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Role of MAPK and JNK Signaling Pathways in Skin Cancer Progression and Therapeutic Approach

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Abstract: Mitogen-activated protein kinase (MAPK) and c-Jun N-terminal kinase (JNK) pathways exhibit complex signal transduction pathways that modulate multiple processes and the deregulated form of MAPK is involved in many types of cancers including skin cancer. These signaling pathways regulate cellular processes such as differentiation, inflammation, cell proliferation, and survival. Moreover, MAPKs are crucial signaling pathways in regulating various cellular processes, including cell proliferation, differentiation, survival, and apoptosis. Their dysregulation is commonly observed in cancer, making them attractive targets for therapeutic intervention. The critical mechanisms and pathways of MAPKs and JNKs in skin cancer including basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma are summarized in this review. In addition to providing new insights into MAPK and JNK pathways in cancer progression and proliferation, we also offered the significance of the mechanism of JNK in drug resistance and the association of KLF4 in influencing JNKs for future endeavors to be targeted as therapeutic approaches as understanding the molecular aspects of these signaling pathways are crucial for novel therapeutic breakthroughs.

Keywords: Cancer; MAPK and JNK pathways; Deregulation; Treatment

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1. Introduction

Mitogen-activated protein kinase (MAPK) pathways comprise three kinases that regulate various cellular signaling processes, the main upstream kinase (MAPKKK) controls multiple inside and outside signals and stimulates the middle kinase (MAPKK) through phosphorylation. Only MAPKs can phosphorylate and activate MAPKs, which usually have a large number of substrates that carry out distinct cell fate selections appropriate for the received information [1]. The suppression of upstream stimulants is a common aspect of MAPK substrate phosphorylation. This arrangement is equivalent to a negative feedback booster since it ensures resilience against noise and graded reactions by combining negative feedback from the finished product back to the source message with signal enhancement via the 3-tiered kinase pathway [2]. MAPKs respond to a broad range of input indications, such as

signals from surroundings and internal stress, along with physiological stimuli comprising hormones, cytokines, and growth regulators. As a result, they are generally divided into two categories: stress- and mitogen-responsive MAPKs. The classic examples of both categories include P38 and JNK as stress-responsive MAPKs and ERK as mitogen-responsive MAPKs [3]. From a biological perspective, the differentiation is imprecise since all three groups react to an extensive range of stimuli that intersect. Since many disorders disrupt MAPK signaling, medicinal developers have focused on developing drugs that target its kinase elements over the past 20 years [4].

c-Jun N-terminal kinases (JNKs) belong to the family of MAPKs and are responsible for influencing cellular activities such as inflammation, migration, cell proliferation, apoptosis, and differentiation. JNK was initially identified as cycloheximide, a stress-activated protein kinase (SAPK), in the liver of mice [5]. It was later dubbed "JNK" to highlight its function in phosphorylating and activating the c-Jun transcription element. JNK1 (MAPK8), JNK2 (MAPK9), and JNK3 (MAPK10) are the three members of the JNK kinase family that are controlled by three different genetic loci in the human genome [6]. While JNK1 and JNK2 are prevalent in most tissues, JNK3 expression primarily occurs in the brain, with smaller amounts also identified in the heart and testes. JNKs are similar to other MAPKs highly stimulated in reaction to ultraviolet radiation, cytokines, stress, and chemicals that damage DNA; they are also less commonly induced by activation of G-protein-coupled receptors (GPCRs), serum, and growth factors [7]. Two upstream mitogen-activated protein kinase kinases (MAP2Ks) (MKK4 and MKK7) phosphorylate JNKs specifically on the threonine (Thr183) and tyrosine (Tyr185) residues, hence initiating the JNK cascade. Apoptosis signal-regulating kinase (ASK)1/2, MEKK1-4, MLK2 and 3, TPL-2, DLK, TAO1 and 2, TAK1, and other mitogen-activated protein kinase kinase kinases (MAP3Ks) are among the upstream mechanisms that promote MKK4 and MKK7. Every MAP3K might have a distinct stimulus response [8].

Mitogen-activated protein kinase 8 (*MAPK8*) gene also known as C-Jun N-terminal kinases 1 (*JNK1*) is located on chromosome 10q11.22 and is associated with the phosphorylation of c-Jun at position serine 63 and serine 73 in those cells that are under the influence of ultraviolet radiations. C-Jun N-terminal kinases are associated with SAPKs, encoded by three types of genes, which are *MAPK8* (*JNK1*), *MAPK9* (*JNK2*), and *MAPK10* (*JNK3*), producing many products through splicing [9]. The significant component of the MAPK family is C-Jun N-terminal kinases. The increase in activity of *MAPK8* can control the proliferation of cells positively and the MAPK family is involved in many pathways such as cell survival, stress response, migration, apoptosis, proliferation, and differentiation associated with activated protein 1 (AP1) transcription factors. All these functions connect with other central signaling transduction pathways [10]. Several factors are responsible for the AP1 transcriptional activity like ultraviolet radiations, viral infection, cellular stress, growth factors, and cytokines. These factors are important in many pathways like differentiation, inflammation, proliferation, and apoptosis. Moreover, MAPK pathways are highly influenced by various external stimuli such as ultraviolet radiations and inflammatory cytokines [11]. Every MAPK cascade has at least three kinds of kinases such as a mitogen-activated protein kinase (MAPK), a mitogen-activated protein kinase kinase (MEK), and an MEK kinase (MEKK). MEK is phosphorylated by initiated MEKK, which leads to phosphorylation of MAPK. Many different types of targets are phosphorylated by these activated MAPKs like transcriptional factors. The mostly used MAPKs are MAPK8, MAPK9 (JNK1, JNK2), P38 kinases, and ERK kinases (ERK1, ERK2) [12]. MAPK pathway consists of many regulator proteins (kinase c and ras), AP1 (transcription factors), and MAPK module. Phosphorylation and activation of these sequential kinases cause the increased activity of AP1 transcriptional factor as well as DNA response element binding to the target gene [13]. All these processes lead to the enhanced transcription of the target gene. This pathway commands keratinocyte proliferation, differentiation, and apoptosis and is also associated

with tumor development and progression. The MAPK pathways are involved in the activation of many genes in keratinocyte differentiation [14].

The activation of MAPK kinases is associated with the signal coming from membrane receptors by TRAF2/6 protein. AP1 transcription factors like Fos and Jun family members act as the downstream target for MAPK pathways that function for gene transcription regulation [15]. These c-Jun and c-Fos are proto-oncogenes in many types of cancer. In many cases, targeting of MAPK is associated with the responsive behavior of target genes that are involved in regulating many cellular pathways like cell cycle progress, migration, and survival [16]. In addition, MAPK is involved in the phosphorylation and expression of the *P53* tumor suppressor gene. For that reason, lower expression of *P53* causes cell senescence. The target for the MAPK signaling is the *P53* tumor suppressor gene involved in P53 phosphorylation on ser34. The binding of JNK with phosphorylated P53 stabilizes the P53 protein by inhibiting the degradation of ubiquitin. From these studies, it was concluded that the MAPK family (JNK) is necessary in controlling the expression of P53. MAPK pathway activation is involved in many diseases and disorder conditions including prostate carcinoma, glioma, atherosclerosis, diabetes, arthritis, colon cancer, squamous cell carcinoma (SCC), and skin cancer [17-19].

