Exploring the Molecular Mechanisms of the ERK/MAPK Pathway in Melanoma Development

Danyang Chen *

Department of Pharmacy, Guangdong Medical University, Dongguan, China

* Corresponding Author Email: danyangchen@gdmu.edu.cn

Abstract. Although melanoma is a less prevalent form of skin cancer, its malignancy is rather high. Specifically, malignant granulocytic melanoma has emerged as one of the most common causes of mortality from skin cancer. Melanoma patients have a good prognosis as long as the cancer is identified and treated early in the disease. However, as the cancer spreads, it becomes more aggressive and metastasizes, making treatment more challenging. In recent years, scientists have conducted in-depth studies on the molecular mechanisms of cancer development and progression, and have discovered many signaling pathways associated with cancer progression. Among them, the ERK/MAPK pathway has been confirmed to be one of the key signaling pathways in a variety of cancers. This paper reviews the mechanism of the ERK/MAPK pathway in tumor progression and focuses on its function in melanoma. This article highlights the significance of therapeutic approaches that target this route in the treatment of melanoma by offering insights into it. These insights may offer crucial hints for the creation of therapeutic methods that target this pathway. These treatment approaches might involve the creation of drugs that specifically target important pathway molecules as well as the use of technologies like gene editing to control the pathway's activity.

Keywords: ERK/MAPK pathway; melanoma; treatment strategies.

1. Introduction

Every year, over 55,500 people pass away from melanoma. Globally, the disease's incidence and mortality rates vary significantly depending on an individual's access to primary care and timely diagnosis. If melanoma spreads, it can quickly become fatal. There have been few therapy alternatives available for over 40 years, and all clinical trials have failed. Because of advances in biology and the availability of novel therapeutics, advanced melanoma has emerged as a new therapy option for solid tumors in the last ten years. Activated protein kinase inhibitors that target the BRAF V600 (V600E) mutation in conjunction with specific BRAF inhibitors have greatly increased response rates and overall survival. Furthermore, advanced cutaneous melanoma has been used as a model to test checkpoint inhibitors, providing hope for both possible cures and long-term tumor management. The efficacy of targeted medicines and antibodies that block programmed cell death protein 1 (PD-L1) in localized or regional disease, which extends overall survival, distant metastasis survival, and recurrence-free survival, supports these assumptions [1].

Despite making up just 2% of all skin cancer cases, skin melanoma (SKCM) is an aggressive form of the disease that develops from melanocytes. Because of its severe malignancy and aggressiveness, SKCM has the highest death rate of any kind of skin cancer, accounting for almost 75% of cases. The molecular processes behind SKCM remain elusive, despite the preliminary understanding of its etiology and clinical characteristics. Research has demonstrated the significant roles oncogenes and oncogenes play in the development of several malignancies, including SKCM. These important genes may offer novel indicators and targets for the detection and therapy of tumors in addition to furthering people's comprehensive understanding of the developmental processes of SKCM [2].

The staging of cutaneous melanoma is mainly based on the AJCC 7th edition TNM staging system. It is worth noting that there are no uniform staging criteria for other types of melanomas except for ocular-derived melanoma (e.g., conjunctival, eyelid, and choroidal) and mucosal melanoma. Diagnosis of melanoma requires a combination of pathologic and clinical diagnostic criteria and is performed by physical examination, pathophysiology, and imaging. The importance of early

diagnosis is especially emphasized, as early diagnosis is the key to saving lives. When conditions permit, molecular marker tests of tumor tissues, such as BRAF-V600E and C-kit mutations, can also be performed to provide more accurate diagnostic information.

In terms of treatment, early-stage melanoma is largely dependent on surgery, especially extended resection. The extent of resection is determined based on T-staging (i.e., depth of infiltration). For patients who have developed metastases, isolated limb heat infusion chemotherapy (ILP) or isolated limb heat infusion chemotherapy (ILI) is recommended. These therapeutic strategies are chosen to minimize tumor load and improve patient survival and quality of life.

