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The Multifaceted Role of MAPK/ERK Signaling Pathways in Cancer Drug Resistance: An Update

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ABSTRACT

Cancer is among the leading causes of global mortality. In addition to uncontrolled proliferation, cancer cells activate survival pathways that favor the expansion of malignant cell populations. A critical component of these survival mechanisms is drug resistance, which often prevents the achievement of optimal therapeutic outcomes. At a cellular level, drug resistance arises from the modulation of multiple cellular processes, including apoptosis, DNA repair system, cancer stem cells, drug-metabolizing enzymes, and transporters. Among oncogenic signaling pathways, the MAPK/ERK cascade is frequently hyperactivated in cancer cells and serves as an upstream regulator of key effectors that drive drug resistance mechanisms. Consequently, patient profiling and therapeutic strategies aimed at targeting specific components of this pathway may not only counteract drug insufficiency but also facilitate personalized treatment approaches. This review provides an updated overview of the role of MAPK/ERK signaling in mediating drug resistance in cancer cells and discusses current and emerging therapeutic strategies, including combination therapies, pathway inhibitors, and novel drug development.

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1. Introduction

Cancer represents one of the foremost contemporary global medical challenges, posing a substantive threat to survival while imposing a considerable socioeconomic burden. Carcinogenesis stems from a complex interplay between genetic and epigenetic alterations and environmental and behavioral exposures; accordingly, a wide spectrum of risk factors has been implicated, including inherited and somatic mutations, a positive family history, environmental insults (tobacco, pollution, ionizing radiation, and chemical carcinogens), lifestyle determinants, chronic inflammation, and oncogenic infections (e.g., human papillomavirus, Helicobacter pylori).[1,2] The canonical hallmarks of cancer, including sustained proliferative signaling, evasion of growth suppressors, resistance to apoptosis, replicative immortality, angiogenesis, invasion and metastasis, metabolic reprogramming, immune evasion, genomic instability, and tumor-promoting inflammation provide a conceptual framework for tumor biology. Recent advances in cancer research have refined our understanding of this complexity and emphasize that early detection substantially enhances the manageability of this multifaceted, progressive disease.

The evolutionary acquisition of adaptive capabilities in cancer cells to withstand new conditions poses a major challenge to current cancer treatment strategies. Therapeutic resistance has been implicated, directly or indirectly, in up to 90% of cancer-related mortality.[3] In this context, cancer cells manipulate intrinsic cellular mechanisms to induce adaptability and attenuate the efficacy of interventions. These molecular adaptations are primarily manifested through several key processes, including the accelerated efflux of antitumor agents, alterations or substitutions of drug targets, modulation of DNA repair capacity, regulation of apoptosis, epigenetic reprogramming, and the unique properties of cancer stem cells. In light of these considerations, overcoming resistant cancer cell populations requires a precise understanding of resistance mechanisms and the implementation of an integrated strategy encompassing combination therapies, patient-tailored treatment regimens, and the discovery of novel therapeutic agents.[3]

Within the cellular signaling network, the MAPK/ERK pathway functions as a pivotal branch regulating cellular responses to environmental stimuli. Activation of this pathway triggers a cascade of phosphorylation events, culminating in the activation of the downstream effector, ERK. Key genes involved in critical physiological processes such as differentiation, growth, and survival are recognized as downstream targets of ERK.[4] Hyperactivity of MAPK/ERK signaling is a common feature in a variety of malignancies, and studying this pathway in the context of carcinogenesis has made it a significant focus of research. Importantly, dysregulated MAPK/ERK signaling has been directly implicated in mediating cancer drug resistance, highlighting its potential as a therapeutic target.[5] Despite extensive research on cancer drug resistance, the precise mechanisms by which MAPK/ERK signaling mediates adaptive responses in diverse malignancies remain incompletely understood. Most previous studies have focused on specific cancer types or individual downstream effectors, leaving a comprehensive, up-to-date synthesis of the pathway's multifaceted role lacking. Moreover, the rapid emergence of drug-resistant phenotypes and the development of novel targeted therapies underscore the need for continuous reassessment of MAPK/ERK-related mechanisms. This review aims to fill this gap by providing an integrated overview of current knowledge on MAPK/ERK signaling in cancer drug resistance, highlighting recent

advances, emerging therapeutic strategies, and potential avenues for future research. To achieve this, the study comprehensively analyzed relevant literature from major scientific databases without language restrictions. By consolidating these findings, the study offers a valuable resource for researchers and clinicians seeking to design effective interventions against resistant cancer cells.

2. Intrinsic and extrinsic mechanisms in drug resistance

Drug resistance represents a major obstacle in cancer therapy, arising from a dynamic and interconnected network of cellular mechanisms that enable cancer cells to evade the cytotoxic effects of therapeutic interventions. This network not only underscores the complexity of resistance but also reflects the sophisticated adaptive strategies employed by malignant cells to survive under selective therapeutic pressures. Extensive research has elucidated that drug resistance is primarily driven by a constellation of molecular alterations. These multifaceted mechanisms act in concert, forming the core processes that underlie the emergence and persistence of therapeutic resistance in cancer. In the following sub-sections, these resistance mechanisms will be introduced.

2.1. Apoptosis: As an intrinsic resistance mechanism

Apoptosis, or programmed cell death, is a fundamental process essential for maintaining tissue homeostasis. It plays a multilayered role in biological systems, encompassing the elimination of unnecessary cells during development, the removal of damaged cells, contributions to wound healing, and the regulation of immune responses. Two canonical apoptotic programs, the intrinsic mitochondria dependent pathway and the extrinsic death receptor mediated pathway, are commonly altered in therapy resistant tumours. In the intrinsic pathway, a shift in the balance among BCL-2 family proteins toward anti-apoptotic members such as BCL-2, BCL-XL and MCL-1, together with reduced levels of pro-apoptotic effectors like BAX, BAK and proteins containing a BH3 domain, governs mitochondrial outer membrane permeabilization and cytochrome c release.[6,7] Consequently, upregulation of anti-apoptotic proteins or compensatory induction of MCL-1 frequently drives chemoresistance.[8] Defects in the extrinsic death-receptor pathway reduce receptor-mediated apoptosis. These defects include loss or inactivation of FAS and TRAIL receptors.[9] As a result, therapies that depend on death-receptor signaling or immune-mediated killing become less effective.