The upregulation of the MAPK pathway (Ras/RAF/MEK/ERK (MAPK) pathway) induces approximately more than 40% of cancer cases. One gene family that frequently has mutations in cancer is *RAS*. *KRAS* mutations are a particularly common type of cancer, and they include colorectal and pancreatic ductal adenocarcinomas [20]. On the membrane, *RAS* is often triggered after growth factor receptors. *H-RAS*, *K-RAS*, and *N-RAS* are the three gene isoforms of *RAS*. Despite having very similar sequences, they serve multiple purposes that result in various physiological processes. RafA, RafB, and RafC are the three isoforms of the RAF protein family kinases, together with two closely related pseudokinases (KSR1/2) [21]. Furthermore, 8% of tumors have *BRAF* alterations, which are highly prevalent in melanomas. The most common mutation frequency in this conventional route is 22% for *RAS*, 8% for *BRAF*, and <1% for *MEK*, although *ERK* alterations are sporadic. By activating *RTK* and *RAS*, the three-layered MAPK-signaling pathway is started. Several physiological processes are regulated by the three RAF subtypes, as well as downstream MEK1/2 and ERK1/2 from a constitute-signaling mechanism [22]. Crucial functions for the P38 MAPK cascade are seen in signaling cascade actions. The four members of P38 kinase in mammals are P38α, P38β, P38γ, and P38δ. The downstream effector and upstream activator exhibit different levels of expression. The regulation of cell development, proliferation, and death is mediated by P38 MAPK. MKK4 kinase, a component of JNK, can also phosphorylate it. Normally, MKK3 and MKK6 kinases stimulate it [23]. Typically, upon activation, the P38 protein moves from the cytoplasm to the nucleus in order to control downstream signaling molecules. Three subtypes of JNK exist: JNK1, JNK2, and JNK3. While JNK1 and JNK2 are found in many different tissues, JNK3 is mostly found in the testis, cardiac myocytes, and neural tissues. They react to a range of stresses, including oxidative stress and chemicals that damage DNA. Comparable to the P38 MAPK pathway, JNK MAPK is primarily activated by the upstream kinases MKK4 and MKK7. This necessitates the dual phosphorylation of Tyr and Thr residues in their activation loops within a conserved Tyr–Pro–Thr motif. This facilitates the control of several biological procedures, such as growth, differentiation, and autophagy [24,25].

An additional protein kinase involved in the triple MAPK-signaling pathway is called ERK5. Three varieties exist: ERKa, ERKb, and ERKc, a transcriptional transactivation domain and a nuclear localization signature are components of the C-terminal extension of ERK5. MEK5 phosphorylation is the method by which it is activated [26]. ERK5 has the ability to bind to many residues between its C-terminus when its kinase region is active. Following their characterization, phosphorylation-specific antibodies against S753 and T732

were developed. The transcription levels of *ERK5* vary across different tissues, with the brain, thymus, and spleen exhibiting the highest levels of expression. This signaling system is linked to malignancies and takes a role in the growth, differentiation, and destruction of cells [27].

The possible mechanism of initiation of the JNK pathway in tumor progression is given in **Figure 1**.

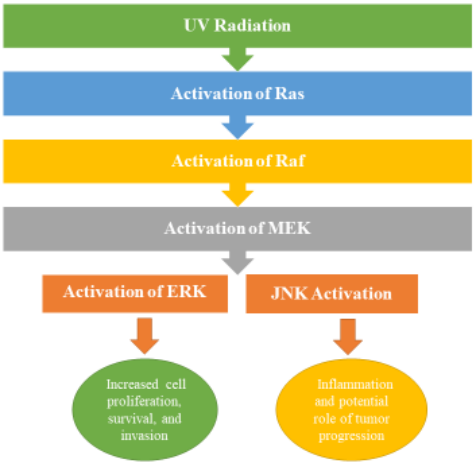

Figure 1. The activation of JNK signaling and ERK pathways by activating Ras, Raf, and MEK on UV radiation exposure. MEK activation plays a significant role in MAPK signaling pathways.

2. JNK regulation

2.1. JNK regulation of cell cycle progression

Several cellular activities, such as cell migration, survival, growth, senescence, apoptosis, and stress reactions, are mediated by the JNK signaling pathway. Premature senescence and growth arrest of mouse embryonic fibroblast cells in G2/M are caused by genetic knockdown of *MKK7*. JNK controls the G2/M transition and the advancement of the G1 cell cycle [28]. In Jurkat cells, JNK is activated during the G2/M transition. In human HeLa cervical cancer cells, activated JNK was similarly discovered to be concentrated in the centromeres during early S-phase to late anaphase, with the greatest expression during metaphase [29]. Phosphorylation of c-Jun occurs regularly during mitosis and the initial stages of the G1 phase. It has also been discovered that JNK stimulates mitosis via Aurora B Kinase. NIH-3T3 fibroblasts and CIGC ovarian granulosa cells undergo G2/M transition suppression when JNK is inhibited pharmacologically or genetically by small interfering (siRNA)-mediated methods. This is because JNK suppression inhibits Aurora B kinase, ultimately leading to a reduction of histone-H3 (Serine 10) phosphorylation [30].

2.2. JNK regulation of cell survival and apoptosis

JNK has contradictory functions in both apoptosis and cell maintenance. Tumor necrosis factor (TNFα)-induced cell suicide can affect JNK1 and JNK2 fibroblasts, suggesting that JNK facilitates cell survival. According to the research, JNK is necessary for the development of the JunD transcription element, which works with NF-κB in promoting the development of genes that are favorable for survival in fibroblasts, like cIAP-2 [31]. By downregulating FoxO1, JNK has also been shown to increase the lifespan of fibroblast-like synoviocytes in rheumatoid arthritis. Research from other sources indicates that JNK enhances cell survival by working in concert with NF-κB and

JAK/STAT. However, it is widely recognized that JNK is crucial for apoptosis. By phosphorylating Bad and Bim, JNK specifically affects mitochondria [32]. These pro-apoptotic proteins counteract the effects of anti-apoptotic proteins like Bcl-2 and Bcl-xL. Furthermore, JNK triggers the breakdown of cytochrome c (Cyt C) via a Bid-Bax-dependent process. This results in the assembly of apoptosomes made up of Apaf-1, caspase-9, and Cyt C, and in turn, activates caspase 9-dependent apoptosis [33]. Additionally, JNK blocks TRAF2/IAP1 signaling by causing Smac/Diablo to be released from mitochondria and activating caspase 8 as a consequence. Endoribonuclease 1α (IRE1α)/transmembrane kinase needing inositol requires TRAF2 recruitment in order to stimulate ASK1 and JNK, which in turn inhibits anti-apoptotic proteins such as Bcl-2, Bcl-xl, and Mcl-1. JNK triggers apoptosis in response to DNA damage through P53 phosphorylation, P73 stabilization, and P53/P73-dependent production of pro-apoptotic molecules Bax and Puma [30,34].

3. MAPK family and squamous cell carcinoma

The tumorigenic effect of the *MAPK8* (*JNK1*) gene has been observed in the human squamous cell carcinoma model, where human keratinocytes were subjected to the analysis of gene regulation in immunodeficient mice. In this model, it was proved the importance of JNK1 and c-Jun in human epidermal tumors activated by tumorigenic Ras. Therefore, the coupling of c-Jun with oncogenic Ras is responsible for the conversion of normal human epidermal cells to malignancy. Contrary to this, JNK1 is also involved in the blockage of Ras-induced NF-κB stimulation, which was previously involved in the activation of human epidermal cell senescence and growth arrest [20]. Therefore, the understanding of initiation of JNK1 and Ras is necessary because this creates a molecular environment for tumorigenesis.