Extracellular signal-regulated kinase (ERK), originally known as ERK1, was subsequently renamed as mitogen-activated protein kinase (MAPK) in separate research. Cloned in mammalian cells, ERK1 is a cell cycle-regulating Ser/Thr protein kinase. These days, the majority of people are aware that ERK is the effector kinase in a highly selective three-layered kinase cascade and that it is crucial for the development of the cell cycle, differentiation, and survival. Numerous medical illnesses are associated with the dysregulation of this system. Thanks to recent research, people now have a much better knowledge of the signaling of the MAPK-ERK pathway, which opens up a wide range of potential treatment methods that target the route [3].

Melanoma is a malignant tumor derived from melanocytes, and its development is often accompanied by mutations in a series of genes within the cells. Recent studies have revealed that there is a close interaction between these mutated genes and the ERK/MAPK pathway, which jointly regulate the growth, migration, and apoptosis of melanoma cells. Therefore, an in-depth discussion of the specific mechanism of the ERK/MAPK pathway in melanoma in this paper not only helps us to better understand the law of tumorigenesis and development but also can provide new ideas and methods for the clinical treatment of melanoma. Meanwhile, therapeutic strategies targeting the ERK/MAPK pathway have become a hot research topic, and a variety of novel drugs and therapeutic methods are emerging. These results not only demonstrate the potential of targeting this pathway for treatment but also foretell the possible breakthroughs in melanoma treatment in the future.

2. Biological Functions of the ERK/MAPK Pathway In Cancer

The MAPK/ERK pathway plays a crucial role in cancer progression, and it is a signaling pathway closely related to cell growth, proliferation, and apoptosis. The pathway is activated when the cell encounters external stimuli such as receptor tyrosine kinase (RTK) binding to ligands, which initiates a series of complex signaling processes that ultimately promote cell growth and proliferation.

In the context of cancer, mutation or over-activation of the MAPK/ERK pathway often leads to uncontrolled cell growth and resistance to apoptosis, which undoubtedly accelerates the process of cancer development. Because of this, researchers are working on the development of novel anti-cancer drugs that target this pathway. These drugs are designed to inhibit the growth and proliferation of cancer cells, providing new therapeutic strategies to defeat cancer.

Figure 1 shows the process by which this pathway is activated. Receptor tyrosine kinase (RTK) is a transmembrane protein. A signaling cascade event is triggered when a ligand, such as a growth factor, cytokine, or hormone, attaches to its extracellular region. The cytoplasmic structural domain of RTK is phosphorylated when the ligand binds to two of the subunits, forming dimers of the subunits and starting this process. When cytoplasmic junction proteins attach to the phosphorylated RTK, guanine nucleotide exchange factor (GEF) is drawn to the plasma membrane.

Small G proteins like RAS, which are typically inactive and bound to guanosine diphosphate (GDP), are activated at the plasma membrane by GEF. On the other hand, RAS is momentarily active when GDP is substituted with an activator and binds to it. This activation of RAS then triggers the activation of BRAF, one of the mitogen-activated protein kinases (MAPKKK). BRAF activation additionally encourages MAPKK (MEK), the second protein kinase in the cascade, to become phosphorylated.

The ability of MAPKKs to selectively bind both tyrosine and serine/threonine amino acid residues is crucial for the activation of MAPK, the cascade's last and third enzyme (ERK). MAPK has to have nearby threonine residues and tyrosine residues dual phosphorylated to be active. After dual phosphorylation is finished, MAPK acts as an enzyme and moves to the nucleus, where it phosphorylates and activates transcription factors that control gene expression, affect cellular activity, and help cells react to outside stimuli. One of the primary methods of cellular signaling and communication, this process makes sure that cells can react to external stimuli fast and accurately [4].

