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ERK 1/2 Pathways: Discoveries in Disease Causation and Developments in Their Treatment

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ABSTRACT

This study delves into recent research on ERK1/2 signaling pathways, exploring their critical role in cellular processes such as proliferation, differentiation, migration, and apoptosis. Dysregulation of these pathways contributes to various human diseases, including cancers, autoimmune disorders, and neurodegenerative conditions. The study highlights the potential therapeutic benefits of targeting ERK1/2 through inhibitors, which demonstrate efficacy in treating autoimmune and inflammatory diseases, as well as cancer. However, issues like drug resistance, off-target effects, and unintended consequences of systemic MEK/ERK inhibition present challenges. Tumor progression locus 2 (TPL2) is an important regulator of immune responses that conveys inflammatory signals to downstream effectors, targeting upstream regulators like TPL2 or employing combinatorial therapies such as inhibition of Akt may offer more precise treatment approaches. The study also explores emerging treatments, including kinase inhibitors from extremophilic microorganisms, which offer new perspectives on drug development. Ultimately, a comprehensive understanding of ERK1/2's potential targets is crucial to developing effective therapies for a range of diseases, promising significant advances in public health.

Keywords: Autoimmune and Inflammatory diseases, MEK/ERK inhibition, Public Health

INTRODUCTION

The ERK1/2 signaling pathways play a crucial role in a wide range of cellular processes. They are fundamental components of the broader RAS/RAF/MEK/ERK pathway and are implicated in multiple disease mechanisms. Dysregulation of these pathways leads to the development of various pathological conditions, ranging from cancers and neurodegenerative diseases to autoimmune and inflammatory disorders [1]. The pathways also influence non-immune cellular activities, such as protein aggregation, thereby contributing to conditions like Alzheimer's disease and amyotrophic lateral sclerosis (ALS). Given their pervasive involvement in pathological processes, ERK1/2 inhibitors present potential therapeutic benefits. However, challenges like drug resistance and off-target effects highlight the necessity of comprehensive research into their mechanisms, applications, and the development of effective therapeutic strategies. Understanding the role of ERK1/2 pathways in disease causation will aid in creating targeted treatment modalities and providing patients with symptomatic relief. [2].

Features of ERK 1/2

Extracellular signal-regulated kinases (ERKs) are downstream effectors in the mitogen-activated protein kinase (MAPK) signaling cascade. In mammals, there are three conventional families of MAPKs: JUN N-terminal kinases (JNK1, JNK2, and JNK3), p38 kinases (p38-α, p38-β, p38-γ,

and p38-δ), and extracellular signal-regulated kinases (ERK1, ERK2, and ERK5). ERK1/2 are the final components of the MAPK phosphorylation cascade, playing a vital role in various signaling pathways that shape cellular behavior. The role of MAPKs in these pathways has been extensively studied. Among the members of the MAPK pathway, ERK1/2 has attracted the most significant amount of literature, focusing on its role in shaping fundamental cellular behaviors [3]. Research has examined the role of ERK1/2 activation in Toll-like receptor (TLR) pathways, providing insights into the processes involved in the recruitment, compartmentalization, and activation of innate immune cells. These cells form the first line of defense against infection through the activation of germline-encoded transmembrane pattern recognition receptors (PRRs). These innate immune PRRs activate ERK1/2 MAPK pathways, which play a crucial role in the inflammatory response.

