. Available at: http://doi.org/10.1016/j.apsb.2021.12.022
40. Ward RA, Anderton MJ, Bethel P, et al. Discovery of a Potent and Selective Oral Inhibitor of ERK1/2 (AZD0364) That Is Efficacious in Both Monotherapy and Combination Therapy in Models of Nonsmall Cell Lung Cancer (NSCLC). *J Med Chem.* 2019;62(24):11004–11018. Available at: http://doi.org/10.1021/acs.jmedchem.9b01295
41. Wydra VR, Ditzinger RB, Seidler NJ, Hacker FW, Laufer SA. A patent review of MAPK inhibitors (2018 – present). *Expert Opin Ther Pat.* 2023;33(6):421–444. Available at: http://doi.org/10.1080/13543776.2023.2242584
42. Song Y, Bi Z, Liu Y, Qin F, Wei Y, Wei X. Targeting RAS–RAF–MEK–ERK signaling pathway in human cancer: Current status in clinical trials. *Genes Dis.* 2023;10(1):76–88. Available at: http://doi.org/10.1016/j.gendis.2022.05.006
43. Habashy P, Lea V, Wilkinson K, et al. KRAS and BRAF Mutation Rates and Survival Outcomes in Colorectal Cancer in an Ethnically Diverse Patient Cohort. *Int J Mol Sci.* 2023;24(24):17509. Available at: http://doi.org/10.3390/ijms242417509
44. Giopanou I, Pintzas A. RAS and BRAF in the foreground for non-small cell lung cancer and colorectal cancer: Similarities and main differences for prognosis and therapies. *Crit Rev Oncol Hematol.* 2020;146:102859. Available at: http://doi.org/10.1016/j.critrevonc.2019.102859
45. Prior IA, Hood FE, Hartley JL. The Frequency of Ras Mutations in Cancer. *Cancer Res.* 2020;80(14):2969–2974. Available at: http://doi.org/10.1158/0008-5472.Can-19-3682
46. Brown JS, Amend SR, Austin RH, Gatenby RA, Hammarlund EU, Pienta KJ. Updating the Definition of Cancer. *Mol Cancer Res.* 2023;21(11):1142–1147. Available at: http://doi.org/10.1158/1541-7786.Mcr-23-0411
47. Shen L, Zhang C, Cui K, Liang X, Zhu G, Hong L. Fer-mediated activation of the Ras-MAPK signaling pathway drives the proliferation, migration, and invasion of endometrial carcinoma

cells. *Mol Cell Biochem.* 2023;479(7):1787–1799. Available at: http://doi.org/10.1007/s11010-023-04890-1
48. Shi X, Ma Q, Huo Y, Su Y. 5-Aminoimidazole-4-carboxamide ribonucleotide formyltransferase/inosine monophosphate cyclohydrolase promotes pulmonary arterial smooth muscle cell proliferation via the Ras signaling pathway. *Am J Physiol Cell Physiol.* 2024;327(4):C901–C912. Available at: http://doi.org/10.1152/ajpcell.00262.2024
49. Liu X, Xing Y, Li M, et al. Licochalcone A inhibits proliferation and promotes apoptosis of colon cancer cell by targeting programmed cell death-ligand 1 via the NF-κB and Ras/Raf/MEK pathways. *J Ethnopharmacol.* 2021;273:113989. Available at: http://doi.org/10.1016/j.jep.2021.113989
50. Ullah R, Yin Q, Snell AH, Wan L. RAF-MEK-ERK pathway in cancer evolution and treatment. *Semin Cancer Biol.* 2022;85:123–154. Available at: http://doi.org/10.1016/j.semcancer.2021.05.010
51. Saleban M, Harris EL, Poulter JA. D-Type Cyclins in Development and Disease. *Genes.* 2023;14(7):1445. Available at: http://doi.org/10.3390/genes14071445
52. Su CC. Tanshinone IIA inhibits gastric carcinoma AGS cells by decreasing the protein expression of VEGFR and blocking Ras/Raf/MEK/ERK pathway. *Int J Mol Med.* 2018;41(4):2389–2396. Available at: http://doi.org/10.3892/ijmm.2018.3407
53. Suman I, Šimić L, Čanadi Jurešić G, Buljević S, Klepac D, Domitrović R. The interplay of mitophagy, autophagy, and apoptosis in cisplatin-induced kidney injury: involvement of ERK signaling pathway. *Cell Death Discov.* 2024;10(1):98. Available at: http://doi.org/10.1038/s41420-024-01872-0
54. Eriten B, Caglayan C, Gür C, Küçükler S, Diril H. Hepatoprotective effects of zingerone on sodium arsenite-induced hepatotoxicity in rats: Modulating the levels of caspase-3/Bax/Bcl-2, NLRP3/NF-κB/TNF-α and ATF6/IRE1/PERK/GRP78 signaling pathways. *Biochem Biophys Res Commun.* 2024;725:150258. Available at: http://doi.org/10.1016/j.bbrc.2024.150258