Multiple regulatory layers act in concert to suppress apoptosis in therapy-resistant cancer cells. Upregulation or stabilization of Inhibitor of Apoptosis Proteins (IAPs), including XIAP, survivin, livin, and NAIP, directly blocks caspase activation and impedes apoptotic execution. Mutations or post-translational modifications affecting caspases further diminish their proteolytic efficiency. Additionally, loss or inactivation of the tumor suppressor TP53 (p53), a key mediator of pro-apoptotic programs, compromises apoptotic priming and facilitates cell survival following genotoxic stress (Figure 1).[10,11]

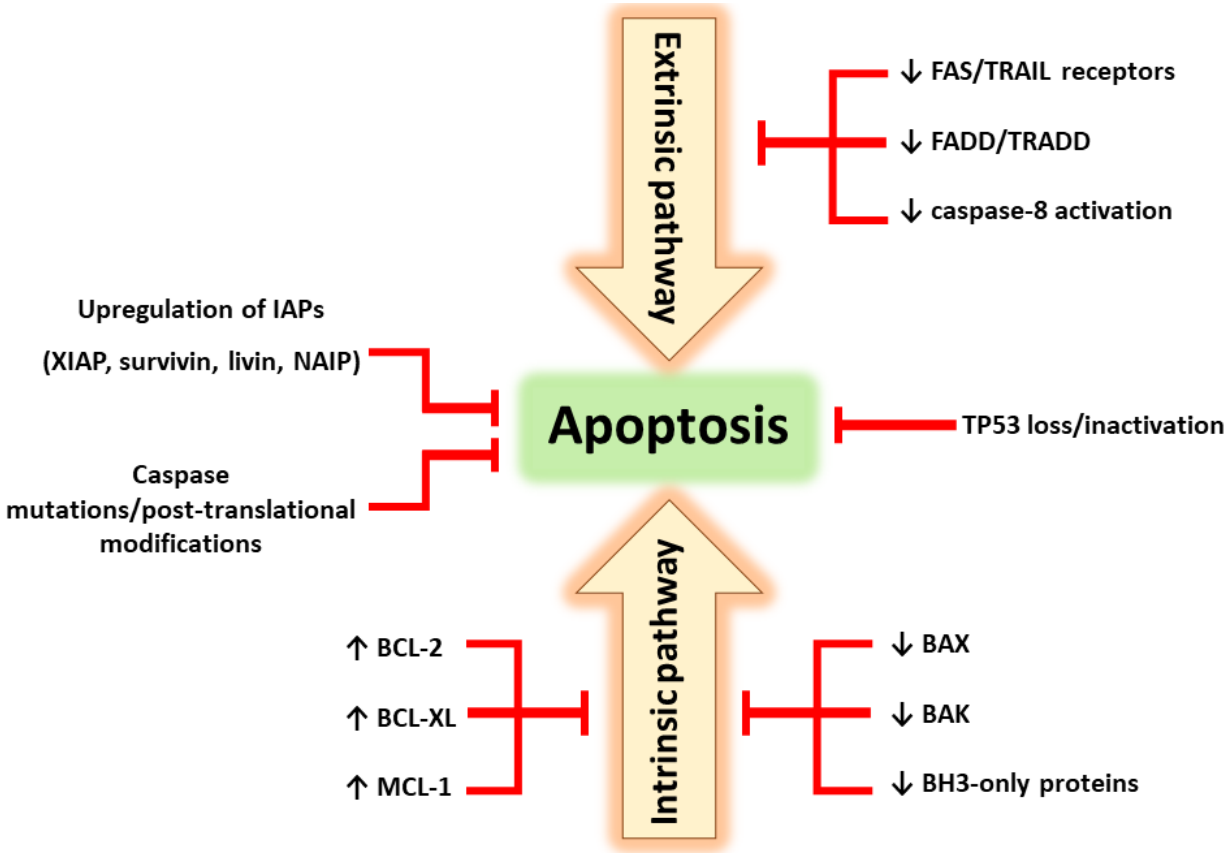

Figure 1. Schematic representation of the major mechanisms by which cancer cells evade apoptosis. Intrinsic pathway alterations (e.g., BCL-2 family imbalance), extrinsic pathway defects (e.g., impaired death receptor signaling), and additional regulatory networks (e.g., IAP upregulation, TP53 loss, Caspase mutations/post-translational modifications) converge to suppress apoptotic priming and promote tumor survival under treatment pressure.

From a therapeutic standpoint, restoring apoptotic function remains an attractive strategy, yet its clinical translation faces significant challenges. BH3-mimetic inhibitors targeting BCL-2 family proteins can restore mitochondrial apoptosis and have shown promising efficacy in certain hematologic malignancies. However, dual targeting of BCL-2 and BCL-XL often leads to severe thrombocytopenia, and tumors frequently develop resistance by upregulating alternative anti-apoptotic proteins such as MCL-1.[12,13] To overcome these hurdles, current approaches under development include selective MCL-1 inhibitors, next-generation BH3-mimetics, and rational combination therapies; for instance, combining BH3-mimetics with MCL-1 inhibitors, proteasome modulators, epigenetic drugs, or inhibitors of pro-survival kinases.[14] Parallel strategies, such as SMAC mimetics or IAP inhibitors to activate caspases, and TRAIL receptor agonists to restore extrinsic apoptosis, have shown promise in preclinical models.[15] Yet, optimizing these approaches to minimize toxicity and address resistance in clinical studies remains imperative.

In conclusion, apoptosis represents a complex and dynamic determinant of drug resistance. Successful therapeutic exploitation of this pathway relies on accurately mapping the apoptotic dependencies of each tumor (apoptotic priming), identifying reliable predictive biomarkers, and applying combination regimens that block compensatory escape routes. To achieve durable clinical benefit, it will be essential to integrate molecular profiling with functional assays such as BH3 profiling and to design mechanism-based combination trials.

2.2. DNA damage response: Shielding genome stability

The delicate cellular defense mechanism known as the DNA damage response (DDR) is designed to preserve the stability and integrity of the genome against both endogenous and exogenous genotoxic insults. DDR constitutes a complex, multi-step network that involves the recognition of DNA lesions by specialized sensors, activation of checkpoint kinases such as ATM, ATR, and CHK1/2, and the coordination of specialized repair pathways, including homologous recombination (HR), non-homologous end joining (NHEJ), base excision repair (BER), and mismatch repair (MMR).[16]

In cancer cells, DDR capacity is not uniformly elevated, as many tumors exhibit defects in DNA repair pathways, such as BRCA-mutant cancers, which render them sensitive to PARP inhibitors. Resistance may emerge when DDR function is restored or compensated, allowing tumor cells to survive genotoxic stress.[17] Upregulation of key homologous recombination proteins, such as RAD51 and DNA-PKcs, as well as enhanced activity of repair enzymes including PARP1 and DNA ligase I, enables tumor cells to repair therapy-induced genomic lesions more rapidly and accurately, exploit cell cycle checkpoints, and evade apoptotic pathways.[16,18] Furthermore, BRCA functional restoration or reversion mutations, replication fork protection, and microenvironmental and epigenetic alterations can shift repair pathway utilization and DDR dependency, thereby contributing to secondary resistance to PARP inhibitors or agents that induce double-strand DNA breaks.[19,20]

Clinical evidence indicates that the assessment of biomarkers, such as RAD51 foci formation, homologous recombination deficiency genomic signatures, and BRCA reversion mutations, can predict drug sensitivity and potential resistance.[21-23] From a therapeutic perspective, targeting DDR with inhibitors of PARP, CHK1, ATR, ATM, and DNA-PK, alone or in combination with chemotherapy or radiotherapy, represents a rational strategy to overcome resistance.[24,25] However, secondary resistance mechanisms, including HR restoration, replication fork protection, and epigenetic alterations, remain significant challenges.