ERK1/2 are serine-threonine protein kinases that are ubiquitously expressed and evolutionarily conserved, functioning as structurally related isoforms within the MAPK family. They were the first mitogen-activated protein kinases identified, discovered through early observations of the rapid phosphorylation of similarly sized proteins in response to growth factor stimulation. Although both ERK1 and ERK2 are ubiquitously expressed, ERK2 is typically found at higher levels in mammalian tissues. Despite their similar roles, ERK1 and ERK2 display functional redundancy in various signaling pathways. Notably, mice lacking ERK1 exhibit normal development and embryonic viability, whereas those deficient in ERK2 experience severe developmental abnormalities and embryonic lethality. However, this can be mitigated by over-expressing ERK1 transgenically, highlighting their overlapping functions [4]. When activated, ERK1/2 phosphorylate a range of cytoplasmic and nuclear substrates. Key targets in cellular proliferation and growth pathways include immediate early genes such as the FOS, JUN, MYC, and EGR transcription factor families, which are rapidly transcribed following mitogen stimulation. ERK1/2 also activates regulatory metabolic proteins across various cellular metabolic pathways. In particular, they primarily phosphorylate c-FOS, a crucial player in inflammatory cytokine production. Recent research has shown that TPL2-mediated activation of ERK1/2 leads to diverse cytokine responses, encompassing both pro-inflammatory and anti-inflammatory cytokines. This variability underscores the diverse genetic targets and substrates of ERK in inflammatory pathways, suggesting that ERK1/2's association with inflammatory diseases presents a potential therapeutic opportunity. Moreover, transmembrane scaffolding proteins for targeted ERK1/2 recruitment have been identified in other receptor signaling pathways. One such protein, SCIMP (SLP adaptor and CSK-interacting membrane protein), serves as a transmembrane scaffold for ERK in TLR pathways. SCIMP recruits ERK2 to TLR4 signaling sites within specific membrane domains, such as cell surface ruffles and macropinosomes in macrophages. Advanced live imaging techniques confirmed the recruitment and enrichment of cytoplasmic ERK2 to these dynamic membrane domains, providing high-resolution evidence of ERK partitioning during TLR signaling. SCIMP forms a complex with TLR4, enabling ERK1/2 to phosphorylate c-FOS, leading to increased production of pro-inflammatory cytokines while not affecting anti-inflammatory cytokine levels. This contrasts with canonical TLR-activated ERK1/2, which displays a broader cytokine profile [5].Further studies have revealed that SCIMP also activates NF-κB in response to TLR stimulation through ERK or other kinases. This further leads to immune and inflammatory responses, and is involved in stress responses and regulation of cell proliferation and apoptosis. Emerging research using pathway probes has

highlighted fluctuations in ERK activity within individual cells, and the propagation of this activity to neighboring cells [3-6]. Additionally, new advancements have uncovered various modes of ERK pathway stimulation. An increased baseline of ERK activity promotes single-cell and collective-cell migration and invasion. Experiments monitoring ERK activity in mouse skin revealed that ERK activity amplitude decays during propagation from random activity pulses rather than from wounds. This observation suggests synchronization of ERK pulses rather than wound-induced changes. Ultimately, the ERK1/2 pathways represent a sophisticated signaling mechanism within the broader RAS/RAF/MEK/ERK cascade. Their intricacies highlight the potential for further research into therapeutic strategies targeting ERK1/2 in inflammation and other diseases, given their central role in cellular behavior.

Functions of ERK 1/2

The ERK1/2 signaling pathway plays a central and multifaceted role in various fundamental cellular processes and behaviors. It regulates critical biological functions like cellular stress responses, cell survival, cell cycle progression, cell adhesion, cell migration, differentiation, metabolism, transcription, proliferation, development, and apoptosis. Furthermore, it orchestrates numerous cellular activities, including neuronal apoptosis through the induction of excitotoxicity, neuroinflammation, and innate immunity. By shaping many aspects of the inflammatory response and influencing immune cell fate, the ERK1/2 pathway critically affects cell physiology and pathophysiology, regulating many pathophysiological functions of cells [5,6]. Downstream of ERK activation, the signaling pathways significantly contribute to regulating cellular homeostasis. Recent research demonstrates that ERK1/2 is essential downstream of immune receptors, promoting inflammatory gene expression in response to infection and tissue damage. One notable observation is that ERK1/2 primarily phosphorylates the transcription factor c-FOS to mediate the production of inflammatory cytokines. This pathway also triggers gene expression changes, influencing additional regulatory elements that support NF-κB activation. ERK2-mediated phosphorylation of PARP1 modulates NF-κB transcriptional activity following TNF stimulation, revealing the role of ERK1/2 in regulating NF-κB activation in response to inflammatory mediators. Moreover, a significant downstream target of ERK1/2 within the RAS-ERK1/2 pathway is the ternary complex factors (TCFs). ERK1/2 regulates c-FOS transcription through TCF and ELK1 activation, further modulating c-FOS-dependent cytokine expression following Toll-like receptor (TLR) stimulation. This interaction illustrates how ERK1/2 signaling influences the differentiation and activation of cells in the adaptive immune system. Such signaling builds upon innate immune responses, promoting acute inflammation to safeguard the body against invading pathogens [1-4]. Tissue-specific inactivation of ERK2 has been strategically employed to circumvent embryonic lethality observed in ERK1-deficient mice, revealing that ERK1/2 plays a vital role at multiple stages of thymic development during T-cell differentiation and maturation. Proteomic analysis of T-cell receptor (TCR) activated CD8 T cells shows that ERK1/2 controls many transcriptional regulators crucial for T-cell differentiation and activation. Therefore, ERK1/2 governs a wide range of signaling pathways in both innate and adaptive immune cells, emerging as a pivotal regulator of immune cell function. The compartmentalization of ERK1/2 downstream of TLRs provides spatiotemporal control of signaling and thresholds of inflammatory responses in innate immune cells. The RAS-ERK pathway has been studied primarily for its involvement in cell proliferation and differentiation. Still, recent insights reveal that it also plays a conserved role in promoting cell migration and invasion. Recent findings have elucidated specific