In SCC, JNK expression is commonly seen and SCC cell lines and tissues have higher levels of JNK2 phosphorylation than healthy keratinocytes as well as healthy skin specimens. JNK1 demonstrated a tumor suppressor role, in opposition to JNK2. Mice lacking JNK1 had a greater prevalence of papilloma than mice of the wild type. These results are consistent with the fact that constitutively active MKK7 and MKK7-JNK2 fusion proteins—but not MKK7-JNK1—can link with the oncogenic Ras (V12) to convert normal keratinocytes into lesions resembling SCC, provided that c-Jun activity is maintained [35]. Furthermore, c-Jun can combine with Ras to cause epidermal cancer, but not JunB. Finally, by inhibiting JNK, squamous cell carcinoma antigen 1 (SCCA1) keeps keratinocytes from going through apoptotic cellular death. These findings suggest that epidermal cancer is promoted by MKK7, JNK2, and c-Jun, but not by JNK1 or JunB [3].

In K14-CYLDm transgenic mice, epidermis-targeted expression of a catalytically deficient CYLD mutant (CYLDm) resulted in enhanced JNK stimulation, lysine-63 (K63)-ubiquitination, and phosphorylation of the transcription elements c-Jun and c-Fos. K14-CYLDm mice treated with DMBA/TPA had more papillomas; by week 32, 66% of these had progressed to SCC and metastasized. Applying the JNK inhibitor SP600125 topically to K14-CYLDm mice eliminated skin cancer spread to lymph nodes and dramatically decreased the frequency of tumors generated by DMBA/TPA. Histone H3's lysine 9 and 36 residues are particularly demethylated by the demethylase KDM4A. When comparing metastatic human SCC tissues to primary SCC tissues, there was a rise in protein concentrations corresponding with higher transcription of KDM4A, c-Jun, and FOSL1 (Fra1). Moreover, FRA1 was discovered to promote the growth and multiplication of head and neck SCC cells in a way that was related to c-Jun [30].

JNK function has been studied in both human and animal tissue models of SCC. Ultraviolet light or a two-

stage chemical carcinogenesis procedure with a single topical dosage of 7,12-dimethylbenzanthracene (DMBA) and monthly 12-O-tetradecanoylphorbol-13-acetate (TPA) are commonly used to produce skin cancers in animal research. Compared to their WT counterparts, Jnk1$^{-/-}$ mice showed a greater degree of tumor formation kinetics and carcinoma development, indicating a high susceptibility to DMBA/TPA-induced skin tumorigenesis. The higher amount of TPA-induced AP1 DNA interaction ability and activation of extracellular signal-regulated kinases and Akt were implicated in the improved tumor growth phenotype observed in Jnk1$^{-/-}$ animals [36]. These results support the idea that Serpin SCC antigen (SCCA1)-induced JNK1 inhibition inhibits ultraviolet-induced epithelial cell division and, as a result, enhances carcinogenesis. On the contrary, fewer papillomas grew in JNK2-deficient (Jnk2$^{-/-}$) mice than in WT mice after a DMBA/TPA chemical assault, suggesting that these mice remained immune to tumor formation. Moreover, the Jnk2$^{-/-}$ papillomas showed noticeably lower levels of AP1 and Erk activity and were not likely to develop into cancer. These data suggest that JNK1 and JNK2 have opposing roles in the development of skin cancer, with JNK2 acting as a tumor promoter [37]. The regenerated human SCC model, in which primary human keratinocytes were employed for skin regrowth on immunodeficient mice after undergoing multiplex gene transduction to produce genes under examination, also revealed the carcinogenic consequences of JNK2. Applying this approach, it was proved that JNK2 and c-Jun are necessary for the aggressive human epidermal neoplasia that is caused by oncogenic Ras and NF-κB blockage. Furthermore, it only takes the production of constitutively active mutations of c-Jun, JNK2 (MKK7-JNK2 fusion), or MKK7 to partner with oncogenic Ras and cause malignant transformation in normal human epidermal cells [38]. On the other hand, Ras-driven human epidermis cancer cannot be sufficiently promoted by the expression of active MKK7-JNK1 fusion protein. JNK2 and c-Jun, but not JNK1, are substantially activated in human SCC, which is consistent with the results from experimental animals and indicates that these compounds are therapeutically important [39]. Interestingly, JNK2 but not JNK1 enhances Ras-induction of glycolysis, a procedure that produces energy and is frequently employed by cancer cells. This is sometimes referred to as the Warburg effect. Conversely, JNK2 inhibits NF-κB activation triggered by Ras, which has been shown to cause growth inhibition and senescence in human epidermal cells. Hence, JNK2 and Ras coactivation create the ideal metabolic and molecular milieu needed for carcinogenesis [40]. JNK targets AP1 proteins downstream in murine SCC cell lines and is less likely to develop tumors *in vitro* and *in vivo* when the dominant-negative mutant of c-Jun (DNc-Jun, also called TAM67) is expressed. Epidermal elimination of c-Jun frequently decreases cancer development of murine skin caused by chemicals, ultraviolet light, or the oncogene of the papillomavirus. Furthermore, skin cancers produced by Ras do not grow malignantly in animals lacking c-fos. These results highlight the critical function that AP1 plays in the development of skin tumors [41]. However, because AP1 activity is so diverse, distinct AP1 subunits have varying roles across various biological activities. For instance, the malignant phenotype of converted rat keratinocytes is enhanced by JunB overexpression *in vitro*, indicating that JunB may be involved in tumor formation [42]. Conversely, JunB reduces carcinogenesis as evidenced by the JB6(P-) SCC cells' immunity to tumor advancement, as well as the inhibition of cell growth and the epithelial-to-mesenchymal transition (EMT) of various SCC cell lines. The latest research has demonstrated that exogenous expression of JunB prevents epidermal neoplasia caused by co-expression of MKK7 and Ras oncogene and that the nuclear level of JunB is decreased in spontaneous human SCC, which is consistent with these latter results [43]. These findings demonstrate the opposing roles of c-Jun and JunB in neoplasia and epidermal development.

The roles of MAPK and JNK signaling in skin cancer types such as BCC, SCC, and melanoma are given in **Table 1**.

Table 1. Roles of MAPK and JNK signaling in skin cancer

Skin cancer type	MAPK/JNK signaling	Role	Mechanism of action	Upregulation/ downregulation	Therapeutic target
Basal Cell Carcinoma (BCC)	MAPK, JNK	Promotes cell proliferation, survival, and invasion	Activation of downstream transcription factors (e.g., AP-1, Elk-1) leading to increased expression of genes involved in cell cycle progression, anti-apoptosis, and matrix metalloproteinases	Upregulated expression	MAPK/JNK inhibitors
Squamous Cell Carcinoma (SCC)	MAPK, JNK	Promotes cell proliferation, survival, invasion, and angiogenesis	Similar to BCC, with additional roles in inflammation and immune response	Upregulated expression	MAPK/JNK inhibitors, combination therapies
Melanoma	MAPK (ERK, MEK)	Drives cell proliferation, survival, migration, and invasion	Activation of downstream effectors (e.g., ERK, p90RSK) leading to increased expression of genes involved in cell cycle progression, anti-apoptosis, and cell motility	Higher expression	MAPK inhibitors (e.g., MEK inhibitors), combination therapies

4. MAPK family, JNK pathways, and basal cell carcinoma

The association of MAPK with BCC has been studied. The target c-Jun for MAPK was found to be reactive and expressive in many basal cell carcinoma samples. In basal cell carcinoma, MAPK and c-Jun are significant for the tumorigenic activity of Hedgehog/Gli proteins. In addition, the signaling pathways of Hedgehog/GLI proteins are linked with signaling pathways of epidermal growth factor receptors to move the tumorigenic condition in the mouse basal cell carcinoma cell line [44].