Recent studies have highlighted additional layers of complexity in DDR-mediated resistance. The temporal dynamics of DDR, which vary according to the cell cycle stage and type of DNA damage, can influence transient or adaptive resistance. Multiscale modeling studies indicate that intrinsic cell-cycle fluctuations and microenvironmental interactions drive heterogeneity in drug response, with slow-cycling cells showing reduced sensitivity and fostering resistance.[26]

Non-canonical repair pathways, such as microhomology-mediated end joining (MMEJ), may compensate when classical HR or NHEJ is compromised. RNA molecules and RNA-binding proteins have emerged as regulators of DDR, stabilizing mRNAs of repair factors or modulating translation of key proteins like RAD51 and BRCA.[27,28] DDR also intersects with the tumor microenvironment and immune evasion, influencing PD-L1 expression and inflammatory signaling,[29] and DDR activation is coupled with metabolic adaptations, particularly glycolysis and nucleotide biosynthesis, to supply the energy needed for efficient DNA repair.[30]

2.4. Cancer stem cells: Compatible subpopulation

Cancer stem cells (CSCs) possess distinct characteristics that play a critical role in mediating resistance to anticancer therapies. Among these, enhanced DNA repair capacity and self-renewal potential are pivotal in sustaining the malignant cell population. In addition, CSCs exploit their intrinsic plasticity and quiescence to evade therapeutic pressure. Plasticity refers to the ability of CSCs to dynamically transition between differentiated and undifferentiated states, allowing adaptation to changes in the tumor microenvironment (TME).[16] Quiescence, also known as dormancy or slow-cycling, represents a crucial mechanism underlying drug resistance and tumor relapse. Under stress conditions, CSCs enter a dormant state, markedly reducing the efficacy of anticancer treatments and complicating long-term disease management.[31]

Drug-resistant CSCs frequently exhibit elevated expression of efflux pumps, particularly ABC transporters, which limit intracellular drug accumulation and reduce therapeutic efficacy. Stemness maintenance is regulated by several interconnected mechanisms, including quiescence, efflux pump activity, and signaling pathways that support self-renewal and survival. Among these, the MAPK/ERK cascade plays a central role by modulating the expression of key transcription factors such as Nanog, Sox2, and Oct4. Through this regulatory network, MAPK/ERK contributes to the preservation of stem cell-like properties and ultimately promotes therapeutic resistance.[3] The TME provides supportive signals, hypoxic conditions, and cell-cell interactions that play a key role in maintaining and enhancing CSC resistance. Under hypoxia, elevated HIF-1α further promotes CSC survival and increases resistance to chemotherapeutic agents.[32]

2.5. Drug metabolism and drug transporters: The main resistors

A thorough understanding of the complex interplay among drug absorption, distribution, metabolism, and excretion (ADME), together with the role of membrane transporters, is essential for optimal pharmacotherapy and achieving desired clinical outcomes. Drug metabolism encompasses a series of biochemical transformations that primarily occur in the liver, although the kidneys and intestines also contribute substantially.[33,34] These transformations, which commonly categorized into two phases, can activate, deactivate, or otherwise modulate drug activity and thus alter therapeutic efficacy. Phase I reactions, predominantly hepatic, involve oxidation, reduction, and hydrolysis and are largely mediated by cytochrome P450 enzymes. Phase II reactions conjugate hydrophilic moieties (e.g., sulfate, glucuronide, or glutathione) to Phase I metabolites, increasing water solubility and facilitating excretion.[35]

Cellular uptake and efflux of drugs are regulated by membrane transporters, which are broadly classified as influx (uptake) and efflux transporters. Key influx systems include organic cation transporters (OCTs), organic anion transporters (OATs), and peptide transporters (PEPTs), which facilitate the cellular entry of a variety of drugs and metabolite. OCTs (solute carrier family) preferentially transport positively charged compounds, and preliminary evidence suggests that imatinib may be a substrate of OCT1; although this mechanism requires further confirmation.[36] Increased OCT2 expression has been correlated with cisplatin accumulation and nephrotoxicity.[37] PEPTs (SLC15 family), predominantly expressed in intestine and kidney, transport peptide-like

compounds, including di- and tri-peptides, and have been implicated in the uptake of 5-aminolevulinic acid used in photodynamic therapy.[38] Counterbalancing influx systems, the ABC transporter family mediates ATP-dependent efflux of drugs and xenobiotics against concentration gradients.[39] Prominent members include ABCB (e.g., P-glycoprotein), ABCG (e.g., breast cancer resistance protein, BCRP), and ABCC (e.g., multidrug resistance-associated protein 1, MRP1) subfamilies.[40] Overexpression of ABC transporters, whether intrinsic or acquired, is a major mechanism by which cancer cells reduce intracellular drug concentrations and develop resistance.[41]

Functionally, efflux transporters prevent anticancer agents from reaching cytotoxic intracellular concentrations. P-glycoprotein (P-gp) has been shown to confer resistance to a broad spectrum of chemotherapeutics, including doxorubicin and docetaxel.[42] Tada et al. found that MRP1 expression was substantially increased in recurrent bladder cancer, reaching levels approximately 5.7 times higher than those observed in untreated primary tumors. MRP1 actively transports chemotherapeutic substrates such as vincristine and doxorubicin, thereby contributing to treatment failure.[43,44]

3. MAPK/ERK signaling pathway; an overview

The MAPK/ERK signaling cascade plays a central role in various biological processes, such as growth and proliferation, differentiation, cell survival, and autophagy. Activation of the pathway is typically initiated when extracellular ligands, such as growth factors, bind to receptor tyrosine kinases (RTKs), provoking receptor dimerization and autophosphorylation. This ligand-receptor interaction stimulates receptor dimerization and subsequent autophosphorylation. Phosphorylated residues in the receptor's intracellular domain recruit adaptor proteins; Grb2, in particular, links activated receptors to the guanine nucleotide exchange factor SOS, thereby promoting Ras activation.[3]

Ras, a small G-protein, cycles between an inactive GDP-bound state and an active GTP-bound state. SOS activates Ras by promoting the exchange of GDP with GTP. Subsequently, Ras sets the stage for the activation of Raf, also referred to as MAPKKK, through phosphorylation. Raf, a serine/threonine kinase, plays a central role in the activation of MEK, also known as MAPKK, within the signaling cascade.[45] MEK is pivotal in the activation of ERK, encircling both tyrosine kinase and serine/threonine kinase. Translocation of active ERK to the nucleus activates various transcription factors to express target genes.[46]