ERK signaling patterns and effectors involved in various forms of cell migration. For instance, ERK stimulates actin polymerization and adhesion turnover at the leading edge, driving contraction that aids in cell movement. ERK activity patterns are especially significant in coordinating the movement of epithelial sheets and inducing ERK activity waves that govern collective migration and invasion. Recent technological advances have highlighted low-frequency ERK activity pulses in cells undergoing random-walk migration. Sustained ERK activation induces cell contraction and generates activity waves that collectively drive cell movement. However, several critical questions remain regarding the timing and control of ERK signaling during different forms of physiological cell migration and invasion. Furthermore, ERK activity peaks coalesce at elevated growth factor concentrations and substrate stiffness, raising the baseline of activity. Thus, the ERK pathway is indispensable in transducing extracellular signals into intracellular responses [7].In conclusion, ERK pathways provide an integral link between external signals and cellular processes, translating extracellular cues into intricate intracellular responses. They shape immune function, drive cellular migration, and regulate gene expression, highlighting their central role in both normal physiology and pathological processes. Further understanding of ERK signaling will likely uncover novel therapeutic targets to treat immune and proliferative disorders effectively. Figure 1 shows the graphical version of the functions carried out by ERK ½.

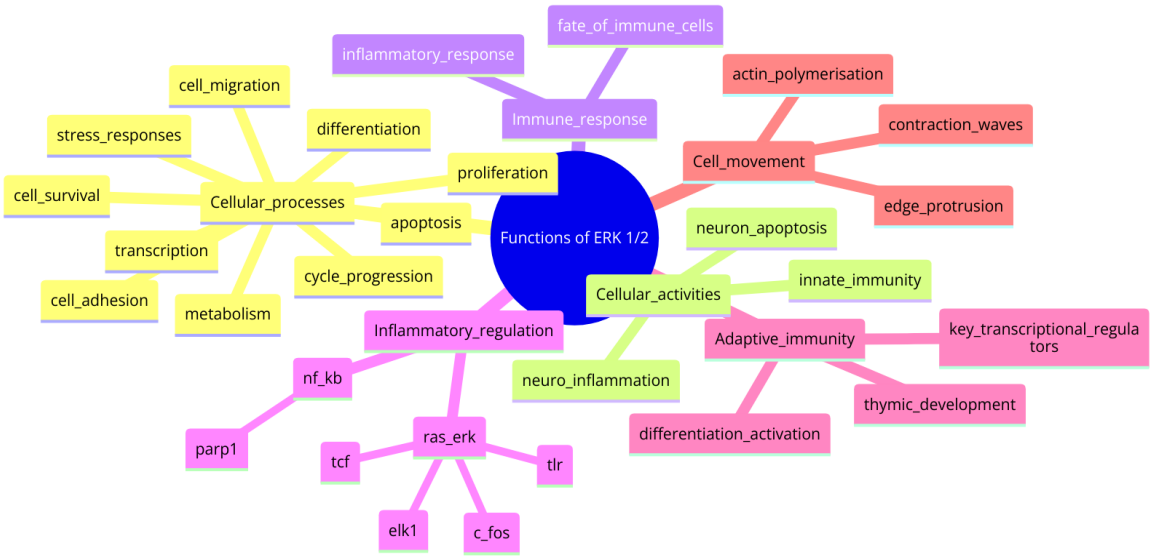

Figure 1: Functions of ERK ½.

