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REVIEWING ADVANCES IN UNDERSTANDING AND TARGETING THE MAPK SIGNALING PATHWAY IN HEPATOCELLULAR CARCINOMA PROGRESSION AND THERAPEUTICS

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ABSTRACT

Hepatocellular carcinoma (HCC) is a severe and increasingly prevalent health issue affecting individuals globally. Recent research endeavors in the clinical domains have lately focused more on the MAPK signaling pathway in HCC. Activating mutations in the RAS and RAF genes, which greatly activate the MAPK pathway in malignancies, are rare in HCC patients, yet over 50% of them have activated the pathway. This suggests that other factors may be responsible for the activation of the signaling pathway in HCC. MAPK signaling is important to carcinogenesis, and it is often altered in human cancers. The drug resistance in targeted therapy against RTKs in HCC may arise from mutations in downstream components (RAS, RAF, MEK, ERK), resistant mutations within RTKs, and additional alternative pathways like PI3K and YAP may also develop the resistance. Epigenetic processes and chromatin remodeling are crucial to pharmacological tolerance to MAPK regulation. This review will focus on the latest developments in our knowledge of the cellular and molecular processes to activate the MAPK signaling pathway, as well as possible treatment approaches that specifically target this pathway in relation to HCC. The study also investigates the clinical efficacy of molecular-targeted treatments, including tyrosine kinase inhibitors and immunological checkpoint inhibitors and highlights the use of combination therapy for HCC.

***Keywords*:** Hepatocellular carcinoma, MAPK signaling pathway, Growth factors

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1. INTRODUCTION

Liver cancer is the third most deadly disease, according to the World Health Organization, which estimated that 830,000 people died from it in 2020 (Ibrahim et al. 2022). Hepatocellular carcinoma (HCC) is a significant worldwide health concern since it represents up to 80% of all primary liver malignancies and is predicted to continue increasing in development (Yang et al. 2019). Studies in epidemiology and molecular biology have shown that the course of HCC development is prolonged over many decades (Caldwell and Park 2009; Chidambaranathan-Reghupaty et al. 2021). Individuals who have a persistent infection with hepatitis B (HBV) or hepatitis C (HCV), particularly when cirrhosis is present, are more likely to develop HCC than the general population (Perz et al. 2006). Insult misuse, obesity, diabetes, and metabolic disorders are further risk factors for HCC. All these risk factors result in chronic inflammation, hepatic fibrosis, cirrhosis, and finally, liver failure (Stickel and Hellerbrand 2010; Nevola et al. 2023).

Numerous molecular pathways contribute to the carcinogenesis of HCC, a phenotypically and genetically diverse tumor (Takeda et al. 2022). Recent developments in molecular pathogenesis research have identified a number of signaling pathways essential to the development, propagation, and metastasis of HCC tumors (Jayachandran 2017; Zhao et al. 2022). An increasing number of researchers are actively searching for new therapeutic targets for important signaling molecules as their understanding of the carcinogenic molecular pathways in HCC. The MAPK pathway is recognized as an important way in the HCC development among those found in relationship to the disease (Dimri and Satyanarayana 2020). This review discusses clinical studies that target the MAPK pathway in HCC as well as the molecular processes associated in the activation. Furthermore, we suggest novel and promising treatment alternatives that specifically target the MAPK pathway.

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1.1. Unraveling the MAPK Pathway in Hepatocellular Carcinoma

1.1.1. The MAPK Signaling Pathway: Mammalian cells have at least three distinct MAPK pathways, such as ERK, c-Jun NH2-terminal kinase (JNK), and p38, to trigger signals to the nucleus and activate responsive genes (Junttila et al. 2008; Liu et al. 2023). The two members of the ERK kinase family are ERK1 (p. 44) and ERK2 (p. 42). The three members of the JNK kinase family are JNK1-3 (Fig. 1) (Dent, 2022). p38α/β/γ/δ are the last groups into which the p38 MAPK family is split (Alshehade et al. 2022). Growth factors are the primary initiator of signals that are intimately linked to the ERK pathway. JNK and p38 signaling are triggered by several stimuli, including growth factors and environmental challenges (Ronkina and Gaestel 2022; Dharshini et al. 2023).