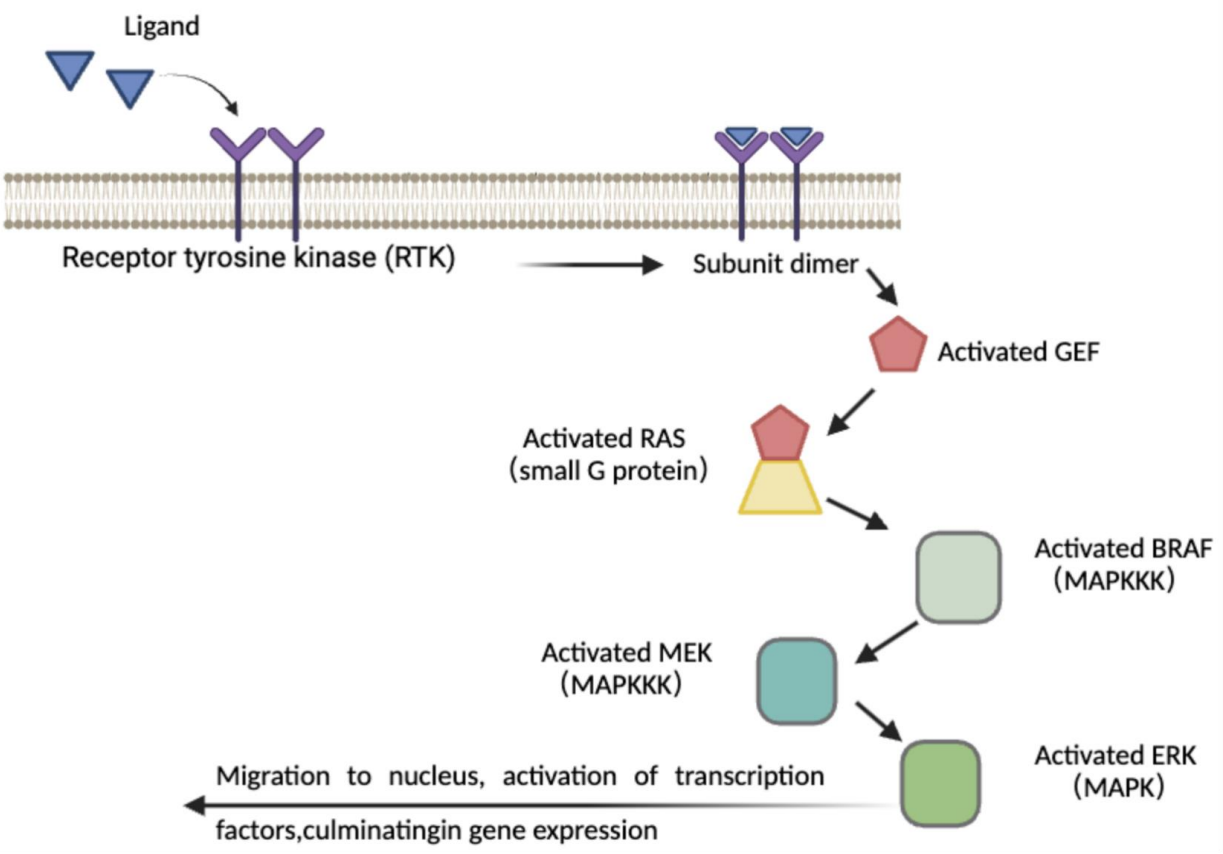

Fig 1. MAPK (ERK) pathway.

3. Mechanism Of EPK/MAPK Signaling Pathway In Melanoma

3.1. Analysis of oncogenes in melanoma tissues

To delve into the functions of different genes and their interactions in melanoma, researchers such as Ma et al. conducted an exhaustive analysis of the genes of melanoma patients. They skillfully used immunobiological staining techniques to delicately process and analyze the tissue samples, aiming to quantify the protein expression levels of the oncogenes. This approach not only provided the researchers with direct evidence of the degree of oncogene activity within the cell but also revealed the dynamics of protein production. These data were organized into Table 1, which provides an important reference for subsequent gene function studies and the development of melanoma treatment strategies [5].