Diseases Caused by ERK 1/2 Dysfunction

The ERK1/2 signaling pathway, due to its fundamental role in the regulation of diverse cellular functions and processes, becomes crucial when its normal activity is altered. Deviations or signaling dysfunctions in this pathway have well-established implications for the development of a variety of human diseases affecting different organs and systems. One significant set of disorders, known as RASopathies, are linked to mutations in ERK signaling and manifest as autosomal-dominant syndromes. These conditions often lead to severe complications, including congenital cardiac defects and hypertrophic cardiomyopathy [8]. Moreover, ERK signaling is associated with multiple pathological conditions in the nervous system, such as strokes and autism. Overexpression or hyperactivation of ERK plays a pivotal role in the pathogenesis of various disorders within the RAS/RAF/MEK/ERK pathway, resulting in heart diseases, neurological conditions, and

cancers. Recent research has also uncovered compelling evidence of dysfunctional ERK1/2 signaling in inflammatory diseases. Intriguingly, various internalized pathogens have evolved sophisticated mechanisms to manipulate ERK signaling within inflammatory pathways as a strategy to evade the immune response. For instance, *Mycobacterium tuberculosis* secretes tyrosine phosphatase MptpB to reduce ERK1/2 phosphorylation in macrophages, blocking the production of IL-6 and activating the Akt pathway to promote cell survival. Meanwhile, *Salmonella enterica* and *Shigella flexneri* secrete phosphor-threonine lyases targeting the Thr-X-Tyr activation motif of ERK1/2, utilizing phosphate cleavage to irreversibly inhibit kinase activity [9].Additionally, other pathogens like *Yersinia* spp. and *Vibrio parahaemolyticus* secrete acetyltransferase enzymes to acetylate upstream MEK1/2 while directly inhibiting ERK1/2 kinase activity and phosphorylation. Extensive research has reviewed ERK1/2 signaling dysregulation in cancer, revealing its role in inflammatory pathways and associations with various immune-linked diseases characterized by chronic inflammation. Elevated ERK1/2 activity in inflamed joints of rheumatoid arthritis (RA) patients emphasizes the potential therapeutic benefits of ERK1/2 inhibitors in reducing RA-related inflammatory cytokine production, including TNF, IL-1, and IL-6. ERK1/2 pathway dysregulation is also implicated in chronic lung inflammation. Sustained ERK1/2 activation in bronchial epithelial cells, resulting from the Z mutation in alpha1-antitrypsin, maintains excessive NF-κB activation, contributing to emphysema's early onset. Rodent models of chronic alcohol-induced liver inflammation revealed that ERK1/2 activation downstream of TLR4 modulates altered TNF expression in liver macrophages. Experimental autoimmune encephalomyelitis (EAE), an animal model of multiple sclerosis (MS), demonstrated that inhibiting ERK activation with the MEK inhibitor U012 blocked IL-23 and IL-1β production in dendritic cells (DCs), suppressing Th17 and Th1 cell auto-antigen responses and reducing disease severity [10].Unlike cancer, no specific inflammation-associated ERK1/2 genetic variants have been identified. Nevertheless, genetic associations between ERK1/2 pathway components and inflammatory diseases strengthen the understanding of this pathway's role in disease development. For instance, a single nucleotide polymorphism (SNP) in TPL2 (rs1042058) increases the risk of inflammatory bowel diseases like Crohn's disease and ulcerative colitis. This SNP correlates with increased ERK phosphorylation and IL-1β and IL-18 secretion in human monocyte-derived macrophages in vitro, along with reduced anti-inflammatory IL-10 in patient intestinal biopsies [5-7]. ERK signaling is further linked to neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS), which are all characterized by neuroinflammation and abnormal protein aggregation in the central nervous system (CNS). ERK1/2 signaling plays a pivotal role in microglial activation, which are resident macrophages in the CNS. Recent studies indicate that ERK1/2 promotes pro-inflammatory microbial activity and disease-related gene expression via TLRs in Alzheimer's disease. In Parkinson's disease, ERK1/2 promotes leucine-rich repeat kinase 2 (LRRK2)-mediated microglial activation, triggering inflammation, apoptosis, and in vivo inflammatory responses.Additionally, ERK1/2 activities affect non-immune pathways, disrupting mitochondrial morphology and function in Alzheimer's disease, and leading to mitochondrial biogenesis defects and dopaminergic neuronal degeneration in Parkinson's disease. In ALS, ERK1/2 signaling in motor neurons induces glutamate excitotoxicity and axonal transport defects, which are tightly linked to disease progression [2]. In light of these findings, it is evident that pharmacological inhibition of ERK has the potential to address many of these pathogenic