Regulating this cascade can be implemented by multiple mechanisms, such as modulating ligand concentration; however, feedback regulation is the most important mechanism. Crucially, the influence of ERK on upstream components serves as the primary basis for feedback regulation within this cascade. ERK, via phosphorylation, suppresses the activities of SOS and Raf. Another aspect of this regulation is related to the activation of dual-specificity phosphatase (such as DUSP6) by ERK, specifically targeting ERK.[5,16] Furthermore, ERK exerts control over this signaling cascade by promoting the upregulation of proteins that impair cascade activity, such as the Sprouty protein, which impedes the interaction between Grb2 and the receptor (Figure 2).[47]

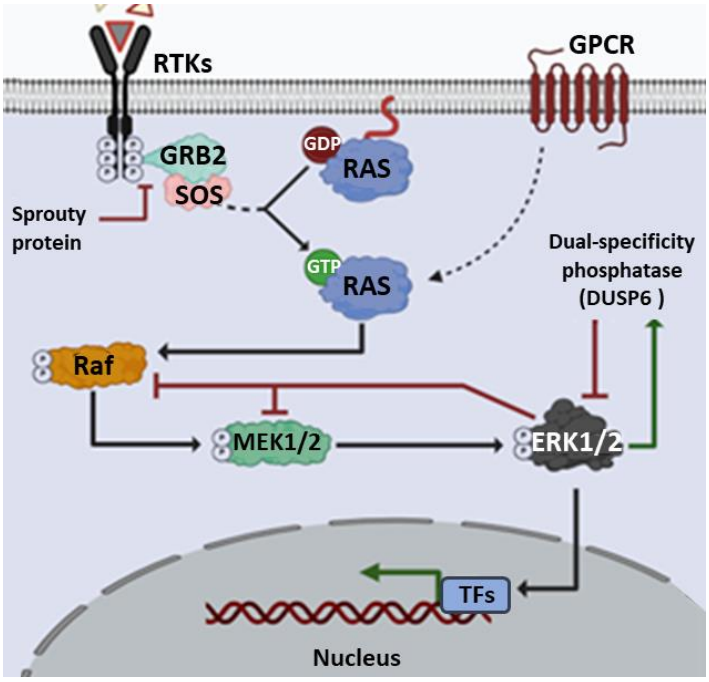

Figure 2. Schematic illustration of the MAPK/ERK signaling pathway. Mechanism of negative feedback regulation between ERK1/2 and Raf, MEK, DUSPs.

4. MAPK/ERK signaling in cancer pathogenesis

A multifaceted and finely regulated signaling network governs the biological processes essential for the cellular lifecycle. Among its key components, the MAPK/ERK signaling cascade plays a pivotal role not only in maintaining normal cellular functions but also in driving malignant transformation. Dysregulation of the MAPK/ERK pathway is recognized as a critical factor in the initiation, progression, and survival of cancer cells, contributing to nearly one-third of all human malignancies.[48]

Uncontrolled proliferation is a defining hallmark of cancer cells and is closely linked to dysregulation of the MAPK/ERK pathway, most commonly through mutations in Ras and BRAF. Such dysregulation not only promotes continuous cell division but also suppresses apoptosis, thereby expanding the population of malignant cells. In response to diverse stimuli, including Fas ligand, TRAIL, and hypoxic matrix detachment, ERK signaling actively inhibits apoptotic activation, functioning as a key pro-survival mechanism.[49,50]

ERK signaling also affects the potential of cancer cells to invade. Beyond the upregulation of matrix metalloproteinases (MMPs), it drives the epithelial-mesenchymal transition (EMT), a process through which epithelial cancer cells acquire mesenchymal traits, thereby increasing motility and altering differentiation states.[16] As the tumor cell population expands, additional requirements such as immune evasion, sustained survival, and metabolic reprogramming become increasingly critical. To meet the heightened demands for oxygen and nutrients, cancer cells predominantly rely on angiogenesis, a process in which the MAPK/ERK pathway promotes tumor progression largely through the upregulation of vascular endothelial growth factor (VEGF) expression.[51]

Hyperactivation of survival signaling pathways such as MAPK/ERK is closely associated with the reprogramming of cellular metabolism. A well-known example is the Warburg effect, or aerobic glycolysis, whereby cancer cells shift their metabolic profile

to counteract the detrimental impact of oxygen deprivation on glucose utilization efficiency.[52] However, the Warburg effect represents only one of the diverse metabolic outcomes of MAPK/ERK signaling. This pathway exerts broad regulatory influence over several metabolic processes, including enhanced glucose uptake through Glut1 upregulation and promotion of glycolysis via increased expression of pyruvate kinase M2. Beyond glucose metabolism, ERK signaling also plays a pivotal role in stimulating lipogenesis and nucleotide biosynthesis, thereby supporting the anabolic requirements of rapidly proliferating cancer cells.[53-55]

Because the immune system is inherently capable of recognizing and eliminating malignant cells, tumor progression depends on effective immune evasion, a process strongly facilitated by MAPK/ERK hyperactivation. In this regard, ERK can exploit the inflammation's dual effect. on one hand, elevated levels of pro-inflammatory cytokines such as interleukin-6 and interleukin-8 establish an immunosuppressive microenvironment, while on the other hand, upregulation of anti-inflammatory cytokines such as interleukin-10 further promotes conditions favorable to tumor growth.[56-58] Moreover, ERK activity has been positively correlated with the expression of PD-L1, which suppresses T-cell receptor signaling. It is also associated with the expansion of regulatory T cells (Tregs) that inhibit cytotoxic T-cell function, both of which undermine cellular immunity, a crucial antitumor defense.[59] Importantly, hyperactivation of ERK signaling has been associated with immune evasion mechanisms, including upregulation of PD-L1, which may contribute to reduced efficacy of PD-1/PD-L1 inhibitors in certain tumors.[60] In addition, MAPK/ERK signaling disrupts antigen presentation by impairing dendritic cell maturation, thereby weakening another essential component of immune surveillance.[61]

5. Targeting MAPK/ERK signaling in cancer treatment

Efforts to suppress cancer have been ongoing since the mechanisms underlying its development were identified. Hyperactivity of the MAPK/ERK cascade in various cancers is known as an oncogenic factor, which is mostly related to the constant activity of pathway components, especially Ras, Raf, and MEK1/2. Given the carcinogenic function of the MAPK/ERK signaling cascade, the development of drugs that selectively target its components represents a promising therapeutic strategy (Table 1). Currently, only a limited number of agents directly inhibit ERK; however, ulixertinib (BVD-523), a first-in-class ERK1/2 inhibitor, has been investigated in clinical trials and highlights the growing interest in ERK as a therapeutically actionable target.[62]

Mutations in Raf destabilize its inactive form. The substitution of valine with glutamic acid at residue 600 (V600E) is one of the most important mutational changes in Raf. Drugs such as Vemurafenib, Dabrafenib, and Encorafenib selectively inhibit this mutant form by competitively binding to the ATP-binding site.[63,64] The drug design process for the small-molecule Raf inhibitor BAY 43-9006 has reached the clinical trial stage for the V599E mutant variety of Raf.[65]