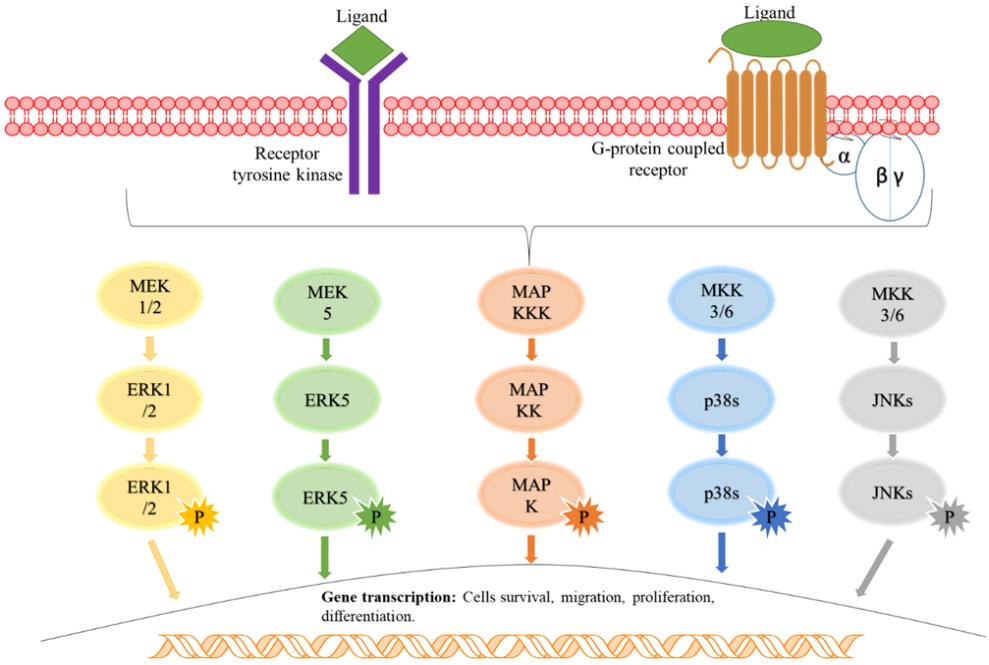

Fig. 1: The conventional Ras/MAPK signaling pathway. The common MAPK signaling pathway includes p38 a/b/c/d, ERK 1/2/5, and JNK 1/2/3. These perform a role in the cell signaling from GPCR or RTK on the cell surface to the nucleus, which activates several biological processes, including cell survival, differentiation.

Signal transmission via cell surface receptors like G-protein-coupled receptors (GPCRs) or receptor tyrosine kinases (RTKs) initiates the MAPK signaling cascade (Girych et al. 2023). The cellular activity resulting from improper manner control promotes carcinogenesis by increasing cell growth, survival, proliferation, and de-differentiation (Shah and Cat 2004; Cattaneo et al. 2014). The platelet-derived growth factor receptor (PDGFR), fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (HGFR; also known as c-Met), and stem cell growth factor receptor (SCFR, also known as KIT) are among the receptors, may stimulate the MAPK pathway (Zwick et al. 2001; Rozen and Shohet 2022).

The binding of ligands to these receptors activates cytoplasmic TKs to phosphorylate tyrosine residues. This process involves the recruitment of GRB2/Shc/SOS adapter complexes to the cell membrane, leading to the conversion of GDP-bound RAS to its active GTP-bound form (Matteson 2013). Subsequently, activated RAS attracts and activates RAF isoforms (A-RAF, B-RAF, and C-RAF) through phosphorylate and dimerize via scaffolding complexes at the cell membrane (Zhao and Luo 2022). By directly regulating mitogen/extracellular protein kinases (MEK), RAF proteins phosphorylate downstream signaling kinases (ERK1/2, also called MAPK3 and MAPK1) (Fig. 2) (Thiriet and Thiriet 2013; Moon and Ro 2021a). Surprisingly MEKs are dual-specificity kinases that may phosphorylate both tyrosine and serine/threonine. Two essential transcription factors (TF) of the AP-1 family, c-JUN and c-FOS are initiated when phosphorylated ERKs go to the nucleus (Fig. 3). These two substances attach to the AP-1 binding site of the promoter regions, which causes the gene transcription involved in the progression of the cell cycle and cellular functions (Deng et al. 2023). Furthermore, transcriptional activators are triggered by the MAPK pathway, which has binding sites on promoters to encode growth factors (Ivanenko et al. 2022). As a result, aberrant stimulation of the MAPK pathway produces an autocrine/paracrine loop that sustains cell growth and produces proliferative signals on its own (Yang et al. 2022).