In BCC, the sonic hedgehog (SHH)/GLI signaling pathway is primarily involved, and GLI-induced cell cycle progression was decreased by JNK reduction with SP600125 and c-Jun siRNA knockdown, suggesting that JNK and c-Jun are critical for Hedgehog (HH)/GLI-driven BCC. Elevated JNK expression in HaCaT keratinocytes was associated with the BCC-like phenotype brought on by SHH activation. Furthermore, in a BCC tumor model created by injecting TetON inducible CRISPR-Yap ASZ mouse cells subcutaneously into immunocompromised (nu/nu) mice, it was discovered that the Yap null cancers showed lower degrees of pJNK1/2 and pJun(S63/S73) than the WT BCC cancers following a one-week doxycycline therapy [45]. Furthermore, SP600125-treated BCC cells and YAP-negative BCC clones showed a considerable reduction in c-Jun mRNA. Lastly, it was shown that the WNT gene family member WNT16B was elevated in BCC tissues. In a JNK-dependent way, this boosted the growth of primary and immortalized human keratinocytes. When combined, these findings suggest that the SHH, YAP, and WNT signaling pathways work with the JNK signaling pathway as a crucial mediator to support BCC [46]. Additionally, the JNK function has lately been associated with BCC. In human BCC specimens, the JNK target c-Jun is substantially active. Furthermore, GLI-mediated target gene activation and cell cycle advancement are eliminated by siRNA-mediated c-Jun gene suppression or the pharmaceutical JNK inhibitor SP600125. These results suggest a role for JNK and c-Jun in the carcinogenic activity of Hedgehog/GLI proteins in BCC. Furthermore, the oncogenesis of a mouse BCC cell line is discovered to be driven by the Hedgehog/GLI signaling system working in concert with the epidermal growth factor receptor signaling pathway. Here, c-Jun activation by MEK/ERK is necessary for GLI-driven carcinogenesis, but not JNK. When combined, JNK plays a cell-context-dependent role in BCC [47].

5. Melanoma

The growth and migration of melanoma cells are encouraged by the JNK/AP1 axis, which is frequently active in both benign and malignant melanoma. According to one study, JNK is active in more than 75% of benign nevi, and its function is thought to be to limit unchecked cell survival or multiplication. For patients with superficial spreading melanomas, stimulation of JNK is linked to growing cells and decreased relapse-free survival time during tumor growth. It is well recognized that there is a functional contradiction in the JNK signaling pathway between cell survival and proliferation. This contradiction can be seen in the contentious functions that JNK/AP1 proteins play in melanoma [30]. Aspirin-induced inhibition of B16 melanoma cell growth is mediated by JNK stimulation. The growth and soft agar colony formation of human and mouse melanoma cell lines are increased upon expression of dominant negative mutants of c-Jun or c-Fos, respectively. This suggests that AP1 inhibits the proliferation of melanoma cells. In opposition to these conclusions, more recent research has identified the JNK signaling axis as having a significant involvement in melanoma [48]. One important step in the development of melanoma tumors is the constitutively active MEK-ERK signaling axis activation of JNK and c-Jun. Target genes like cyclin D1 and *RACK1* have increased transcription as a result of ERK's raised c-Jun transcription and stability. The JNK-AP1 pathway is forced to function as a feed-forward process by *RACK1*, which in turn permits PKC to phosphorylate and increase JNK function. Our recent research has demonstrated that CYLD loss-of-function and JNK activity correlate in human melanoma, which is consistent with these findings [49]. Intravenous tumor growth analysis in mice is used to determine whether exogenous production of MKK7 or c-Jun inhibits the inhibition of melanoma growth and metastasis caused by CYLD. On the other hand, as demonstrated in melanoma cells 1205Lu and WM983B, respectively, JNK reduction with the small molecule inhibitor SP600125 causes melanoma cell proliferation arrest or apoptosis through P53-dependent production of P21 cell cycle inhibitor and induction of P53, Bad, and Bax apoptotic molecules [50]. Furthermore, JNK1 but not JNK2-directed gene silencing reduces the development and growth of melanoma cells. When combined, these data highlight the critical function that the JNK1-AP1 signaling pathway plays in the development of melanoma tumors [51].

The proliferation, invasion, and metastasis of WM164 melanoma cells were eliminated by siRNA-mediated suppression of JNK1 and JNK2. Similarly, the development of melanoma cell lines expressing substantial amounts of pJNK1 was suppressed by JNK1-specific gene silencing. These results show that most malignant melanoma cell lines and tissues studied had enhanced JNK activity, which is linked with lower levels of CYLD. After subcutaneous and tail vein injections, respectively, the development of melanoma xenografts in the skin and lung was suppressed by the restoration of CYLD expression in metastatic human melanoma cell lines [52]. Co-expression of a c-Jun mutant or permanently active MKK7 inhibited CYLD-inhibited metastasis and development of melanoma. Additionally, JNK/c-Jun facilitates MALT1-driven melanoma cell migration and development. The CREB/MITF/c-Jun melanogenesis axis was suppressed by upregulation of Urothelial Cancer Associated 1 (UCA1), but it was enhanced by *UCA1* gene silencing [53]. It was shown that PRDM5 (PRDI-BF1 and RIZ domain-containing) enhanced melanoma migration and multiplication by upregulating JNK in a mouse melanoma model. A tumor-associated gene called *SHARPIN* is elevated in a lot of malignancies. These findings suggest that JNK2 is necessary for the aggressiveness of melanoma and its tolerance to *BRAF* suppression [54].

6. Roles of JNK in melanoma progression and treatment

Melanoma resistance to treatment is significantly influenced by JNK/c-Jun. In particular, by its relationship

with MITF and induction of immune-suppressive myeloid cells into the tumor microenvironment, c-Jun stimulates the dedifferentiation of melanoma and the generation of inflammatory mediators. Decreased JNK phosphorylation is thought to be the reason behind the inhibition of A875 malignant melanoma cell growth caused by shRNA-mediated gene silencing of c-FLIP, Fas-associated mortality domain-like interleukin-1β-converting enzyme (FLICE)-like regulating protein [55]. Decreased pJNK transcription was seen in conjunction with cell proliferation inhibition produced by inhibition of IL-1β in IL-lβ-positive melanoma cells. In stage III melanomas, immunohistochemistry revealed that 20% of the 51 instances had positive pJNK expression, 75% of cases had high JNK expression, and all pJNK-positive tumors were IL-1β-positive. JNK is triggered by IL-1β in melanoma, as demonstrated by the reduction of pJNK in A375 and WM793 melanoma cells by siRNA-mediated gene suppression of IL-1β without altering total JNK concentrations [30,56].

The JNK/AP1 pathway plays a significant role in the adaptive reactions to vemurafenib, a MEK inhibitor. BRAF inhibitor-naive and resistant melanoma cells experienced death and decreased cell proliferation when JNK reduction was applied with the small molecule drug BI-78D3. After being treated with PF-3758309, a PAK inhibitor, melanoma cells showed enhanced stimulation of JNK, β-catenin, and the mTOR signaling pathway [57]. Additionally, melanoma cell survival was significantly reduced by shRNA-mediated gene suppression of JNK and β-catenin. Furthermore, suppression of the JNK cascade made *BRAF* mutant melanoma cells more susceptible to genetically altered vaccinia virus-mediated cell death [13]. Interestingly, JNK has also been shown to trigger apoptosis in melanoma cells. Plant-derived quercetin is a polyphenol chemical that increased pJNK expression *in vitro* and *in vivo*, causing A375SM and A375P melanoma cells to undergo apoptosis. Similarly, adding protein-bound polysaccharides produced from the *Coriolus versicolor* fungus to the human SKMel-188 melanoma cell line caused apoptosis and raised ROS levels, both of which were reduced by SP600125 [58].