Several malignancies are also known to be linked to elevated MEK activity. High MEK activity is caused by two mechanisms: (i) MEK1/2 activation irrespective of the upstream effectors, and (ii) amplification of the MEK1 or MEK2 gene. Constitutive activation of the MEK1/2 kinases can be triggered by mutations such as the replacement of lysine for asparagine at residue 57 (MEK1 K57N), glutamine for proline at residue 56 (MEK1 Q56P), cysteine for serine at residue 125 (MEK2 C125S), and proline for serine at

residue 124 (MEK1 P124S).[66-68] Discovering or combining existing drugs to reach an acceptable therapeutic level is one of the strategies to deal with mutational MEK1/2 (table 1). Additionally, research has indicated that PD-098059 inhibits MEK1/2; however, U0126 exhibits a higher affinity (about 100-fold) and higher efficiency than PD-098059.[69,70] It is important to distinguish between preclinical pathway inhibitors and clinically developed therapeutics. PD-98059 and U0126 are commonly used experimental inhibitors of the MAPK/ERK pathway, primarily for mechanistic studies, whereas they have not been approved for clinical use. Despite the potential of Ras and ERK as therapeutic targets in cancers with MAPK/ERK hyperactivation, only a limited number of licensed drugs currently address these components.

Table 1. MAPK/ERK signaling cascade inhibitors.

Class	Drug Name	Target	Indications	Approval Status	Ref.
Raf inhibitors	Vemurafenib	BRAF V600E	Melanoma	FDA approved	71
	Dabrafenib	BRAF V600E	Melanoma	FDA approved	72
	Encorafenib	BRAF V600E	Colorectal cancer	FDA approved	73
	Sorafenib	BRAF, CRAF	Hepatocellular (HCC) and renal cell carcinoma	FDA approved	74
	Regorafenib	BRAF, CRAF	Colorectal, Gastrointestinal Stromal Tumors, HCC	FDA approved	75
	PLX8394	BRAF	Melanoma (clinical trials)	Investigational	76
MEK inhibitors	Trametinib	MEK1/2	Melanoma, Non-small cell lung cancer	FDA approved	77
	Cobimetinib	MEK1	Melanoma	FDA approved	78
	Selumetinib	MEK1/2	Neurofibromatosis type 1	FDA approved for pediatric patients	79
	Binimetinib	MEK1/2	Melanoma	FDA approved	80
	Pimasertib	MEK1/2	Solid tumors, melanomas	Investigational, not yet FDA approved	81
	Refametinib	MEK1/2	Solid tumors	Investigational, not yet FDA approved	82
	Mirdametinib	MEK1/2	Neurofibromatosis type 1, solid tumors	Investigational, not yet FDA approved	83
	PD0325901	MEK1/2	Solid tumors	Investigational, not yet FDA approved	84
	Selumetinib-Osimertinib combination	MEK1/2, epidermal growth factor receptor (EGFR)	Non-small cell lung cancer	Investigational, combination therapy	85
	Trametinib-Dabrafenib combination	MEK1/2, BRAF	Melanoma, Non-small cell lung cancer	FDA approved	86
	Cobimetinib-Vemurafenib combination	MEK1, BRAF	Melanoma	FDA approved	87
Ras inhibitors	Sotorasib	KRAS G12C	Non-small cell lung cancer	Approved by FDA (2021)	88
	Adagrasib	KRAS G12C	Non-small cell lung cancer, colorectal cancer	Investigational, in clinical trials	89
	Tipifarnib	Farnesyltransferase	Hematologic malignancies, solid tumors	Investigational, in clinical trials	90
	Salirasib	RAS signaling	Various solid tumors	Investigational, in clinical trials	91

	MRTX1133	KRAS G12D	Solid tumors	Preclinical/early clinical trials [92]
	LY3499446	KRAS G12C	Solid tumors	Investigational, in clinical trials [93]
ERK inhibitors	Ulixertinib (BVD-523)	ERK1/2	Solid tumors, melanoma, colorectal cancer	Investigational (Clinical Trials) [94]
	LY3214996	ERK1/2	Solid tumors, non-small cell lung cancer	Investigational (Clinical Trials) [95]
	MK-8353	ERK1/2	Advanced solid tumors	Investigational (Clinical Trials) [96]
	CC-90003	ERK1/2	Advanced solid tumors	Investigational (Clinical Trials) [97]
	GDC-0994	ERK1/2	Advanced solid tumors	Investigational (Clinical Trials) [98]

6. MAPK/ERK signaling in cancer drug resistance

Investigating the connection between drug resistance in cancer cells and the MAPK/ERK pathway necessitates a focused inquiry into the hyperactivation of this oncogenic cascade. For example, Tamoxifen resistance in breast cancer has been linked to MAPK/ERK pathway hyperactivity.[99] Suppression of the MAPK/ERK signaling pathway can significantly impact drug resistance due to the widespread influence of this cascade. The primary causes of persistent MAPK/ERK activation include mutations in key components, such as Ras (found in approximately 30% of human cancers) and BRAF (found in approximately 7% of human cancers).[100,101] In the following sub-sections, the interaction of the MAPK/ERK pathway with the identified resistance mechanisms will be presented and analyzed.

6.1. MAPK/ERK signaling and apoptosis

MAPK/ERK has a dual nature in dealing with apoptosis depending on the type of cell and stimulation, although the anti-apoptotic action is more noticeable. The simplest example of the pro-apoptotic action of MAPK/ERK is associated with p53. In response to DNA damage, p53 can increase the expression of pro-apoptotic genes such as NOXA and PUMA. Phosphorylation of this checkpoint protein by ERK causes functional protection by increasing stability.[102,103]

Studies have shown that MEK inhibitors increase the dephosphorylated form of BAD. In this state, BAD can induce apoptosis by binding to and inhibiting anti-apoptotic proteins such as BCL-XL. RSK and MSK are ERK-dependent kinases that counteract this effect. They exhibit anti-apoptotic activity by phosphorylating BAD at Ser112, preventing its pro-apoptotic function.[104,105] In addition to ERK-dependent kinases, AKT is another important kinase that phosphorylates BAD, highlighting the convergence of multiple survival pathways on the regulation of apoptosis.[106] Research has demonstrated the positive connection of MSK with Sp1 and c-Myc, which raise survivin levels.[107] Bim can induce apoptosis through various mechanisms, such as activating Bax and Bak or inhibiting Bcl-

2, Bcl-XL, and Mcl-1. ERK can facilitate the proteasome system's breakdown of Bim by phosphorylating this proapoptotic protein.[108,109] In addition, ERK can stabilize MCL-1 through phosphorylation, although this effect is context-dependent and may vary according to cell type and signaling environment.[110] Conversely, ERK can enhance the survival of cancer cells through direct phosphorylation of MCL-1, a labile member of the BCL-2 protein family.[111]