conditions. This underscores the broad influence of ERK signaling in neurodegenerative pathways and its potential as a therapeutic target across these disease states. Ultimately, ERK1/2 signaling dysregulation is linked to a wide range of human pathological conditions, including chronic and uncontrolled inflammation. Future studies are needed to further develop therapeutic strategies that effectively target the ERK1/2 pathway in inflammatory diseases and other pathological conditions.

Role of ERK 1/2 in Cancers

ERK plays a fundamental role in tumourigenesis, particularly in cancer cell proliferation and has hence been widely investigated as an anti-cancer target molecule, specifically in experimental pathways suppression. Some side-effects of anti-cancer therapies such as cardiotoxicity due to chemotherapeutic treatments have also been linked to ERK pathways. ERK1/2 signalling downstream of the extracellular growth factor receptor (EGFR) has been deeply investigated. The EGFR is an RTK that has a key role in cell proliferation and is associated with the development of many human cancers. Dysregulation of the RAS-regulated RAF-MEK1/2-ERK1/2 signalling pathway is observed in approximately one-third of human cancers [7]. Figure 2 shows a schematic diagram of the Raf/MEK/extracellular signal-regulated kinase (ERK) pathway and its regulators and effector.

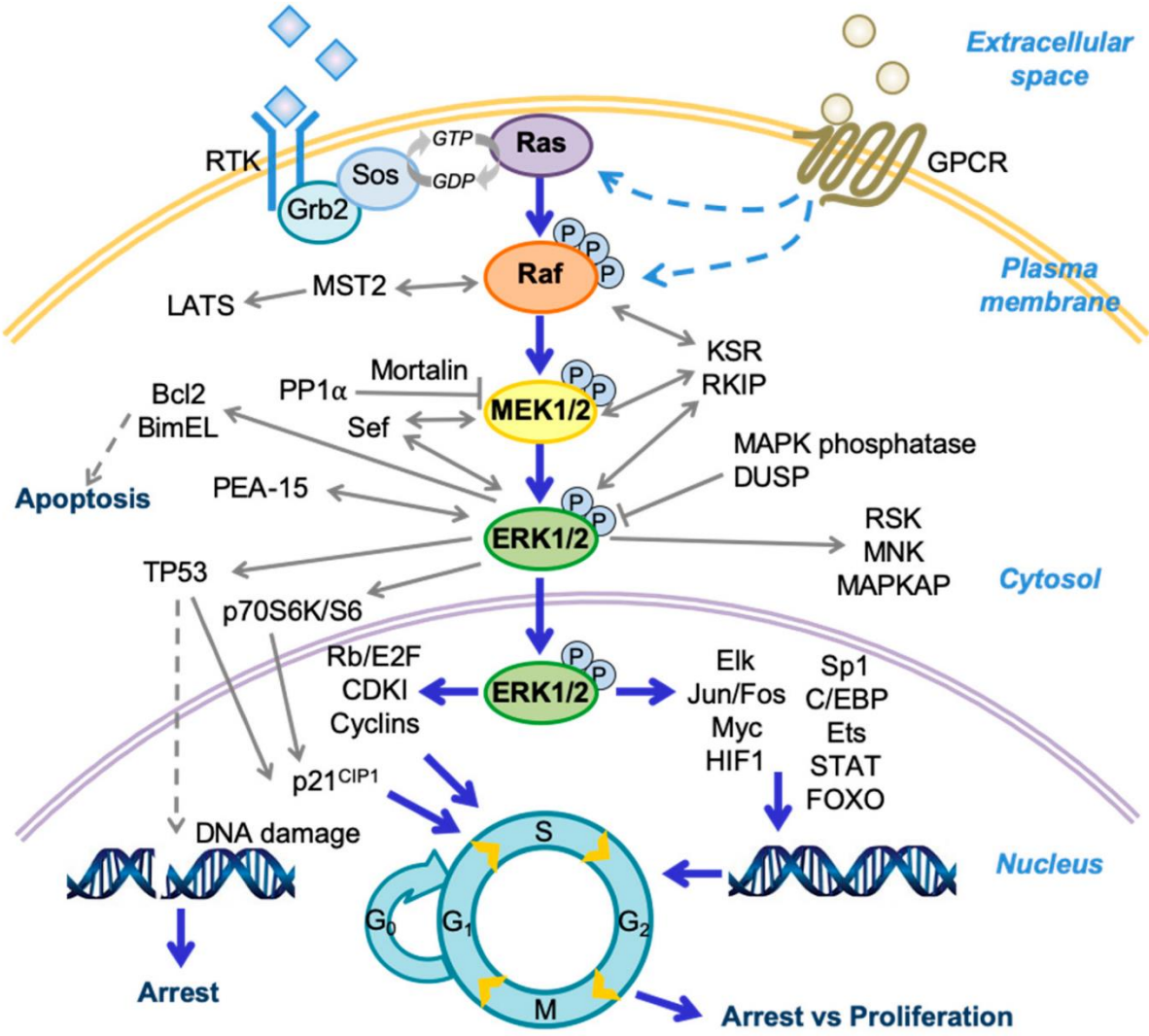

Figure 2: A schematic diagram of the Raf/MEK/extracellular signal-regulated kinase (ERK) pathway and its regulators and effector [The diagram has been taken for reference from [9]]

This can be attributed to the central role it plays in cell growth, proliferation and survival pathways. In a recent genome sequencing study, it was observed that activating TPL2 mutations are present in 33% of childhood spitzoid melanomas. Melanomas also frequently exhibit activation of BRAFV600E/K and NRASQ61L/K mutations. These cells are addicted to the activity of these mutant oncoproteins. There have been no cancer-associated mutations identified in ERK itself, but K-RAS and B-RAF are commonly recognised as oncogenes in which constitutively active mutations, such as K-RASG12D and B-RAFV600E have been observed to lead to colorectal cancer, breast cancer, leukemia, and melanoma through the activation of RAF/MEK/ERK and PI3K/AKT/mTOR signalling pathways. These pathways are often activated by mutations and