Table 1 details the data of the two groups of melanoma patients, in which the primary group is mainly in stage II/III, while the metastatic group is mainly in stage III-IV. Through in-depth analysis of these data, we found that mutations in certain genes were closely associated with the development of melanoma, such as the DMKN gene. To further reveal the mechanism of action of these genes in melanoma, we conducted an in-depth investigation of the relationship between these genes and the ERK/MAPK pathway. Based on previous studies and our experimental data, we summarized the important roles of these genes in melanoma.

Table 1. The common carcinogenic factors in patient research [5].

Oncogenic variable	Melanoma patients	
	Primary (n = 12)	Metastasis (n = 19)
DMKN	35.32 ± 3.92	49.25 ± 6.22
P53	23.25 ± 3.35	58.32 ± 2.43
Ki67	40.12 ± 5.41	69.32 ± 10.11
Melan-A	41.12 ± 7.76	25.74 ± 12.8
S-100	32.04 ± 2.63	59.43 ± 1.06
HMB-45	28.75 ± 2.81	25.12 ± 2.81
CK-8	27.19 ± 8.33	30.14 ± 4.40
SAM	19.84 ± 0.65	24.24 ± 1.96

3.2. DMKN

DMKN is a novel oncogene that plays an important role in melanoma. It has been found that DMKN expression levels are significantly elevated in malignant melanoma and that this expression is strongly associated with patient prognosis, especially in melanoma patients harboring BRAF mutations.

To better understand the role of DMKN and its underlying mechanisms in the development and progression of malignant melanoma, Ma et al. produced Table 2, a table of data on clinicopathologic features and DMKN expression in malignant melanoma (MM). The correlation between different genders, ages, tumor stages, anatomical sites, pathological types, and differentiation degree with DMKN mRNA and protein expression is listed. The relationship between DMKN and patient characteristics can be better understood through in-depth analysis and mining of these features [5].

Overall, DMKN is highly expressed in malignant melanoma, while different factors have different effects on its expression. For example, female patients had lower levels of DMKN mRNA expression, whereas patients with older age, later tumor stage, anatomical site of the face and neck, superficial diffuse type, and high degree of differentiation had higher levels of DMKN mRNA expression. In addition, although DMKN protein expression was not affected by factors such as gender, age, and tumor stage, it was higher in patients with anatomical sites of the face and neck, deep diffuse type, and a high degree of differentiation.

Subsequent research revealed that DMKN expression suppression and ERK/MAPK signaling pathway activation might both reduce the capacity of melanoma cells to proliferate, migrate, and invade. Ma evaluated the effect of DMKN on MM migration and invasion by transiently transfecting shDMKN in C8161 and MUM-2B cell lines. The in vitro wound healing experiment findings showed that C8161 and MUM-2B cell migration rates were much lower. In advanced melanoma cell lines, DMKN knockdown decreased cell migration after five days of incubation. For the C8161 and MUM-2B cell lines, respectively, the average fluorescence levels correlated with cell migration were 89.20 ± 32.24 (control: 120.00 ± 45.21) and 117.20 ± 9.43 (control: 124.05 ± 11.81). The impact of DMKN on C8161 and MUM-2B cell clone formation inhibition. The results showed that the colony formation of these two cell lines was significantly reduced after transient transfection with shDMKN [5].

The study by Ma investigated the effects of DMKN on melanoma cells and its association with melanoma mutation types by exploring its expression in melanoma. The findings suggest that DMKN plays an important role in the development and progression of malignant melanoma. Experimental methods such as gene knockdown, cell migration invasion, whole gene sequencing, and immunohistochemistry were used in the study. It was found that high expression levels of DMKN were associated with reduced patient survival and revealed that DMKN promotes melanoma development and progression through activation of the ERK/MAPK signaling pathway [5].