6.2. MAPK/ERK pathway and DNA damage response/repair

The MAPK/ERK pathway can ensure the capability of the cell to deal with detrimental factors by mediating the genes engaged in diverse mechanisms responding to various damages posed to DNA. It should be noted that processes for DNA repair entail over 130 genes.[112] The importance of ERK in DNA repair capability under DNA-damaging stressful circumstances such as radiation and chemotherapy has been confirmed through various studies. Cui et al demonstrated that increased activation of the ERK pathway in non-small cell lung cancer with XPC deficiency is linked to reduced efficacy of the NER repair system and damage accumulation.[113] One essential component of the NER system is XPC, which is positively regulated by the MAPK/ERK signaling pathway and performs vital tasks such as damage identification and repairing protein complex formation.[114,115]

XRCC1 is a crucial gene involved in multiple aspects of DNA repair, particularly in single-strand break repair and in maintaining the stability of DNA polymerase beta within the BER pathway. In addition, XRCC1 serves a scaffolding function, facilitating the assembly of repair complexes.[116,117] ERCC1 is considered the rate-limiting component of the NER system and also participates in inter-strand crosslink repair (ICLR) and NER through the formation of a heterodimer with XPF, generating a structure-specific endonuclease.[118-120] Radiation has been proposed to activate MAPK/ERK signaling, a process linked to Ras mutations and the expression of growth factor receptors. Consequently, the increased expression of ERCC1 and XRCC1 by radiation is attributed to the upregulation of MAPK/ERK signaling.[121-124] The study conducted based on BrdU photolysis (low levels) also emphasizes the exploitation of ERK by cells in response to DNA damage.[125]

Phosphorylation of histone H2AX (γH2AX) is a critical factor in facilitating the first step of response to DNA double-strand breaks, i.e., reduction of chromatin density. In DNA damage, Chk1 can trigger the response to damage by phosphorylating a significant range of substrates. Therefore, employing a Chk1 inhibitor as an adjunctive therapy can make the damage caused by radiotherapy/chemotherapy more lethal for cancer.[126-128] In this regard, research has proven that blocking ERK1/2 signaling increases the effectiveness of Chk1 inhibitors.[129]

RAD51, an ATPase that interacts positively with the MAPK/ERK pathway, assembles nucleoprotein filaments on single-stranded DNA to facilitate the repair of DNA breaks.[130,131] In addition to this role, ERK signaling can modulate the efficiency of NHEJ, an alternative pathway for repairing DNA double-strand breaks.[132]

6.3. MAPK/ERK signaling and cancer stem cells

The development and maintenance of fundamental characteristics of CSCs are mediated by various genes that are associated with the MAPK/ERK signaling pathway. In cancer, CSCs are the origin of the unique resistance properties. Despite limited research, notable insights have emerged regarding the relationship between stemness-associated genes and the MAPK/ERK pathway. Elevated expression of these stemness-related genes in circulating tumor cells of glioblastoma is associated with increased resistance to trastuzumab and radiation.[133,134] Transcription factors such as Oct-4 and SOX2 are crucial for preserving CSC pluripotency, self-regeneration capacity, and differentiation potential by connecting and forming heterodimeric complexes in order to bind DNA.[135,136] It is established that resistance to cisplatin, doxorubicin, paclitaxel, and tamoxifen develops in correlation with increased expression of Oct-4.[137]

Studies conducted on cancer cells with resistance to EGFR treatments have elucidated the relationship between ERK and the expression level of SOX2. Phosphorylated ERK levels have been reported to be significantly reduced by EGFR inhibitors such as gefitinib. As a result, the analysis of SOX2 expressions also showed a decrease.[138] Moreover, tamoxifen resistance in breast cancer is tied to Sox2.[139] Increasing evidence indicates that ERK activation in the context of tamoxifen resistance is largely mediated by compensatory PI3K/AKT signaling. Aberrant PI3K/AKT activity can bypass endocrine blockade by restoring ERK activity.[140] This inter-pathway cross‑talk represents a central mechanism of endocrine escape in breast cancer.

NANOG promotes pluripotency in stem cells by blocking differentiation; ERK can have two distinct effects on this protein. The interaction of ERK-CSCs is more interpretable by the conducted study on the rile of lncRNA DUXAP8 in sorafenib-resistant HCC. DUXAP8 is known to be associated with increased resistance to sorafenib, proliferation, and increased expression of stemness-associated genes such as Sox2, NANOG, and OCT4. One of the main causes of the oncogenic properties of DUXAP8 has been described as up-regulating MAPK1 through miR-584-5p suppression.[141,142] However, additional research indicates that ERK1 destabilizes the population of CSCs by phosphorylating NANOG, which subsequently undergoes degradation by the proteasome system.[143] Not to mention that ERK can disrupt the stability and intracellular accumulation of transcription factors such as OCT4 by phosphorylation.[144] Additionally, cancer recurrence is actively influenced by the interplay between ERK and CSCs. Sublethal doses of chemotherapy or radiation therapy believed to activate ERK in CSCs induce a rise in the number of CSCs, which in turn causes tumor recurrence.[145,146]

6.4. MAPK/ERK signaling and drug metabolism/drug transporters

Metabolizing enzymes and transporters are the two main targets of the MAPK/ERK signaling pathway that impacts drug metabolism in cancerous cells. Drug metabolism involves a variety of enzymes, depending on the type of drug. One of the first-phase drug metabolism enzymes that ERK can downregulate is human carboxylesterase 1 and 2 (CES1/2).[147,148] Fluorouracil (5-fluorouracil or 5-FU) is a chemotherapeutic medication with an extensive list of medicinal applications.[149] The dihydropyrimidine dehydrogenase (PDP) enzyme, which deactivates approximately 80% of 5-FU to diminish associated toxicity, is primarily responsible for initiating the first phase of eliminating the process of 5-FU.[150,151] The study of EGFR-mutated NSCLC has linked the decrease in the sensitivity of cancer cells to 5-FU with the increase in PDP expression as a result of the increasing phosphorylated form of ERK by EGFR hyperactivity.[152]

Paying attention to the growth demand of breast cancer cells for estrogen has led to the development of a hormone therapy approach to reduce the production of this hormone. The aromatase enzyme plays a key role in the production of estrogen from androgens.[153,154] One resistance strategy is based on the enhanced elimination system to deal with lipophilic medicine. The UGT1A enzyme, by adding glucuronic acid, plays a prominent role in resistance to compounds such as methotrexate.[155,156]

Research on topotecan- and paclitaxel-resistant cancer cells revealed elevated expression of aldehyde dehydrogenase 1A1 (ALDH1A1).[157] Furthermore, resistance to apoptosis and platinum-base anticancer drugs has been identified as associated with glutathione S-transferase Pi (GSTP1).[158] ERK can be implicated in forming hormone therapy or chemotherapy resistance through up-regulating aromatase, UGT1A, ALDH1A1, and GSTP1.[159-162]