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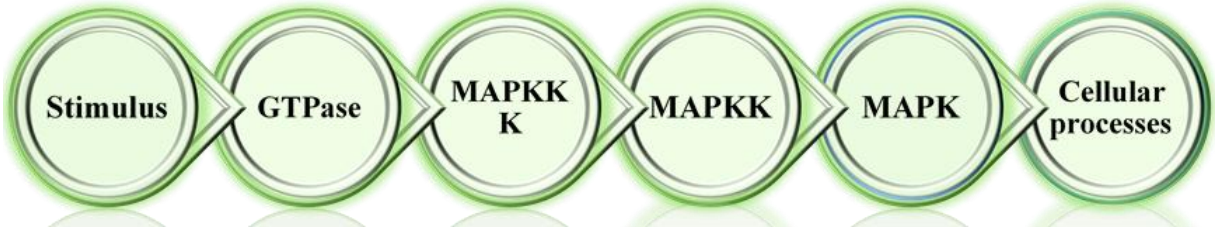

Fig. 2: The MAPK pathway is organized linearly. The linear arrangement of the MAPK pathways is as follows: a small GTPase triggers a MAP kinase kinase kinase (MAP3K or MEKK), it activates a MAP kinase kinase (MAP2K or MEK), and in turn to MAP kinase (MAPK). As a result, it specifies the particular cascade.

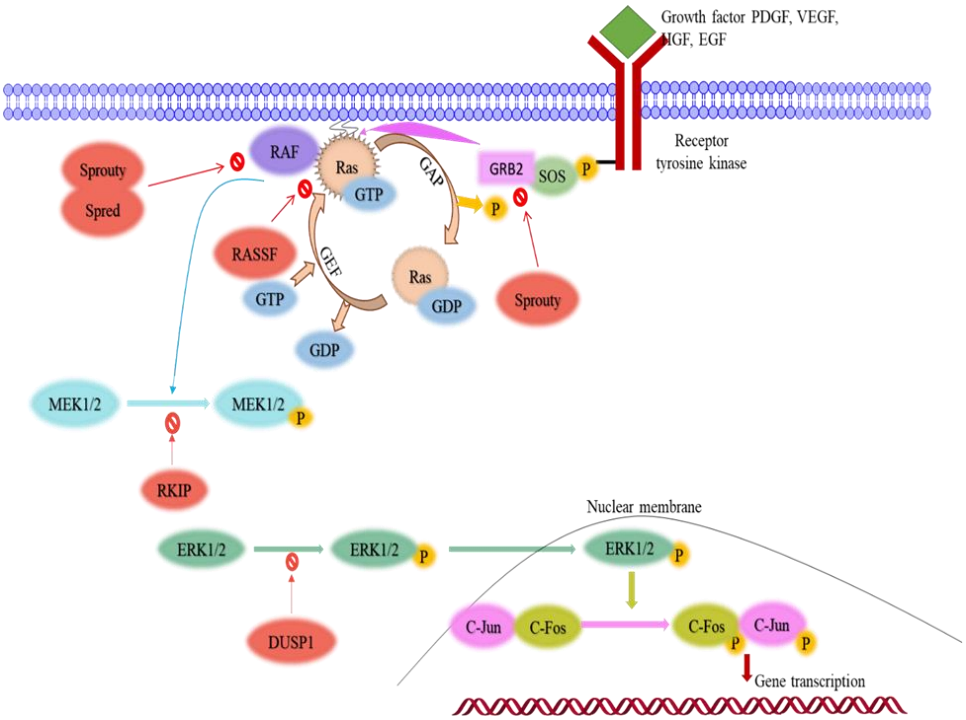

Fig. 3: The Ras/Raf pathway. Ras constitutes the initial ERK 1/2 cytoplasmic effector. Several external stimuli as growth factors through activation of GPCR and RTK trigger the Ras/MAPK pathway. The state of Ras is altered by these stimuli, converting it from an inactive GDP-bound form to an activated GTP-bound form. Once active, GTP-Ras transfers Raf-1 kinase to the cellular membranes to phosphorylate MEK1/2, turning to activate ERK1/2, then translocates into the nucleus to trigger two TF of the AP1 family, c-Fos and c-Jun. GAPs and GEFs are the several proteins that regulate the MAPK pathway by controlling the GTP level. GEFs trigger the conversion of GDP to GTP, and GAPs encourage the GTP-Ras hydrolysis. The RASSF members control the anti-apoptotic and proliferative signals beginning with Ras. Moreover, the Spred family prevents Raf activation and RKIP blocks MEK phosphorylation by Raf-1. Hence, there are additional factors to regulate the Ras/Raf pathway. Sprouty proteins potentially alter the GRB2-SOS complex or inhibit Raf from controlling the Ras/Raf pathway. Eventually, DUSP1 is a particular ERK inhibitor.