Table 2. DMKN expression and baseline clinic-pathological features in cancer specimens [5].

Variable	No.	DMKN			
		mRNA level	P-value	Protein level	P-value
Gender					
Female	15	0.18±0.05	0.731	33.35±4.8	0.483
Male	16	0.16±0.06		47.7±5.7	
Ag					
>=60	19	0.22±0.06	0.035	47.37±5.08	0.042
<60	12	0.09±0.02		30.17±4.82	
TNM stage					
II-III	12	0.07±0.02	0.032	35.32±3.92	0.041
IIIB-IV	19	0.22±0.05		49.25±6.22	
Anatomic location					
Face	3	0.15±0.04	0.585	33.34±9.91	0.323
Trunk and neck	2	0.09±0.02		24.61±2.51	
Upper limb and shoulder	2	0.08±0.01		20.32±6.01	
Lower limb and hip	19	0.15±0.04		42.89±5.02	
NA(Not applicable or not available)	5	0.30±0.13		51.61 ±9.67	
Pathology type					
Superficial spreading	16	0.19±0.01	0.632	52.80±11.54	0.117
Nodular	8	0.14±0.02		50.03±9.43	
Acral lentiginous	5	0.09±0.06		38.70±6.71	
Others	2	0.11±0.01		38.44±2.73	
Differentiation					
Poorly or none	9	0.08±0.13	0.021	42.02±8.05	0.032
Well or moderately	22	0.19±0.21		60.12±9.32	
Chemotherapy					
Yes	10	0.24±0.08	0.816	33.75±6.61	0.923
No	21	0.13±0.04		44.05±4.73	
Radiotherapy					
Yes	7	0.23±0.11	0.398	39.58±6.22	0.219
No	24	0.16±0.04		41.05±4.75	

3.3. AURKA

AURKA overexpression was linked to a bad prognosis, according to research by Puig-Butille, Joan Anton, et al. It was also linked to the existence of a mutation in the BRAFV600E gene and a high-copy number gene, the AURKA locus. AURKA overexpression could be brought on by the MAPK/ERK signaling pathway being activated, in contrast to other mutations that cause the pathway to become more active. Activation of the ERK signaling pathway. Through RNA sequencing analysis of gene expression profiles in melanoma cells, we can ascertain whether the AURKA gene is overexpressed in these cancer cells. We can also observe the impact of AURKA gene overexpression on cell growth and survival. Finally, we can investigate the relationship between AURKA and this signaling pathway by blocking the MAPK/ERK signaling pathway with small molecule inhibitors and monitoring the changes in the expression level of the AURKA gene [6].

Their evaluation of Aurora protein kinase 189 primary melanomas was expressed using tissue microarrays using immunohistochemistry. Eleven of the ninety-nine cancers were assessed, and Aurora protein kinase 56.3% (63/112) of the tumors had cytoplasmic staining (Fig. 2A). Furthermore, they discovered that a higher risk of local recurrence was connected with the expression of Aurora protein kinase A (Fig. 2B). Figure 2C shows that patients who did not express Aurora kinase A had a much higher chance of survival than those who did, indicating that the expression of Aurora kinase A is a key predictor of prognosis in melanoma [6]. Tumor analysis revealed a link between mutant BRAF (BRAFm) and AURKA mRNA and protein expression. Therefore, BRAFV600E-specific small interfering RNAs were used to silence BRAFV600E expression. This resulted in a decrease in

phosphorylated ERK levels as well as a decrease in AURKA promoter activity and Aurora kinase A levels in BRAFV600E-positive melanoma cells. In BRAFV600E cells, treatment with the selective BRAFV600E inhibitor PLX4720 reduced the levels of phosphorylated ERK and Aurora kinase A, while most NRASQ61 cell lines showed an increase in Aurora kinase A. Furthermore, in MeWo cells, PLX4720 increased phosphorylated ERK. On the other hand, in all cell lines, PD98059-mediated ERK inhibition lowered AURKA promoter activity and decreased Aurora A protein, independent of BRAF/NRAS status. These findings validate Aurora kinase A's ERK-mediated expression in melanoma [6].