The importance of drug transporters in resistance mechanisms and their interaction with the MAPK/ERK signaling pathway is indisputable. By controlling transporters, ERK can make cancer cells more susceptible to the effects of chemotherapy agents.[163,164] Although important results have been reported from research on the impact of MAPK/ERK signaling on enzymes and transporters involved in drug metabolism, a great deal is still unknown. Table 2 is a summary of the most important transporters implicated in drug resistance under the influence of MAPK/ERK signaling. Not to mention that confirming the effect of MAPK/ERK signaling on these transporters necessitates additional studies. Another important mechanism contributing to chemoresistance is the enhanced detoxification of chemotherapeutic agents through glutathione conjugation. Increased activity or expression of glutathione S-transferases (GSTs) promotes the conjugation of glutathione (GSH) to several anticancer drugs, thereby facilitating their detoxification and, in some cases, their export from tumor cells. This process reduces the effective intracellular concentration and cytotoxicity of chemotherapeutic agents, ultimately contributing to therapy resistance. In addition, enhanced antioxidant defenses, particularly those involving glutathione, may attenuate apoptosis by buffering intracellular ROS and reducing oxidative stress. Given that many chemotherapeutic agents exert part of their cytotoxicity through ROS-dependent apoptotic mechanisms, increased antioxidant capacity may diminish apoptosis and contribute to therapy resistance.[3,17]

Table 2. Summary of the main drug resistance-related transporters impacted by MAPK/ERK signaling.

Transporter	Effect of MAPK/ERK	Related Drug Resistance	Key associated Cancer	Ref.
ABCB1 (P-glycoprotein, MDR1)	Increased expression and activity	Doxorubicin, Paclitaxel, Olaparib	Breast, Ovarian	[165,166]
ABCC1 (MRP1)	Upregulation	Vincristine, Etoposide, doxorubicin, mitoxantrone	Lung, Breast	[167,168]
ABCG2 (BCRP)	Upregulation	Mitoxantrone, Topotecan	Breast, Colorectal	[169,170]
SLC22A1 (OCT1)	Downregulation	Metformin	Liver, Leukemia	[171,172]
SLC47A1 (MATE1)	Upregulation	Metformin	Various	[173,174]
OATP1B1 (SLCO1B1)	Modulated expression	Statins	Liver	[175,176]
OATP1B3 (SLCO1B3)	Upregulation	Various	Liver	[177,178]
MRP2 (ABCC2)	Increased activity	Platinum derivatives, such as cisplatin, carboplatin, and oxaliplatin	Liver	[179,180]
MRP3 (ABCC3)	Increased expression	Etoposide, Teniposide, Methotrexate	Pancreatic, Ovarian	[181,182]
OAT1 (SLC22A6)	Modulated expression	Methotrexate	Kidney	[183,184]
OAT3 (SLC22A8)	Modulated expression	Methotrexate	Kidney	[183,185]
OAT2 (SLC22A7)	Modulated expression	Platinum-based drugs, Methotrexate	Kidney	[183,186]
OAT4 (SLC22A11)	Modulated expression	Methotrexate	Bladder	[183,187]

6.5. MAPK/ERK signaling and ncRNA

The impact of ncRNAs on the process of gene expression has increased consciousness regarding their intimate relationship with signaling pathways. The control of cancer cells' sensitivity to drugs is also influenced by the primary interaction between the MAPK/ERK pathway and ncRNAs. Research on gastric cancer has shown that altered expression profiles of miRNAs and resistance to paclitaxel are associated with enhanced MAPK/ERK pathway activation. These findings indicate that activation of the MAPK/ERK pathway is associated with upregulation of miR-3127-5p, miR-1287, and miR-4713-5p, alongside downregulation of miR-224, miR-452, miR-424, miR-130a, and miR-193b.[188] Furthermore, increased phosphorylation of the MAPK/ERK pathway through EGFR has been found to be the mechanism of multidrug resistance caused by the up-regulation of miR-20a in gastric cancer.[189] On the other hand, a reduction in resistance to drugs has been attributed to the suppression of this pathway by miRNAs. The treatment approach based on the management of miRNAs has been strengthened by increased apoptosis and sensitivity to sorafenib through suppression of IGF-1R-mediated ERK activation by miR-122.[190]

Studies in breast cancer patients resistant to adriamycin have shown that elevated expression of P-glycoprotein contributes to therapeutic failure by reducing the intracellular accumulation of the drug. The four miRNAs (miR-302a/b/c/d) act in concert to suppress MEKK1, thereby reducing the membrane-associated levels of this kinase.[191]

The study that was conducted on miR-197 provided confirmation of the positive connection between resistance against 5-fluorouracil and the MAPK/ERK pathway. By regulating MAPK1, this miRNA makes the resistant cell more susceptible to 5-

fluorouracil.[192] An additional pertinent example is miR-634. By limiting ERK2 and other effectors, miR-634 makes its anti-tumor properties more apparent. The upregulation of this miRNA contributes to an enhanced response to carboplatin, doxorubicin, and cisplatin by promoting apoptosis and halting the cell cycle.[193] miR-503-3p, which directly targets ERK, can re-sensitize tissues and cells resistant to DDP in choroidal melanoma; however, suppression of miR-503-3p by circBIRC6 has the reverse effect.[194] Although the increase of circ-0006528 has been reported to be associated with resistance to adriamycin, the possible role of ERK in relation to this effect of circ-0006528 requires complementary studies.[195] Moreover, a variety of lncRNAs with elevated ERK molecular levels have the potential to enhance drug resistance; in this regard, NEAT1, SNHG12, lncRNA BC087858, and FAL1, respectively, increase resistance to cisplatin, temozolomide, EGFR-TKIs, and cisplatin.[196-199] Similar to H19, which causes resistance to chemotherapy, CUDR causes resistance to gemcitabine, and 5-FU operates by augmenting the activation of the MAPK/ERK pathway.[200,201] Meanwhile, lncRNA HCP5 employs a distinct mechanism to induce drug resistance to Adriamycin. This lncRNA is translated into HCP5-132aa, a peptide comprising 132 amino acids. This peptide promotes the production of key players in the autophagy process, including Beclin-1, in an ERK-based manner.[202,203]

7. Comparison and interpretation of Findings

The MAPK/ERK pathway is recognized as a central coordinator in the complex landscape of cancer drug resistance, where it integrates multiple cellular processes to confer adaptive survival advantages to malignant cells. Comparative analysis across resistance mechanisms reveals a strong convergence toward a pro-survival role of ERK, such that its hyperactivation intensifies therapeutic resistance by suppressing apoptosis, enhancing DNA repair capacity, maintaining cancer stem cell populations, reprogramming cellular metabolism, and modulating non-coding RNA networks. In the context of apoptotic regulation, ERK predominantly exerts anti-apoptotic effects through phosphorylation-dependent stabilization of proteins such as MCL-1 and survivin, accompanied by accelerated degradation of pro-apoptotic factors including Bim and BAD (Section 6.1). This survival-biased function is consistent with ERK-mediated upregulation of DNA repair genes, including XRCC1, ERCC1, and RAD51, which collectively enhance cellular tolerance to genotoxic stress induced by platinum-based chemotherapeutics or radiotherapy (Section 6.2). This phenomenon is also consistent with the dynamics of CSCs (Section 6.3), in which ERK signaling enhances the expression of stemness-associated factors such as SOX2 and NANOG in resistant models, while in other cellular contexts, ERK activity leads to the destabilization of these factors. This activity threshold-dependent duality parallels the variable effects of ERK on ncRNAs (Section 6.5), where miR-20a promotes drug resistance through EGFR-ERK crosstalk, whereas miR-634 and miR-122 suppress this pathway and restore therapeutic sensitivity.