55. Fang L, Zhang M, Li J, Zhou L, Tamm M, Roth M. Airway Smooth Muscle Cell Mitochondria Damage and Mitophagy in COPD via ERK1/2 MAPK. *Int J Mol Sci.* 2022;23(22):13987. Available at: http://doi.org/10.3390/ijms232213987
56. Kciuk M, Gielecińska A, Budzinska A, Mojzych M, Kontek R. Metastasis and MAPK Pathways. *Int J Mol Sci.* 2022;23(7):3847. Available at: http://doi.org/10.3390/ijms23073847
57. Rubio K, Romero-Olmedo AJ, Sarvari P, et al. Non-canonical integrin signaling activates EGFR and RAS-MAPK-ERK signaling in small cell lung cancer. *Theranostics.* 2023;13(8):2384–2407. Available at: http://doi.org/10.7150/thno.79493
58. Jo HW, Kim MM. β-Caryophyllene oxide inhibits metastasis by downregulating MMP-2, p-p38 and p-ERK in human fibrosarcoma cells. *J Food Biochem.* 2022;46(12):e14468. Available at: http://doi.org/10.1111/jfbc.14468
59. Li X, Liu C, Zhang X, et al. Bruceine A: Suppressing metastasis via MEK/ERK pathway and invoking mitochondrial apoptosis in triple-negative breast cancer. *Biomed Pharmacother.* 2023;168:115784. Available at: http://doi.org/10.1016/j.biopha.2023.115784
60. Huang L, Chen S, Fan H, Ji D, Chen C, Sheng W. GINS2 promotes EMT in pancreatic cancer via specifically stimulating ERK/MAPK signaling. *Cancer Gene Ther.* 2020;28(7–8):839–849. Available at: http://doi.org/10.1038/s41417-020-0206-7
61. Urosevic J, Garcia-Albéniz X, Planet E, et al. Colon cancer cells colonize the lung from established liver metastases through p38 MAPK signalling and PTHLH. *Nat Cell Biol.* 2014;16(7):685–694. Available at: http://doi.org/10.1038/ncb2977
62. Xu Y, Kong W, Zhao S, Xiong D, Wang Y. Capsaicin enhances cisplatin-induced anti-metastasis of nasopharyngeal carcinoma by inhibiting EMT and ERK signaling via serpin family B member 2. *Carcinogenesis.* 2024;45(8):556–568. Available at: http://doi.org/10.1093/carcin/bgae032
63. Ungefroren H, Konukiewitz B, Braun R, Wellner UF, Lehnert H, Marquardt JU. TAp73 Inhibits EMT and Cell Migration in Pancreatic Cancer Cells through Promoting SMAD4 Expression and SMAD4-Dependent Inhibition of ERK Activation. *Cancers.* 2023;15(15):3791. Available at: http://doi.org/10.3390/cancers15153791
64. Du R, Wang C, Liu J, Wang K, Dai L, Shen W. Phosphorylation of TGIF2 represents a therapeutic target that drives EMT and metastasis of lung adenocarcinoma. *BMC Cancer.* 2023;23(1):52. Available at: http://doi.org/10.1186/s12885-023-10535-9
65. Kim MP, Li X, Deng J, et al. Oncogenic KRAS Recruits an Expansive Transcriptional Network through Mutant p53 to Drive Pancreatic Cancer Metastasis. *Cancer Discov.* 2021;11(8):2094–2111. Available at: http://doi.org/10.1158/2159-8290.Cd-20-1228
66. Liu OH-F, Kiema M, Beter M, Ylä-Herttuala S, Laakkonen JP, Kaikkonen MU. Hypoxia-Mediated Regulation of Histone Demethylases Affects Angiogenesis-Associated Functions in Endothelial Cells. *Arterioscler Thromb Vasc Biol.* 2020;40(11):2665–2677. Available at: http://doi.org/10.1161/ATVBAHA.120.315214
67. Mezu-Ndubuisi OJ, Maheshwari A. The role of integrins in inflammation and angiogenesis. *Pediatr Res.* 2020;89(7):1619–1626. Available at: http://doi.org/10.1038/s41390-020-01177-9
68. Ansari MJ, Bokov D, Markov A, et al. Cancer combination therapies by angiogenesis inhibitors; a comprehensive review. *Cell Commun Signal.* 2022;20(1):49. Available at: http://doi.org/10.1186/s12964-022-00838-y
69. Song Y-Y, Liang D, Liu D-K, Lin L, Zhang L, Yang W-Q. The role of the ERK signaling pathway in promoting angiogenesis for treating ischemic diseases. *Front Cell Dev Biol.* 2023;11:1164166. Available at: http://doi.org/10.3389/fcell.2023.1164166