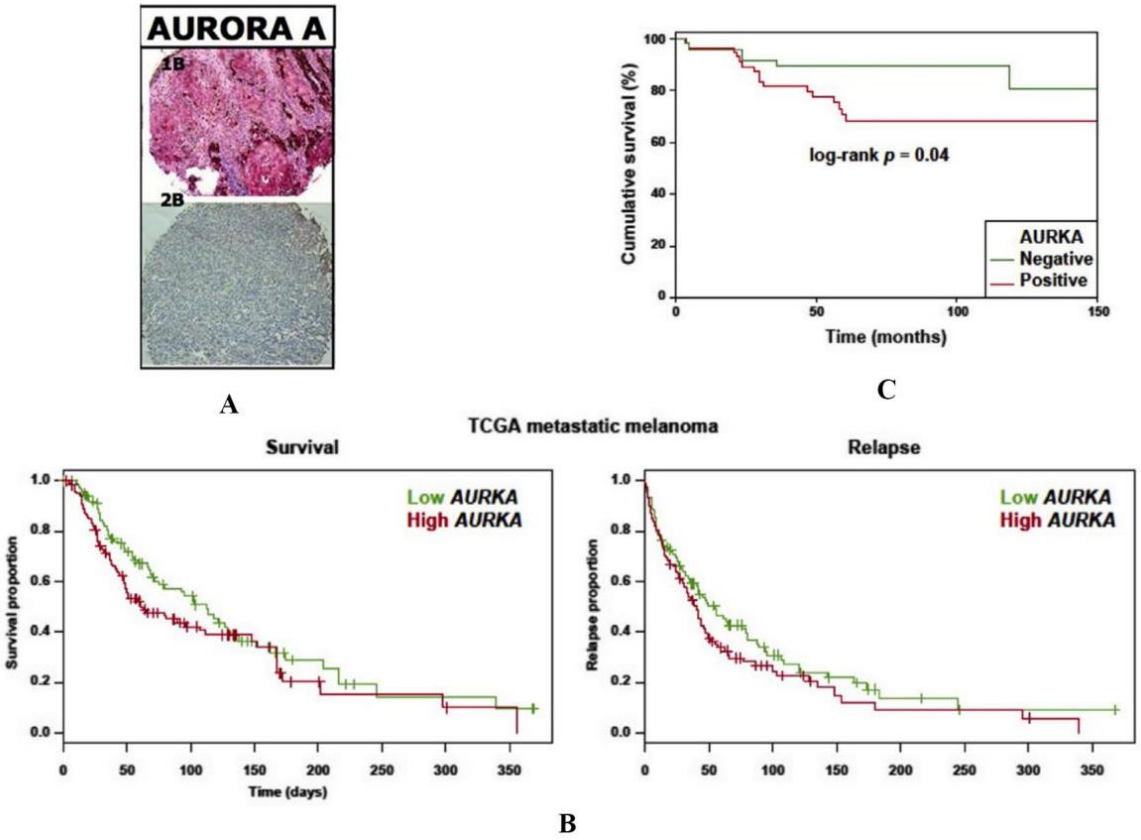

Fig 2. (A) Immunostaining; (B) the survival rate and recurrence rate of patients with high expression of aurka and low expression of aurka; (C) Kaplanmeier survival curve of melanoma patients [6].