In short, JNK proteins have unique and significant functions in a variety of skin malignancies. JNK1/2 stimulates Jun/Fos in BCC and improves its relationship with phosphorylated ATF2, which in turn amplifies the carcinogenesis triggered by SHH/GLI [30]. MKK4/7 stimulates JNK1 and JNK2 in SCC. While JNK2 stimulates tumorigenesis in an AP1-dependent manner, JNK1 produces apoptosis. By suppressing the JNK2/AP1 process, CYLD suppresses SCC, whereas SCCA1 enhances SCC by inhibiting JNK1. The melanoma cell growth and migration are stimulated by the MALT1, MKK4/7, and JNK/AP1 signaling cascade, whereas it is inhibited by CYLD [59].

7. JNK pathway and drug resistance

JNK was identified as a kinase activity that phosphorylates and activates JUN transcription elements to transmit oncogenic RAS activation to nuclear transcription. Upon cloning, it was shown that stress cues including ultraviolet irradiation potentially stimulate the kinase. The idea that oncogenic and stress signals could be connected emerged from this discovery. Subsequent investigation into this relationship led to the conclusion that JNK mostly increases cell stress reactions and apoptosis brought on by inflammatory cytokines and environmental stressors, while ERK primarily boosts proliferation in reaction to mitogenic growth regulators [60]. This differentiation was supported by early findings that these routes frequently function as antagonists and mutually impede one another. Over the previous 25 years, a plethora of studies have refined this straightforward idea. This brings us back to our initial finding, which was that JNK serves two roles and may regulate apoptosis as well as cell transformation via a range of pathways that intersect with ERK in part [61]. Further supporting this dual function is genetic evidence.

The skin, gut, breast, prostate, and hematological systems can all experience a decrease in carcinogenesis when JNK1/2 is present. For example, JNK1 and JNK2 elimination in the mouse mammary epithelium enhances genetic instability and starts significant tumor formation, while the upstream JNK activator MKK4 is frequently altered in breast cancer [30]. However, a number of solid tumors, including malignancies of the liver, colon, skin, lung, and brain also frequently exhibit hyperactivation of the JNK process, suggesting that JNKs are tumor promoters [37]. For example, animals immune to the production of skin cancer by a traditional two-stage paradigm combining chemical mutagenesis of *HRAS* with proinflammatory phorbol ester therapy were produced by deleting *JNK2* or *MKK4* in keratinocytes. Similarly, *JNK1* deletion significantly reduced the mice's vulnerability to chemically caused stomach cancer [62].

A prime example of JNK's dual impact on tumorigenesis is hepatocellular cancer. On the one hand, JNK1 promotes hepatocyte proliferation by decreasing the production of CDKN1A, a cell cycle inhibitor, and is hyperactivated in hepatocellular cancer. On the other side, increased tumor development results from knocking down both *JNK1/2* in hepatocytes, which is caused by increased cell division and adaptive hyperproliferation of remaining hepatocytes [63]. Furthermore, by fostering a favorable tumor microenvironment, liver immune cells' proinflammatory cytokines triggered by JNK signaling add to this phenotype. As a result, the precise function of JNK depends on the tissue and environment, and knowledge of these factors is necessary to comprehend and take advantage of the role that this network plays in drug sensitivity and resistance [64]. Despite the large and even contradictory body of work on this subject, several recurring motifs appear. Therefore, instead of attempting to thoroughly go into contradictory specifics, we concentrate on developing common ideas via instructive instances. To put it succinctly, JNK can promote cancer stem cell renewal, cell migration, and cancer cell survival to promote tumor malignancy and medication resistance, or it can activate apoptotic processes to counteract tumor growth [65].

8. *KLF4* and *JNK1* (*MAPK8*)

Early embryonic development depends on the multistage process known as epithelial-mesenchymal transition (EMT), which can be disrupted by several clinical circumstances, including tissue fibrosis and the spread and metastasis of malignant tumors. Significant changes in gene expression during the development and development of an EMT result in significant changes in cell shape, adhesions between cells and in the matrix, as well as the ability of cells to move and invade [66]. Here, we have identified KLF4 as one important regulator of EMT utilizing genome-wide gene expression profiling. Interestingly, KLF4 is a significant EMT regulator; its deletion causes a loss of epithelial structure as well as a partial initiation and amplification of EMT, whereas its production suppresses EMT and preserves the epithelial topology of breast cancer cells and mammary epithelial cells [67]. Furthermore, we discover that KLF4 inhibits cell movement while promoting cell growth and development [68]. This idea is at odds with other research that shows KLF4 promotes migration in the human breast cancer cell lines MCF7 and MDA-MB-231 and suppresses cell growth in a colon cancer cell line. KLF4 was shown to be downregulated in MCF7 cells following E-cadherin deletion, and recent research also showed that KLF4 inhibits cell migration and invasion in MDA-MB-231 cells [69,70].

KLF4 is well-known for playing two roles in transcription: a repressor and an activator. KLF4 could serve a crucial role in preserving the cell shape of mammary epithelial cells, according to earlier research. In addition to binding directly to the E-cadherin gene activator and up-regulating E-cadherin expression, it also effectively suppresses the regulation of Snail1, one of the main transcriptional repressors of E-cadherin gene expression [71].

KLF4 attachment to the regulators of the Snail1 (*SNAI1*) and E-cadherin (*CDH1*) genes has also been discovered by the combination of genome-wide gene expression monitoring and ChIP-Seq data analysis. As Snai1 expression is markedly up-regulated with KLF4 reduction in lack of TGFβ, it indicates that KLF4 regulates Snai1 expression. Snail1 production is, nevertheless less in KLF4 reduction cells when TGFβ is present, indicating that KLF4-mediated control of the *Snai1* gene is a complicated mechanism requiring additional transcription elements in addition to KLF4 that either promote or inhibit Snai1 transcription [72]. Conversely, in the presence of TGFβ, deletion of KLF4 results in a stimulation of Twist1 expression, which could serve as the primary facilitator of EMT in the mesenchymal state. *KLF4* transcription reduction did not affect Snail2, Zeb1, Zeb2, or other key EMT regulators' expression. Furthermore, we discovered other genes whose expression is either directly promoted or suppressed by KLF4 [73]. Additionally, *KLF4* transcriptional inhibition directly targets several mesenchymal genes, including β-catenin (*CTNNB1*), vimentin (*VIM*), and N-cadherin (*CDH2*). All of the information points to a paradigm where KLF4 suppresses mesenchymal genes and induces the production of genes specific to the epithelium in order to preserve epithelial shape [74]. Mesenchymal genes become active and epithelial gene expression is lost when KLF4 function is lost during EMT. KLF4 has been shown to play an identical impact in the switching of fibroblasts into induced pluripotent stem (iPS) cells. In this process, KLF4 is one of the essential reprogramming variables that triggers CDH1 expression, which in turn causes the MET and reprogramming of fibroblasts [73,75]. These findings provide more evidence that KLF4-mediated transcription regulation plays a crucial role in both the creation and maintenance of epithelial cell integrity. Additionally, KLF4 suppresses many angiogenesis-related genes, such as Endothelin-1 (*EDN1*) and VEGF-A (*VEGFA*). These findings indicate a crucial step in fostering tumor angiogenesis, aggressive tumor growth, and metastasis is the decrease of *KLF4* transcription during EMT [76].