The observed differences are largely driven by substrate-specific adaptive responses. ERK contributes to selective drug resistance by upregulating detoxifying enzymes such as PDP and GSTP1 while concurrently downregulating CES1/2, thereby conferring differential resistance across distinct drug classes. A similar pattern is evident in ncRNA-mediated regulation, where lncRNAs

including NEAT1 and HCP5 predominantly enhance ERK signaling or induce autophagy to reinforce drug resistance, whereas certain miRNAs exert inhibitory effects on this pathway.

From a quantitative perspective, the impact of ERK can be conceptualized as a "resistance index." In the coordinated regulation of apoptosis suppression and DNA repair, ERK inhibition results in a 1.5- to 4-fold increase in sensitivity to cisplatin or radiotherapy. In contrast, at the interface between cancer stem cell maintenance and drug metabolism, ERK activity drives a 2- to 5-fold upregulation of drug efflux and detoxification enzymes. These observations support a "resistance hub" model, in which ERK integrates upstream inputs into adaptive downstream phenotypes. Nevertheless, context-dependent differences, including pro-apoptotic stabilization of p53 under conditions of severe DNA damage, indicate that ERK-driven outcomes are cell type-specific, with epithelial cancers generally exhibiting a stronger anti-apoptotic bias than mesenchymal subtypes. Clinically, genomic profiling for ERK biomarkers (e.g., KRAS/MEK mutations) refines patient stratification, predicting resistance to BRAF inhibitors and guiding combinations like MEK/PI3K blockade in NSCLC.

Collectively, these findings underscore the necessity of integrating multi-omic data into resistance profiling strategies and position ERK as a high-priority nodal therapeutic target. Future approaches may exploit CRISPR-based genome editing to modulate ERK signaling or employ nanoparticle-mediated delivery of ncRNA-based therapeutics to preempt resistance evolution. Ultimately, through detailed dissection of these interconnected mechanisms, MAPK/ERK signaling may be transformed from a driver of therapeutic resistance into an exploitable vulnerability in precision oncology.

8. Clinical implications

Improving the effectiveness of current treatments or expanding the range of available treatments is required to optimize patient outcomes. Understanding drug resistance mechanisms at the molecular level is necessary for both strategies. One of the approaches to overcome this challenge is the individualized treatment of patients, which necessitates the assessment of their genomic profile. A unique treatment plan with low side effects and maximum efficacy must take into account the patients' genetic susceptibility to developing medication resistance, which can be ascertained by analyzing their genomic profiles.[204-206] In this regard, the discovery of the BRAF V600E mutation justifies the employing of inhibitors such as vemurafenib, encorafenib, and dabrafenib.[207] Despite the clinical efficacy of vemurafenib, dabrafenib, and encorafenib against BRAF V600E-mutant tumors, therapeutic resistance often arises via MAPK pathway reactivation. In particular, MEK reactivation and BRAF alternative splicing can restore downstream signaling and limit durable responses. Predicting a patient's response to therapy is regarded as an additional advantage of analyzing the genomic profile.[208] Research has indicated that particular mutations may impact the efficacy of targeted therapy. As an example, mutations in KRAS and MEK (such as KRAS G12V) may diminish the therapeutic benefit of BRAF V600E inhibitors, including dabrafenib.[209] Therefore, the role of

prognostic biomarker/predictor can also be taken into account for the MAPK/ERK signaling pathway, depending on the biological status of the pathway components.[210]

Combination therapy is one approach that can be employed to get around drug resistance. Systematically shifting between MAPK/ERK signaling pathway inhibitors and combining these inhibitors with immunotherapy or other chemotherapy drugs can increase the efficacy of treatment. In addition, inhibitors of the components of the MAPK/ERK pathway can be combined with inhibitors of compensatory pathways, including the PI3K/mTOR signaling pathway, to ensure the reduction of the reinforcing effect exerted on drug resistance mechanisms by oncogenic pathways such as MAPK/ERK.[211,212] Studies have shown that the combination of MEK and PI3K inhibitors can reverse acquired resistance to EGFR-tyrosine kinase inhibitors (TKIs) in NSCLC.[213] Collectively, re-sensitizing resistant tumors can be greatly aided by concentrating on the role of the MAPK/ERK signaling pathway in medication resistance mechanisms.[214]

9. Conclusion and Future Directions

The emergence of drug resistance in cancer cells remains a major obstacle to the long-term success of anticancer therapies, severely limiting treatment efficacy. Increasing evidence highlights the central role of the MAPK/ERK signaling pathway in orchestrating resistance mechanisms by regulating DNA repair, apoptosis, proliferation, stemness, and cross-talk with compensatory pathways such as PI3K/AKT/mTOR. These multifaceted functions underscore MAPK/ERK as both a driver and a mediator of resistance to chemotherapy, radiotherapy, and targeted agents. Therapeutic strategies focused on inhibiting MAPK/ERK signaling, either through selective inhibitors or rationally designed combination regimens, have shown promise in re-sensitizing resistant tumors. In particular, combining MAPK/ERK pathway inhibitors with immune checkpoint blockade, targeted agents, or inhibitors of parallel oncogenic pathways has opened new avenues for overcoming resistance and improving clinical outcomes. Looking ahead, a more comprehensive understanding of MAPK/ERK-driven resistance will be essential for translating these advances into durable clinical benefit. Future research should prioritize the identification of robust predictive biomarkers to enable patient stratification and to determine which tumors are most likely to benefit from MAPK/ERK-targeted interventions. Greater attention should also be given to dynamic resistance monitoring using longitudinal biopsies and liquid biopsy-based approaches, which may help detect early adaptive responses and emerging secondary resistance. In addition, rational optimization of treatment sequencing and dosing schedules, together with the development of more effective combination strategies, will be critical to maximize efficacy while minimizing toxicity. Since resistance is also shaped by tumor heterogeneity, the tumor microenvironment, and immune modulation, these factors should be systematically integrated into preclinical models and clinical trial design. Finally, the incorporation of genomic profiling, single-cell and spatial analyses, and systems biology

approaches into precision oncology frameworks may provide deeper insight into context-specific vulnerabilities and support the design of personalized therapeutic strategies. Collectively, targeting the MAPK/ERK pathway represents not only a promising strategy to overcome drug resistance but also a key foundation for the development of next-generation, individualized cancer therapies. Collectively, targeting the MAPK/ERK pathway not only provides a promising strategy to overcome drug resistance but also represents a cornerstone in the design of next-generation, personalized cancer therapies.

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