chromosomal translocation in vital targets. Dysregulation of the P13K/AKT /mTOR signalling pathway is seen in almost all neoplasms. The interaction of both these pathways facilitates tumourigenesis. Hence dual inhibitors or a promising new development in anti-tumour activity, and targeted inhibitors have the potential to play a fundamental role in malignant neoplasm therapy. Genetic alterations are observed in normal patients as well as tumour patients. Due to the key role of these pathways in facilitating tumours, a comprehensive understanding of them will help greatly in drug selection for tumour therapy [1]. These pathways are frequently involved in cancer therapy and can be regulated by p53 which causes cell proliferation, drug resistance, cell cycle progression, and tumour metastasis. Alterations in upstream receptors of these pathways also contribute to tumour development. The mutations present upstream cause abnormal downstream activation as well. All these factors complicate the treatment of tumours and lead to targeted drug failure as single-target small molecular inhibitors are unable to suppress the downstream factor activity. The development of subsequent mutations contributes to resistance and tumour cell anti-apoptosis, further complicating treatment. To relieve drug resistance, all of these factors should be considered during the development of inhibitors that target these genes. Even though the two pathways have different mechanisms, they share many downstream targets that promote cell proliferation and facilitate drug resistance. Mutations and abnormal activation of the pathways lead to tumour development, drug resistance, and the limited effectiveness of inhibitors. ERK certainly has implications in cancer, but various bioactive products from plants, microbial organisms, or marine organisms, and the chemical structures have the potential to modulate this pathway for the treatment of different types of cancer. The P13K/AKT/mTOR and RAF/MK/ERK pathways are complex cascades with multiple targets and are intriguing aspects of human cancer therapy. Further studies should be conducted to develop treatment options with reduced toxicity and improved effectiveness for cancer patients. Hence, it can be concluded that the prospective development of these drugs provides a hopeful future for cancer patients. Table 1 Shows comprehensive insights from the previously done studies.