70. Lawler J. Counter regulation of tumor angiogenesis by vascular endothelial growth factor and thrombospondin-1. *Semin Cancer Biol.* 2022;86:126–135. Available at: http://doi.org/10.1016/j.semcancer.2022.09.006
71. Nagasaka M, Li Y, Sukari A, Ou S-HI, Al-Hallak MN, Azmi AS. KRAS G12C Game of Thrones, which direct KRAS inhibitor will claim the iron throne. *Cancer Treat Rev.* 2020;84:101974. Available at: http://doi.org/10.1016/j.ctrv.2020.101974
72. Kim D, Herdeis L, Rudolph D, et al. Pan-KRAS inhibitor disables oncogenic signalling and tumour growth. *Nature.* 2023;619(7968):160–166. Available at: http://doi.org/10.1038/s41586-023-06123-3
73. Huang L, Guo Z, Wang F, Fu L. KRAS mutation: from undruggable to druggable in cancer. *Sig Transduct Target Ther.* 2021;6(1):386. Available at: http://doi.org/10.1038/s41392-021-00780-4
74. Garnock-Jones KP. Cobimetinib: First Global Approval. *Drugs.* 2015;75(15):1823–1830. Available at: http://doi.org/10.1007/s40265-015-0477-8
75. Puszkiel A, Noé G, Bellesoeur A, et al. Clinical Pharmacokinetics and Pharmacodynamics of Dabrafenib. *Clin Pharm.* 2018;58(4):451–467. Available at: http://doi.org/10.1007/s40262-018-0703-0

76. Cook FA, Cook SJ. Inhibition of RAF dimers: it takes two to tango. *Biochem Soc Trans.* 2020;49(1):237–251. Available at: http://doi.org/10.1042/bst20200485
77. Kun E, Tsang YTM, Ng CW, Gershenson DM, Wong KK. MEK inhibitor resistance mechanisms and recent developments in combination trials. *Cancer Treat Rev.* 2021;92:102137. Available at: http://doi.org/10.1016/j.ctrv.2020.102137
78. Sugiura R, Satoh R, Takasaki T. ERK: A Double-Edged Sword in Cancer. ERK-Dependent Apoptosis as a Potential Therapeutic Strategy for Cancer. *Cells.*. 2021;10(10):2509. Available at: http://doi.org/10.3390/cells10102509
79. Lee S, Rauch J, Kolch W. Targeting MAPK Signaling in Cancer: Mechanisms of Drug Resistance and Sensitivity. *Int J Mol Sci.* 2020;21(3):1102. Available at: http://doi.org/10.3390/ijms21031102
80. Zhang Z, Richmond A, Yan C. Immunomodulatory Properties of PI3K/AKT/mTOR and MAPK/MEK/ERK Inhibition Augment Response to Immune Checkpoint Blockade in Melanoma and Triple-Negative Breast Cancer. *Int J Mol Sci.* 2022;23(13):7353. Available at: http://doi.org/10.3390/ijms23137353
81. Czarnecka AM, Bartnik E, Fiedorowicz M, Rutkowski P. Targeted Therapy in Melanoma and Mechanisms of Resistance. *Int J Mol Sci.* 2020;21(13):4576. Available at: http://doi.org/10.3390/ijms21134576
82. Bollag G, Tsai J, Zhang J, et al. Vemurafenib: the first drug approved for BRAF-mutant cancer. *Nat Rev Drug Discov.* 2012;11(11):873–886. Available at: http://doi.org/10.1038/nrd3847
83. Ballantyne AD, Garnock-Jones KP. Dabrafenib: First Global Approval. *Drugs.* 2013;73(12):1367–1376. Available at: http://doi.org/10.1007/s40265-013-0095-2
84. Wright CJM, McCormack PL. Trametinib: First Global Approval. *Drugs.* 2013;73(11):1245–1254. Available at: http://doi.org/10.1007/s40265-013-0096-1
85. Markham A, Keam SJ. Selumetinib: First Approval. *Drugs.* 2020;80(9):931–937. Available at: http://doi.org/10.1007/s40265-020-01331-x
86. Shirley M. Encorafenib and Binimetinib: First Global Approvals. *Drugs.* 2018;78(12):1277–1284. Available at: http://doi.org/10.1007/s40265-018-0963-x
87. Blair HA. Sotorasib: First Approval. *Drugs.* 2021;81(13):1573–1579. Available at: http://doi.org/10.1007/s40265-021-01574-2
88. Keam SJ. Tunlametinib: First Approval. *Drugs.* 2024;84(8):1005–1010. Available at: http://doi.org/10.1007/s40265-024-02072-x
89. Dhillon S. Adagrasib: First Approval. *Drugs.* 2023;83(3):275–85. Available at: http://doi.org/10.1007/s40265-023-01839-y