The abnormal initiation of the MAPK pathway is linked to cellular transformation and carcinogenesis since it is a critical regulator of important cellular activities including cell survival and proliferation (Guo et al. 2020; Hussain et al. 2023). The TF phosphorylated by ERK modifies telomere repeats and prevents senescence by stimulating the telomerase catalytic gene (hTERT) (Jäger and Walter 2016). The MAPK pathway increases the likelihood of survival by preventing the stimulation of pro-apoptotic BCL-2 group proteins like BIM and BAX, stimulating the BCL-2 and MCL-1 production, which are anti-apoptotic (Wu et al. 2018; Kaloni et al. 2023). This pathway also contributes to the formation of a mesenchymal state in cancer cells by upregulating the EMT-related gene expression, such as those expressing transcription inhibitors of epithelial genes through the Rho/Rac-actin route and the activation of metalloproteinase. This signaling also promotes the invasiveness and motility of cancer cells (Neuzillet et al. 2014). Moreover, B-RAF triggers angiogenesis via HIF-1α and VEGF, while C-RAF (RAF-1)

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enhances endothelial cell viability, a crucial aspect of the relationship between stromal cells and cancer (Niault and Baccarini 2010; Chen et al. 2015).

1.2. Role of the MAPK Pathway in HCC

Human malignancies often have alterations in the MAPK pathway, which is essential to carcinogenesis. Mutations in one of the RAS-related genes are reported to be present in 20–30% of all human cancers (Murugan et al. 2019). About 50% of melanoma patients have B-RAF mutations, and in these individuals, B-RAF-targeting medications have improved clinical results. Furthermore, melanoma patients responded significantly to MEK inhibitors (Kim et al. 2021; Xiao et al. 2023).

However, since mutation in RAS/RAF was not widely identified and was found in fewer than 5% of HCC cases, the significance of the MAPK pathway in HCC was overlooked for a very long time (Kim and Viatour 2020). Although the MAPK pathway gene mutations are rare, HCC patients often have the signaling pathway activated. The prognostic relevance of MAPK signaling is shown by the strong correlation between poor survival rates in HCC patients and raised expression levels of RAS effectors (Dimri and Satyanarayana 2020). Additionally, it is thought that RAF-1 overexpression is a distinct early indicator of tumor recurrence and a dismal prognosis (Wu et al. 2016). It is estimated that MAPK signaling is active in around 50% of patients with initial-stage HCC and nearly all advanced HCC patients, according to MEK/ERK expression and phosphorylation (Al Noshokaty et al. 2016). Research has shown that overexpression of RAF, MEK, and ERK mRNA was seen in 33, 40, and 50% of patients. MEK phosphorylation was shown to be seven times more in HCC tissues than in nearby benign tissues (Dimri and Satyanarayana 2020).

The MAPK pathway is normally triggered in HCC, but this is primarily explained by mechanisms other than RAS and RAF mutations. These mechanisms include aberrant stimulation of upstream GFs and receptors, downregulation of the pathway's negative modulators, and upregulation of its positive regulators. Thus, in the majority of human HCCs, the wild-type genes for RAS, RAF and downstream elements are found to activate the MAPK pathway (Braicu et al. 2019).

1.3. Alternate Mechanisms Activating the MAPK Pathway in HCC

The primary pathway components, including RTK, RAS, RAF, MEK, and ERK, closely control the MAPK pathway activity. In human malignancies, activating mutations in the genes encoding the main effectors and upregulation of the proteins cause the signaling pathway to become aberrantly activated (Liu et al. 2018; Roberts and Der 2007). Different modulators, both activate and repress MAPK signaling may influence it in addition to directly activating the route via the primary effector molecules. For instance, suppressing regulators that block the MAPK cascades or activating regulators to increase the pathway are two indirect ways to start the MAPK pathway (Braicu et al. 2019).