Serial No.	**Paper Title (Reference)**	**Type of Study**	**Insights**
1	The extracellular signal-regulated kinase 1/2 pathway in neurological diseases: A potential therapeutic target (Review) [1]	Review	Highlights the role of ERK1/2 in the CNS, particularly its involvement in neurological disease pathogenesis. Potential therapeutic strategies that modulate ERK1/2 signaling for disease management are discussed.
2	The Role of ERK1/2 in the Development of Diabetic Cardiomyopathy [2]	Review	Discusses the importance of ERK1/2 signaling in diabetic cardiomyopathy (DCM), emphasizing its dual role in

			promoting both cardiac dysfunction and protection against myocardial injury.
3	Enhanced MAPK1 Function Causes a Neurodevelopmental Disorder within the RASopathy Clinical Spectrum [3]	Clinical Research	Explores the link between MAPK1 variants and neurodevelopmental disorders, revealing how pathogenic variants enhance MAPK signaling and contribute to Noonan syndrome-like phenotypes.
4	ERK1/2 Signalling Pathway Regulates Tubulin-Binding Cofactor B Expression and Affects Astrocyte Process Formation after Acute Foetal Alcohol Exposure [4]	Experimental Study	Investigates how ERK1/2-mediated regulation of TBCB expression affects astrocyte process formation after acute fetal alcohol exposure, contributing to fetal alcohol spectrum disorders.
5	ERK1/2 is an endogenous negative regulator of the gamma-secretase activity [5]	Experimental Study	Demonstrates that ERK1/2 is an endogenous negative regulator of gamma-secretase activity, implicating its role in Alzheimer's disease pathology.
6	Interference with ERK-dimerization at the nucleocytosolic interface targets pathological ERK1/2 signaling without cardiotoxic side-effects [6]	Experimental Study	Describes a cardio-safe approach to inhibit ERK1/2 dimerization, reducing pathological signaling without cardiac side effects. This strategy shows promise in treating heart failure and cancer.
7	ERK1/2 pathway mediates epithelial-mesenchymal transition by cross-interacting with TGFβ/Smad and Jagged/Notch signaling pathways in lens epithelial cells [7]	Experimental Study	Demonstrates the complex interplay between ERK1/2, TGFβ/Smad, and Jagged/Notch signaling pathways in mediating epithelial-mesenchymal transition in lens epithelial cells.
8	ERK1/2 Signalling Pathway Regulates Tubulin-Binding Cofactor B Expression and Affects Astrocyte Process Formation after Acute Foetal Alcohol Exposure [4]	Experimental Study	Shows how acute fetal alcohol exposure disrupts astrocyte process formation via the ERK1/2 pathway, impacting fetal alcohol spectrum disorders.
9	The Role of ERK1/2 in the Development of Diabetic Cardiomyopathy [2]	Review	Highlights ERK1/2's dual role in diabetic cardiomyopathy, promoting cardiac dysfunction and offering cardioprotection depending on context.