90. Shillingford SR, Bennett AM. Mitogen-Activated Protein Kinase Phosphatases: No Longer Undruggable. *Annual Review of Pharmacology and Toxicology.* 2023;63:617-636. Available at: http://doi.org/10.1146/annurev-pharmtox-051921-121923
91. Gershenson DM, Miller A, Brady WE, et al. Trametinib versus standard of care in patients with recurrent low-grade serous ovarian cancer (GOG 281/LOGS): an international, randomised, open-label, multicentre, phase 2/3 trial. *Lancet.* 2022;399(10324):541–553. Available at: http://doi.org/10.1016/S0140-6736(21)02175-9
92. Tian J, Chen JH, Chao SX, et al. Combined PD-1, BRAF and MEK inhibition in BRAFV600E colorectal cancer: a phase 2 trial. *Nat Med.* 2023;29(2):458–466. Available at: http://doi.org/10.1038/s41591-022-02181-8
93. Tawil R, Wagner KR, Hamel JI, et al. Safety and efficacy of losmapimod in facioscapulohumeral muscular dystrophy (ReDUX4): a randomised, double-blind, placebo-controlled phase 2b trial. *Lancet Neurol.* 2024;23(5):477–486. Available at: http://doi.org/10.1016/S1474-4422(24)00073-5
94. Hong A, Piva M, Liu S, et al. Durable Suppression of Acquired MEK Inhibitor Resistance in Cancer by Sequestering MEK from ERK and Promoting Antitumor T-cell Immunity. *Cancer Discov.* 2021;11(3):714–735. Available at: http://doi.org/10.1158/2159-8290.Cd-20-0873
95. Farnsworth DA, Inoue Y, Johnson FD, et al. MEK inhibitor resistance in lung adenocarcinoma is associated with addiction to sustained ERK suppression. *NPJ Precis Oncol.* 2022;6(1):88. Available at: http://doi.org/10.1038/s41698-022-00328-x
96. de Sauvage MA, Torrini C, Nieblas-Bedolla E, et al. The ERK inhibitor LY3214996 augments anti-PD-1 immunotherapy in preclinical mouse models of BRAFV600E melanoma brain metastasis. *Neuro oncol.* 2023;26(5):889–901. Available at: http://doi.org/10.1093/neuonc/noad248
97. Ramanathan RK, Von Hoff DD, Eskens F, et al. Phase Ib Trial of the PI3K Inhibitor Copanlisib Combined with the Allosteric MEK Inhibitor Refametinib in Patients with Advanced Cancer. *Targ Oncol.* 2020;15(2):163–174. Available at: http://doi.org/10.1007/s11523-020-00714-0
98. Thielmann CM, Matull J, Zaremba A, et al. TERT promoter mutations are associated with longer progression-free and overall survival in patients with BRAF-mutant melanoma receiving BRAF and MEK inhibitor therapy. *Eur J Cancer.* 2022;161:99–107. Available at: http://doi.org/10.1016/j.ejca.2021.11.009
99. Rasmussen IML, Soerensen AV, Møller AK, et al. Individualizing the Oncological Treatment of Patients With Metastatic Non–Clear Cell Renal Cell Carcinoma by Using Gene Sequencing and Patient-Reported Outcomes: Protocol for the INDIGO Study. *JMIR Res Protoc.* 2022;11(9):e36632. Available at: http://doi.org/10.2196/36632
100. Zhou Y, Peng S, Wang H, Cai X, Wang Q. Review of Personalized Medicine and Pharmacogenomics of Anti-Cancer Compounds and Natural Products. *Genes.* 2024;15(4):468. Available at: http://doi.org/10.3390/genes15040468
101. Zhang SS, Nagasaka M. Spotlight on Sotorasib (AMG 510) for KRASG12C Positive Non-Small Cell Lung Cancer. *Lung Cancer (Auckl).* 2021;7(12):115–122. Available at: http://doi.org/10.2147/LCTT.S334623
102. Ou SHI, Jänne PA, Leal TA, et al. First-in-Human Phase I/IB Dose-Finding Study of Adagrasib (MRTX849) in Patients With Advanced KRASG12C Solid Tumors (KRYSTAL-1). *J Clin Oncol.* 2022;40(23):2530–2538. Available at: http://doi.org/10.1200/jco.21.02752
103. Ros J, Saoudi N, Baraibar I, Salva F, Tabernero J, Elez E. Encorafenib plus cetuximab for the treatment of BRAF-V600E-mutated metastatic colorectal cancer. *Therap Adv Gastroenterol.* 2022;15:17562848221110644. Available at: http://doi.org/10.1177/17562848221110644