3.4. Others

RAS is an important signaling protein that plays an important role in cell growth, differentiation, and apoptosis. It mainly regulates the MAPK signaling pathway to achieve the regulation of cell physiological functions. Under normal conditions, RAS is in a non-phosphorylated state and cannot be activated. When an external stimulus acts on the cell surface receptor, signaling molecules will bind to RAS and phosphorylate it, thus increasing its activity. Phosphorylated RAS activates mek1/2, which in turn activates erk1/2, which phosphorylates erk1/2 and enters the nucleus to regulate the expression of target genes, ultimately affecting biological processes such as cell growth, differentiation, and apoptosis. However, after RAS is mutated in some cancers, its sustained activated state may lead to uncontrolled cell proliferation and carcinogenesis. Therefore, inhibiting the aberrant activity of RAS has become an important direction in the development of anticancer drugs [7].

NARS is a non-receptor tyrosine kinase inhibitor targeting the RAS/RAF/MEK/ERK signaling pathway, which can block the transduction of the pathway and thus inhibit the proliferation and survival of cancer cells. Among them, NARS mainly acts on RAS protein, selectively binds to and blocks its GTPase activity, which in turn prevents RAF kinase from being activated and ultimately

inhibits the transduction of the downstream signaling pathway. Therefore, NARS is closely related to the ERK/MAPK pathway and can exert anti-tumor effects by blocking the transduction of this pathway [7].

PTEN is a phosphatase whose main function is to remove phosphate groups from lipid molecules, thereby reducing their activity. In cancer, PTEN is often mutated or deficient, resulting in impaired function, which allows the activity of lipid molecules to increase, thereby promoting the growth and spread of cancer cells. There is an interactive relationship between PTEN and the ERK/MAPK signaling pathway. Under normal conditions, PTEN inhibits the PI3K/Akt signaling pathway, which in turn reduces the activation of the downstream ERK/MAPK signaling pathway. However, in some cancers, the function of PTEN is disrupted, leading to over-activation of the ERK/MAPK signaling pathway, which in turn promotes tumor growth and metastasis. Therefore, a balance between PTEN and ERK/MAPK signaling pathways is essential for maintaining normal cell physiological activities and preventing cancer development [7].

BRAF is the activated form of BRAF protein kinase, a small G protein of the Ras family. It functions as part of a signal transduction pathway within cells and can mediate the signaling of a variety of growth factors, thereby promoting cell proliferation and survival. In melanoma, BRAF mutation is one of the most common types of mutation. Mutated BRAF continuously activates the MAPK/ERK pathway, leading to resistance to cell proliferation and apoptosis, and ultimately to tumor formation. Therefore, inhibitors targeting BRAF have become one of the most important tools for the treatment of melanoma [7].

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In addition, oncogenes TP53 and RB1 are also closely related to the regulation of ERK/MAPK pathway activity. Both oncogenes TP53 and RB1 are associated with the ERK/MAPK pathway. They can act as part of the signaling pathway to regulate biological processes such as cell proliferation, differentiation, and apoptosis. For example, in the normal cell cycle, TP53 can promote cells to enter the S phase by inhibiting the phosphorylation of RB1. When cells are subjected to external stimuli, such as growth factor receptor kinase (RTK) activation, the ERK/MAPK pathway is activated, leading to a decrease in the phosphorylation levels of TP53 and RB1, which promotes cell proliferation and inhibits apoptosis. However, when these signaling pathways are aberrant, such as TP53 and RB1 mutations, this leads to a loss of cellular control of the ERK/MAPK pathway, which in turn promotes tumorigenesis and progression [8].

4. Targeting ERK/MAPK Pathway For Melanoma Therapeutic Strategies

4.1. DMKN

Ma and their team concluded that the dmkn gene acts as a new oncogene triggering the VM and EMT processes during melanoma development. These findings regard the dmkn gene as a potential diagnostic biomarker based on the VM+EMT network, which could be highly sensitive and specific in differentiating melanoma patients. The results further imply that DMKN could be a useful technique for prognostic monitoring and early detection of melanoma development via the VM and EMT pathways. Furthermore, translational results verified DMKN as an innovative target for tailored melanoma treatment by downregulating the EMT transcriptional program via EMT cytoskeleton disruption, upregulating the expression of epithelial markers, and downregulating the expression of mesenchymal markers. Thus, future studies may explore the use of DMKN functional inhibitors or

other therapeutic approaches to target DMKN and inhibit its role in melanoma to achieve the goal of personalized therapy.