JNK1 (*MAPK8*) constitutes one of the transcriptionally suppressed target genes of KLF4. When KLF4 is lost during TGFβ-driven EMT, JNK1's expression is increased, and it plays a crucial role in both the initiation of apoptosis and the completion of EMT and cell motility. JNK1 is a serine-threonine protein kinase that belongs to the mitogen-activated protein kinases (MAPK) family [77]. It is essential for cellular reactions to external inputs and takes a role in some signaling processes. JNK1 is mostly phosphorylated at serine-63 and serine-73 residues as a result of cytokines and cellular stressors such as ultraviolet radiation. Such stimulation of JNK is necessary to sustain the mitochondrial apoptosis signaling cascade and to cause ultraviolet-induced apoptosis in primary murine embryonic fibroblasts [78]. Additionally, JNK1 and their target transcription element AP1 (Jun/Fos) have been linked to EMT in previous studies. These findings are consistent with the ability of JNK1 to phosphorylate paxillin, a focal adhesion adaptor necessary for effective cell movement and the creation of focal adhesion plaques [79]. Here, the essential function that JNK1 plays in EMT, cell migration, and the initiation of apoptosis when its primary transcriptional inhibitor, KLF4, is lost. It has been shown in current research that in different animal models of breast cancer, defects in JNK1, JNK2, or composite JNK1 and 2 enhance the growth of primary tumors. Therefore, KLF4 inhibits the creation of metastases while promoting the progression of primary tumors and preventing apoptosis by reducing the expression of the *JNK1* gene [80].

Furthermore, a higher disease-free survival rate in patients is correlated with elevated KLF4 expression. Nevertheless, the outcomes of the experiments also show that KLF4 increases the growth of initial tumors by giving cells a survival benefit and preventing liver and lung metastases. All of the information presented here collectively reveals basic ideas about how transcription elements such as *KLF4* control changes in cell destiny by directly impacting the transcription of underlying genes [81]. Finally, *KLF4* and its transcriptional effectors are

desirable targets for the establishment of innovative treatment strategies due to their crucial roles in maintaining epithelial distinction and preventing EMT and metastasis. Interestingly, JNK1 functions that are increased when KLF4 activity is lost may provide a treatment pathway for metastatic illness [82,83].

9. Future directions and conclusion

One of the main causes of many malignancies is the uncontrolled stimulation of particular proteins in the MAPK signaling cascade. As a result, blocking this signaling system effectively could be a useful approach to treating tumors. In light of the negative consequences of the current MAPK inhibitors, investigating natural molecules offers a fresh approach to the management of cancer. Furthermore, the available data unequivocally demonstrates that MAPK cascades are feasible strategies for cancer treatment. The ERK pathway is among the most widely used targets in clinical practice. However, metabolic and epigenetic modulators, as well as stress-activated MAPK cascades like JNK, have significant modulatory effects that can alter whether cancer cells respond to both targeted treatments and chemotherapies. Nevertheless, these responsibilities are context-specific and hard to predict with conventional techniques of empirical investigation. Numerous biological procedures, such as the cell cycle, cell differentiation, growth, apoptosis, and inflammatory reactions are regulated by JNK proteins. JNK signaling dysfunction is intrinsically associated with both melanoma and non-melanoma skin malignancies. However, the isoform-specific and cell-type-specific responses continue to restrict and challenge our knowledge of JNK actions in these illnesses.

Finally, the future of targeting MAPK and JNK pathways in cancer treatment is bright, with several promising avenues including precision medicine, novel drug development, combination with immunotherapy, and overcoming drug resistance. Advances in genomics and molecular profiling will enable the identification of specific genetic alterations within these pathways in individual patients, aim to selectively kill cancer cells, and may involve the development of combination therapies, targeted drug delivery systems, or novel inhibitors for future prospective.

Disclosure statement

The author declares no conflict of interest.

References

[1] Bahar ME, Kim HJ, Kim DR, 2023, Targeting the RAS/RAF/MAPK Pathway for Cancer Therapy: From Mechanism to Clinical Studies. Signal Transduction and Targeted Therapy, 8(1): 455.

[2] Manna M, Rengasamy B, Sinha AK, 2023, Revisiting the Role of MAPK Signaling Pathway in Plants and its Manipulation for Crop Improvement. Plant, Cell & Environment, 46(8): 2277–2295.

[3] Moon H, Ro SW, 2021, MAPK/ERK Signaling Pathway in Hepatocellular Carcinoma. Cancers, 13(12): 3026.

[4] Moustardas P, Aberdam D, Lagali N, 2023, MAPK Pathways in Ocular Pathophysiology: Potential Therapeutic Drugs and Challenges. Cells, 12(4): 617.

[5] Yu J, Li X, Cao J, et al., 2023, Components of the JNK-MAPK Pathway Play Distinct Roles in Hepatocellular Carcinoma. Journal of Cancer Research and Clinical Oncology, 149(19): 17495–17509.

[6] Pua LJW, Mai CW, Chung FFL, et al., 2022, Functional Roles of JNK and p38 MAPK Signaling in Nasopharyngeal Carcinoma. International Journal of Molecular Sciences, 23(3): 1108.

[7] Musi CA, Agrò G, Santarella F, et al., 2020, JNK3 as Therapeutic Target and Biomarker in Neurodegenerative and Neurodevelopmental Brain Diseases. Cells, 9(10): 2190.

[8] Chen Q, Hou Y, Li D, et al., 2022, Berberine Induces Non-Small Cell Lung Cancer Apoptosis via the Activation of the ROS/ASK1/JNK Pathway. Annals of Translational Medicine, 10(8).

[9] Saeed R, Mohammed AK, Saleh SE, et al., 2023, Dual Role of Mitogen-Activated Protein Kinase 8 Interacting Protein-1 in Inflammasome and Pancreatic β-Cell Function. International Journal of Molecular Sciences, 24(5): 4990.

[10] Kciuk M, Gielecińska A, Budzinska A, et al., 2022, Metastasis and MAPK Pathways. International Journal of Molecular Sciences, 23(7): 3847.

[11] Schneeweis C, Diersch S, Hassan Z, et al., 2023, AP1/Fra1 Confers Resistance to MAPK Cascade Inhibition in Pancreatic Cancer. Cellular and Molecular Life Sciences, 80(1): 12.

[12] Martin-Vega A, Cobb MH, 2023, Navigating the ERK1/2 MAPK Cascade. Biomolecules 13(10): 1555.

[13] Song D, Lian Y, Zhang L, 2023, The Potential of Activator Protein 1 (AP-1) in Cancer Targeted Therapy. Frontiers in Immunology, (14): 1224892.

[14] Wójcik M, Zmarzły N, Derkacz A, et al., 2024, Gene Expression Profile of Mitogen-Activated Kinases and MicroRNAs Controlling their Expression in HaCaT Cell Culture Treated with Lipopolysaccharide A and Cyclosporine A. Cell Cycle, 23(3): 279–293.

[15] Schnoegl D, Hiesinger A, Huntington ND, et al., 2023, AP-1 Transcription Factors in Cytotoxic Lymphocyte Development and Antitumor Immunity. Current Opinion in Immunology, (85): 102397.

[16] Sun M, Cheng H, Yu T, et al., 2023, Involvement of a AS3MT/c-Fos/p53 Signaling Axis in Arsenic-Induced Tumor in Human Lung Cells. Environmental Toxicology, 38(3): 615–627.

[17] Rehman B, Abubakar M, Kiani MN, et al., 2024, Analysis of Genetic Alterations in *TP53* Gene in Breast Cancer. Proceedings of Anticancer Research, 8(3): 25–35.

[18] Schubert L, Mariko ML, Clerc J, et al., 2023, MAPK Pathway Inhibitors in Thyroid Cancer: Preclinical and Clinical Data. Cancers, 15(3): 710.

[19] Sharma D, Singh N, Srivastava S, 2024, Skin Cancer: An Insight on its Association with Aging, Pathogenesis and Treatment Strategies. Current Drug Research Reviews Formerly: Current Drug Abuse Reviews, 16(2): 134–144.