ERK1/2 Inhibitors and Disease Treatment

With a comprehensive understanding of ERK pathways, hundreds of inhibitors have been developed. Some of these demonstrate promising effects in cancer treatment and moderate toxicity in certain cancers, while others were discontinued due to various challenges. It has also become clear that targeting ERK pathways shows potential therapeutic benefits for treating autoimmune and inflammatory diseases. Another potential strategy involves targeting the spatiotemporal membrane recruitment of ERK1/2 through immune-specific adapters like SCIMP. Besides its functions in immune cell signaling, ERK1/2 also plays a central role in many non-immune cell pathways. This often leads to unintended consequences when using systemic MEK/ERK inhibition as anti-inflammatory therapeutics. To avoid this global blockade of ERK pathways, TPL2 upstream of ERK1/2 can be inhibited in inflammatory pathways, offering a more targeted approach to treating ERK1/2-mediated inflammation. It has been observed that MEK inhibitors, within the RAF/MEK/ERK pathway, exhibit the most specificity and benefit only some neoplasm patients. Since other targets may be responsible for the disease beyond MEK activation, the efficacy of MEK inhibition is limited. Thus, it is necessary to combine MEK inhibitors with chemotherapy and radiotherapy, which show promising effects in disease treatment. The PI3K/AKT/mTOR and RAF/MEK/ERK pathways are characterized by complex crosstalk, and their role in independently or jointly regulating cell proliferation, apoptosis, and other

characteristics warrants the use of multi-target inhibitors. Some trials were halted due to toxicity and adverse effects, highlighting the need to address these problems for effective inhibitor use [7]. Additionally, many MAPK inhibitors cause resistance by activating compensatory feedback loops in tumor cells and their microenvironments. Innovative combinatorial treatments for cancer management must incorporate translational research to generate effective therapeutics. To this end, around 150 kinase-targeted drugs are currently in clinical trials, while preclinical research on kinase-specific inhibitors continues. RAS, MEK, and ERK inhibitors have shown promising anti-tumor activity and survival improvements, but drug resistance remains a significant problem. Underlying genomic instability and cancer heterogeneity result in compensatory pathway initiation. Targeting the downstream kinase of ERK and combining ERK inhibition with MEK and RAF inhibition could enhance effectiveness. However, many upstream ERK inhibitors, despite exhibiting clinical efficacy, suffer from problems like ERK signaling reactivation and drug resistance. Emerging ERK inhibitor developments aim to overcome acquired drug resistance in tumors, and promising results have been seen in clinical and preclinical studies. Another observation was that TEN alterations suppressed RAF/MEK/ERK pathway activity through AKT phosphorylation and RAS inhibition. The FDA has supported inhibitors targeting key pathway components, assessing them in multiple clinical trials. The combination of small-molecule inhibitors with traditional regimes offers another promising path. Extremophilic microorganisms that thrive in extreme environments present opportunities for developing biotechnology and pharmaceutical products, such as anti-cancer drugs and kinase inhibitors. Kinase inhibitors have received attention in searching for new drugs and natural bioactive compounds. However, limitations like poor solubility, complexity, and bioavailability must be addressed through comprehensive quality analysis to ensure efficacy, safety, composition, and compliance with international standards. Although MEK inhibitors hold promise in cancer therapy, their clinical use is compromised by acquired resistance due to mutations. ERK1/2-specific inhibitors may help overcome resistance to upstream targets. BRAF inhibitors (BRAFi) have transformed melanoma treatment, especially for BRAFV600E/K-mutant melanomas, although resistance remains a problem. Resistance mechanisms often involve reinstating ERK1/2 signaling, which is why BRAFi is combined with one of three approved MEK1/2 inhibitors (MEKi) for a more durable, albeit transient, clinical response. ERK1/2 inhibitors (ERK1/2i) counteract ERK1/2 signaling, but resistance may arise through a parallel pathway leading to ERK5 activation. In conclusion, a thorough understanding of the pathological mechanisms regulated by ERK pathways will facilitate the development of functional therapies for a diverse range of diseases, profoundly impacting public health [7].

CONCLUSION

In conclusion, the ERK1/2 signaling pathways hold a fundamental position in orchestrating diverse cellular functions and processes. Their dysregulation is intricately linked to the development of a wide array of human diseases, including cancers, autoimmune disorders, neurodegenerative conditions, and inflammatory ailments. Recent advances in research highlight their potential as therapeutic targets, given their pervasive influence on cell proliferation, differentiation, immune response, and survival. However, the challenges of drug resistance and pathway complexity necessitate deeper exploration into their mechanisms to design more effective treatment strategies. By advancing our understanding of ERK1/2 signaling and developing innovative inhibitors, we can better address these conditions, providing more targeted and impactful therapies for

patients suffering from diseases driven by ERK pathway dysregulation.

Declaration by Authors

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