4.2. AURKA

There are no drugs that already exist, but based on the results of the study, therapeutic options that can target the AURKA gene include inhibiting the growth and survival of melanoma cells by inhibiting the expression of the AURKA or FOXM1 genes. Meanwhile, combined inhibition of AURKA and MAPK inhibitors can enhance the therapeutic effect. These studies suggest that AURKA and FOXM1 genes may be targets for melanoma therapy.

4.3. Others

Current therapies for the ERK/MAPK signaling pathway mainly include targeted drug therapy and immunotherapy. Targeted drugs, including inhibitors and kinase inhibitors, can specifically act on key molecules in the signaling pathway, such as BRAF, MEK, EGFR, etc., to block the signaling pathway and achieve therapeutic effects.

In addition, immunotherapy is also one of the research hotspots in recent years. For example, anti-PD-1/PD-L1 antibodies can enhance the body's immunity to tumors by regulating the function of immune cells, thus achieving therapeutic effects. In addition, some new immunotherapeutic strategies are also being explored, such as CAR-T cell therapy and tumor vaccines.

In conclusion, the ERK/MAPK signaling pathway is an important regulator in the process of cancer development, and its precise intervention has important clinical application value. In the future, it is necessary to further study the mechanism of this signaling pathway in different tumor types and develop more effective therapeutic methods [9, 10].

5. Conclusion

Melanoma is a rare but highly malignant form of skin cancer, particularly malignant granulocytic melanoma, which has become the type with the highest mortality rate among melanoma patients. Although early detection and treatment can improve prognosis, as the disease progresses, melanoma usually exhibits potent aggressiveness and metastasis, increasing the therapeutic challenge. Nonetheless, early diagnosis of melanoma also has great significance in the treatment of melanoma. Therefore, understanding the mechanism of melanoma genesis has been one of the research favorites in recent years, and many signaling pathways associated with cancer progression have been discovered.

Among them, the ERK/MAPK pathway has been proven to be one of the key signaling pathways in a variety of cancers. This paper describes the mechanism of the ERK/MAPK pathway in tumor progression and focuses on its function in melanoma. Many studies have found that mutations as well as overexpression of genes lead to enhanced activity of the ERK/MAPK pathway, resulting in melanoma progression as well as recurrence. This paper summarizes the recent studies on the genes related to the ERK/MAPK pathway in melanoma and investigates the relationship between these genes and melanoma using immunohistochemistry, whole-gene assays, and the effects of cell proliferation, migration, and clonogenicity by observing knockdowns of the genes. Therapeutic options and drug studies targeting this pathway are also summarized.

The ERK/MAPK signaling pathway has an important role in melanoma treatment but faces challenges such as drug resistance. There is a need to develop novel drugs or combination therapies and to improve the accuracy of diagnostic and predictive tools. Targeting ERK/MAPK signaling pathway variability in different melanomas is expected to improve efficacy and reduce side effects. Interdisciplinary collaboration will reveal the mechanism of action of this signaling pathway and provide new targets and strategies for treatment. Clinical trials evaluating novel drugs and combination therapies are critical to the treatment options for melanoma patients. Future studies will focus on deepening the understanding of the role of ERK/MAPK in cell biology, exploring its key

roles in different diseases, developing novel drugs to treat related diseases, investigating its interactions with other signaling pathways, and comprehensively modeling and predicting its functions using systems biology approaches. These studies will provide insights into the role of the ERK/MAPK signaling pathway in cell biology and disease.

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