[20] Hendrikse CSE, Theelen PMM, Van Der Ploeg P, et al., 2023, The Potential of RAS/RAF/MEK/ERK (MAPK) Signaling Pathway Inhibitors in Ovarian Cancer: A Systematic Review and Meta-Analysis. Gynecologic Oncology, (171): 83–94.

[21] Shi A, Liu L, Li S, et al., 2024, Natural Products Targeting the MAPK-Signaling Pathway in Cancer: Overview. Journal of Cancer Research and Clinical Oncology, 150(1): 6.

[22] Toye E, Chehrazi-Raffle A, Hwang J, et al., 2024, Targeting the Multifaceted BRAF in Cancer: New Directions. Oncotarget, (15): 486.

[23] Qi XM, Chen, G, 2023, p38γ MAPK Inflammatory and Metabolic Signaling in Physiology and Disease. Cells, 12(13): 1674.

[24] Huang Y, Wang G, Zhang N, et al., 2024, MAP3K4 Kinase Action and Dual Role in Cancer. Discover Oncology, (15): 99.

[25] Zhan X, Kaoud TS, Dalby KN, et al., 2023, Arrestin-3-Dependent Activation of c-Jun N-Terminal Kinases (JNKs). Current Protocols, 3(9): e839.

[26] Albert-Gasco H, Ros-Bernal F, Castillo-Gómez E, et al., 2020, MAPK/ERK Dysfunction in Neurodegenerative Diseases. Encyclopedia, 7(1): 1–8.

[27] Zarrin AA, Bao K, Lupardus P, et al., 2021, Kinase Inhibition in Autoimmunity and Inflammation. Nature Reviews Drug Discovery, 20(1): 39–63.

[28] Deng Y, Adam V, Nepovimova E, et al., 2023, c-Jun N-Terminal Kinase Signaling in Cellular Senescence. Archives of Toxicology, 97(8): 2089–2109.

[29] Ryu M, Sung CK, Im YJ, et al., 2020, Activation of JNK and p38 in MCF-7 Cells and the *In Vitro* Anticancer Activity of *Alnus hirsuta* Extract. Molecules, 25(5): 1073.

[30] Hammouda MB, Ford AE, Liu Y, et al., 2020, The JNK Signaling Pathway in Inflammatory Skin Disorders and cancer. Cells, 9(4): 857.

[31] Xing Y, Liu Y, Qi Z, et al., 2021, LAGE3 Promoted Cell Proliferation, Migration, and Invasion and Inhibited Cell Apoptosis of Hepatocellular Carcinoma by Facilitating the JNK and ERK Signaling Pathway. Cellular & Molecular Biology Letters, (26): 1–16.

[32] Liu Z, Li C, Wu G, et al., 2020, Involvement of JNK/FOXO1 Pathway in Apoptosis Induced by Severe Hypoxia in Porcine Granulosa Cells. Theriogenology, (154): 120–127.

[33] Pan J, Liu H, Wu Q, et al., 2022, Scopoletin Protects Retinal Ganglion Cells 5 from High Glucose-Induced Injury in a Cellular Model of Diabetic Retinopathy via ROS-Dependent p38 and JNK Signaling Cascade. Central European Journal of Immunology, 47(1): 20–29.

[34] Meñaca-Guerrero L, Suarez-Causado A, Díaz-Caballero AJ, 2020, Reactive Species of Oxygen, Oxidative Stress and its Relationship with Tissular Destruction in Periodontitis. CES Odontología, 33(2): 112–127.

[35] Su CC, Lin JW, Chang KY, et al., 2022, Involvement of AMPKα and MAPK-ERK/-JNK Signals in Docetaxel-Induced Human Tongue Squamous Cell Carcinoma Cell Apoptosis. International Journal of Molecular Sciences, 23(22): 13857.

[36] Zhou H, Zhao Q, Yue C, et al., 2022, Interleukin-38 Promotes Skin Tumorigenesis in an IL-1Rrp2-Dependent Manner. EMBO Reports, 23(6): e53791.

[37] Tam SY, Law HKW, 2021, JNK in Tumor microenvironment: present findings and Challenges in Clinical Translation. Cancers, 13(9): 2196.

[38] Cheng Y, Chen J, Shi Y, et al., 2022, MAPK Signaling Pathway in Oral Squamous Cell Carcinoma: Biological Function and Targeted Therapy. Cancers, 14(19): 4625.

[39] Okada M, Kawagoe Y, Takasugi T, et al., 2022, JNK1-Dependent Phosphorylation of GAP-43 Serine 142 is a Novel Molecular Marker for Axonal Growth. Neurochemical Research, 47(9): 2668–2682.

[40] Zhang W, Wang C, Hu X, et al., 2022, Inhibition of LDHA Suppresses Cell Proliferation and Increases Mitochondrial Apoptosis via the JNK Signaling Pathway in Cervical Cancer Cells. Oncology Reports, 47(4): 1–11.

[41] Xu D, Li C, Zhao M, 2022, Attenuation of UV-Induced Skin Photoaging in Rats by Walnut Protein Hydrolysates is Linked to the Modulation of MAPK/AP-1 and TGF-β/Smad Signaling Pathways. Food & Function, 13(2): 609–623.

[42] Wu Q, Wu W, Jacevic V, et al., 2020, Selective Inhibitors for JNK Signaling: A Potential Targeted Therapy in Cancer. Journal of Enzyme Inhibition and Medicinal Chemistry, 35(1): 574–583.

[43] Yao F, Wang X, Cui ZK, et al., 2020, ETS2 Promotes Epithelial-to-Mesenchymal Transition in Renal Fibrosis by Targeting JUNB Transcription. Laboratory Investigation, 100(3): 438–453.

[44] Cierpikowski P, Leszczyszyn A, Bar J, 2023, The Role of Hedgehog Signaling Pathway in Head and Neck Squamous Cell Carcinoma. Cells, 12(16): 2083.

[45] Ma C, Hu K, Ullah I, et al., 2022, Molecular Mechanisms Involving the Sonic Hedgehog Pathway in Lung Cancer Therapy: Recent Advances. Frontiers in Oncology, (12): 729088.

[46] Oliphant MUJ, Kong D, Zhou H, et al., 2020, Two Sides of the Same Coin: The Role of Developmental Pathways and Pluripotency Factors in Normal Mammary Stem Cells and Breast Cancer Metastasis. Journal of Mammary Gland Biology and Neoplasia, (25): 85–102.

[47] Yang J, Wang J, Liu Y, et al., 2021, PGE2-JNK Signaling Axis Non-Canonically Promotes Gli Activation by Protecting Gli2 from Ubiquitin-Proteasomal Degradation. Cell Death & Disease, 12(7): 707.

[48] Ullah A, Ullah N, Nawaz T, et al., 2023, Molecular Mechanisms of Sanguinarine in Cancer Prevention and Treatment. Anti-Cancer Agents in Medicinal Chemistry (Formerly Current Medicinal Chemistry-Anti-Cancer Agents), 23(7): 765–778.

[49] Bao F, Hao P, An S, et al., 2021, Akt Scaffold Proteins: The Key to Controlling Specificity of Akt Signaling. American Journal of Physiology-Cell Physiology, 321(3): C429–C442.

[50] Garmpis N, Damaskos C, Garmpi A, et al., 2021, Histone Deacetylase Inhibitors in the Treatment of Hepatocellular Carcinoma: Current Evidence and Future Opportunities. Journal of Personalized Medicine, 11(3): 223.

[51] Song H, Guja KE, Iagaru A, 2021, 18F-FDG PET/CT for Evaluation of Post-Transplant Lymphoproliferative Disorder (PTLD). Seminars in Nuclear Medicine, 51(4): 392–403.

[52] Chen C, Cheng Y, Lei H, et al., 2023, SHP2 Potentiates anti-PD-1 Effectiveness through Intervening Cell Pyroptosis Resistance in Triple-Negative Breast Cancer. Biomedicine & Pharmacotherapy, (168): 115797.

[53] Hamp I, O'Neill TJ, Plettenburg O, et al., 2021, A Patent Review of MALT1 Inhibitors (2013-present). Expert Opinion on Therapeutic Patents, 31(12): 1079–1096.

[54] Krishnan D, Menon RN, Gopala S, 2022, SHARPIN: Role in Finding NEMO and in Amyloid-Beta Clearance and Degradation (ABCD) Pathway in Alzheimer's Disease? Cellular and Molecular Neurobiology, 42(5): 1267–1281.

[55] Zhong J, Yan W, Wang C, et al., 2022, BRAF Inhibitor Resistance in Melanoma: Mechanisms and Alternative Therapeutic Strategies. Current Treatment Options in Oncology, 23(11): 1503–1521.

[56] Zhai Z, Vaddi PK, Samson JM, et al., 2020, NLRP1 Functions Downstream of the MAPK/ERK Signaling via ATF4 and Contributes to Acquired Targeted Therapy Resistance in Human Metastatic Melanoma. Pharmaceuticals, 14(1): 23.

[57] Beretti F, Gatti M, Zavatti M, et al., 2023, Reactive Oxygen Species Regulation of Chemoresistance and Metastatic Capacity of Melanoma: Role of the Cancer Stem Cell Marker CD271. Biomedicines, 11(4): 1229.

[58] Pawlikowska M, Piotrowski J, Jędrzejewski T, et al., 2020, *Coriolus versicolor*-Derived Protein-Bound Polysaccharides Trigger the Caspase-Independent Cell Death Pathway in Amelanotic but not Melanotic Melanoma Cells. Phytotherapy Research, 34(1): 173–183.

[59] Ke R, Kumar S, Singh SK, et al., 2024, Molecular Insights into the Role of Mixed Lineage Kinase 3 in Cancer Hallmarks. Biochimica et Biophysica Acta (BBA)-Reviews on Cancer, 1879(5): 189157.

[60] Pua LJW, Mai CW, Chung FFL, et al., 2022, Functional Roles of JNK and p38 MAPK Signaling in Nasopharyngeal Carcinoma. International Journal of Molecular Sciences, 23(3): 1108.

[61] Abdelrahman KS, Hassan HA, Abdel-Aziz SA, et al., 2021, JNK Signaling as a Target for Anticancer Therapy. Pharmacological Reports, (73): 405–434.

[62] Chen T, Zhao L, Chen S, et al., 2020, The Curcumin Analogue WZ35 Affects Glycolysis Inhibition of Gastric Cancer Cells through ROS-YAP-JNK Pathway. Food and Chemical Toxicology, (137): 111131.

[63] Liu L, Xing Y, Cao M, et al., 2021, Exogenous NO Induces Apoptosis of Hepatocellular Carcinoma Cells via Positive p38/JNK Signaling Pathway and Negative ERK Signaling Pathways. Molecular and Cellular Biochemistry, (476): 1651–1661.

[64] de los Reyes Corrales T, Losada-Pérez M, Casas-Tintó S, 2021, JNK Pathway in CNS Pathologies. International

Journal of Molecular Sciences, 22(8): 3883.

[65] Meng Q, Xu Y, Li Y, et al., 2023, Novel Studies on *Drosophila melanogaster* Model Reveal the Roles of JNK-Jak/STAT Axis and Intestinal Microbiota in Insulin Resistance. Journal of Drug Targeting, 31(3): 261–268.

[66] Fonseca Teixeira A, Wu S, Luwor R, et al., 2023, A New Era of Integration between Multiomics and Spatio-Temporal Analysis for the Translation of EMT towards Clinical Applications in Cancer. Cells, 12(23): 2740.

[67] Mahgoub E, Taneera J, Ahmed B, et al., 2024, Unraveling the Interplay of Autophagy Genes and KLF3/KLF8 in Colorectal Cancer Metastasis: A Bioinformatics and Cellular Exploration. F1000Research, (13): 850.

[68] He Z, He J, Xie K, 2023, KLF4 Transcription Factor in Tumorigenesis. Cell Death Discovery, 9(1): 118.

[69] Li Y, Li S, Shi X, et al., 2023, KLF12 Promotes the Proliferation of Breast Cancer Cells by Reducing the Transcription of p21 in a p53-Dependent and p53-Independent Manner. Cell Death & Disease, 14(5): 313.

[70] Zheng Y, Wu J, Chen H, et al., 2023, KLF4 Targets RAB26 and Decreases 5-FU Resistance through Inhibiting Autophagy in Colon Cancer. Cancer Biology & Therapy, 24(1): 2226353.

[71] Meyers WM, 2024, Transcriptional Regulation of the Alternative Sex Hormone-Binding Globulin Promoter by KLF4. Gene Expression Patterns, 2024: 119357.

[72] Verstappe J, Berx G, 2023, A Role for Partial Epithelial-to-Mesenchymal Transition in Enabling Stemness in Homeostasis and Cancer. Seminars in Cancer Biology, (90): 15–28.

[73] Li ZY, Zhu YX, Chen JR, et al., 2023, The Role of KLF Transcription Factor in the Regulation of Cancer Progression. Biomedicine & Pharmacotherapy, (162): 114661.

[74] Avendaño-Felix M, Aguilar-Medina M, Romero-Quintana JG, et al., 2023, SOX9 Knockout Decreases Stemness Properties in Colorectal Cancer Cells. Journal of Gastrointestinal Oncology, 14(4): 1735.

[75] Den Hollander P, Maddela JJ, Mani SA, 2024, Spatial and Temporal Relationship between Epithelial-Mesenchymal Transition (EMT) and Stem Cells in Cancer. Clinical Chemistry, 70(1): 190–205.

[76] Prajapati KS, Gupta S, Choudhari S, et al., 2024, Role of ONECUT Family Transcription Factors in Cancer and Other Diseases. Experimental Cell Research, 438(1): 114035.

[77] Blum A, Mostow K, Jackett K, et al., 2021, KLF4 Regulates Metabolic Homeostasis in Response to Stress. Cells 2021, (10): 830.

[78] Mavrogonatou E, Angelopoulou M, Rizou SV, et al., 2022, Activation of the JNKs/ATM-p53 Axis is Indispensable for the Cytoprotection of Dermal Fibroblasts Exposed to UVB radiation. Cell Death & Disease, 13(7): 647.

[79] Bhosale PB, Kim HH, Abusaliya A, et al., 2022, Structural and Functional Properties of Activator Protein-1 in Cancer and Inflammation. Evidence-Based Complementary and Alternative Medicine, 2022(1): 9797929.

[80] Semba T, Sammons R, Wang X, et al., 2020, JNK Signaling in Stem Cell Self-Renewal and Differentiation. International Journal of Molecular Sciences, 21(7): 2613.

[81] Viola L, Londero AP, Bertozzi S, et al., 2020, Prognostic Role of Krüppel-Like Factors 5, 9, and 11 in Endometrial Endometrioid Cancer. Pathology & Oncology Research, (26): 2265–2272.

[82] Waryah C, Alves E, Mazzieri R, et al., 2023, Unpacking the Complexity of Epithelial Plasticity: From Master Regulator Transcription Factors to Non-Coding RNAs. Cancers, 15(12): 3152.

[83] Yang Z, Peng Y, Wang Y, et al., 2023, KLF5 Regulates Actin Remodeling to Enhance the Metastasis of Nasopharyngeal Carcinoma. Oncogene, 43(23): 1779–1795.