GTPase activating proteins (GAPs) and Guanine nucleotide exchange factors (GEFs) are the greatest instances of MAPK signaling modulators. An inactive state (RAS-GDP) and an active state (RAS-GTP) occur in coexistence with normal RAS proteins (Xiao et al. 2023). HCC cell lines, such as Hep 3B and PLC/PRF/5, constitutively downregulate RAS-GAP family members (RASAL1 and DAB2IP) (Delire and Stärkel 2015). Among 88 human HCCs with RAS genes, downregulation of more than one RAS-GAP was discovered in every sample (Dillon et al. 2021). Consequently, it is hypothesized that a key mechanism causing the stimulation of MAPK signaling in HCC is the inactivation of RAS-GAPs (Maertens and Cichowski 2014; Dillon et al. 2021). 73.8, 76.1, and 12.5% of patients, respectively, had downregulated expression levels of RASAL1, DAB2IP, and NF1, which mostly showed hypermethylation of the promoter (Calvisi et al. 2011).

The members of the RASGEFs are SOS, RAPGEF2, RASGRF2, RASGRP1, and RASGRP4. Of these, RASGRP1 was shown to be much more expressed in HCC as compared to the tissues around the tumor, and this high expression was found to be strongly correlated with the size and stage of the tumor (Porras et al. 2021). Furthermore, it was discovered by multivariate analysis that RASGRP1 expression constituted a separate risk factor for the advancement of HCC (Porras et al. 2021; Wang et al. 2022). Furthermore, SOS was shown to be a critical molecule implicated in many pathways triggered in HCC, indicating its carcinogenic function in the disease.

A class of modulators is sprouty proteins interfering with the GRB2/SOS complex, preventing RAS from going into an active state and adversely inhibiting the MAPK pathway (Table 1) (Chou and Bivona, 2022). Sprouty can block the signaling pathway on many different levels. For instance, the phosphorylation of RAF is interfered with by Sprouty-related proteins with EVH1 domains (SPRED) (Table 2). Differential expressions of sprouty homologs are seen in cancer (Al Mahi and Ablain, 2022). Among these, SPRY2/4 has lower expression levels in comparison to the comparable tissues without tumors, indicating that they function as tumor suppressors by inhibiting the MAPK signaling cascade (Samadaian et al. 2018). SPRY2 downregulation is common in HCC, which has a poor prognosis and is thought to provide cancer cells with uncontrolled ERK activation an advantage (Fong et al. 2006;

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Xiao et al. 2018). Through a decrease in ERK phosphorylation, high expression of SPRED prevents HCC cell growth both in vitro and in vivo. Tumor invasion and metastatic features are correlated with decreased levels of SPRED expression. Furthermore, it was revealed that 68% of tumor tissues had lower levels of SPRED-1 and two expressions than the adjacent liver tissues (Delire and Stärkel 2015).

Table 1: The downregulated genes with percentage inactivation and their function in the RAS/RAF signaling pathway of hepatocellular carcinoma.

Downregulated genes	Inactivation (%)	Mechanism of Molecular Inactivation	Physiological function	References
GAPs				
NF1(Ras-GAPs)	31.6	Aberrant hypermethylation of promoters, promoter methylation-mediated silencing, Loss of heterozygosity.	The GAPs increase the Ras GTPase activity, allowing GTP to be converted into GDP and facilitating Ras conversion from its GTP-activated form to its GDP-inactivated form.	(Kawamura et al. 2020)
DAB2IP(GAPs)	76.1	Aberrant hypermethylation of promoters, promoter methylation-mediated silencing, LOH		(Calvisi et al. 2011)
RASAL1(GAPs)	80.0	Aberrant hypermethylation of promoters, promoter methylation-mediated silencing, LOH		(Chen et al. 2018; Kawamura et al. 2020)
IQGAP2	78	Inactivated by promoter methylation, two functionally conserved tryptophans are found in the polyproline domain to interact with normal MAPK and activate downstream signaling pathways, thereby supporting tumor development and progression.	IQGAP2 and IQGAP3 are associated with the most important signaling pathway, the Ras/Raf pathway, to promote tumor growth.	(Gnatenko et al. 2013; Song et al. 2023)
RASSFs				
RASSFs		RASSF suppression involves denovo hypermethylation in its promoter	RASSF induces apoptosis by activating PUMA	(Calvisi et al. 2012; Azumi et al. 2016)
RASSF1A	50-100	Promoter hypermethylation, LOH	Induction of apoptosis, MAPK pathway inhibitor, RASSF1A is a mediator of the Bax(pro-apoptotic protein) pathway.	(Khan et al. 2020; Xu et al. 2020)
RASSF2	95	Methylation-based promoter silencing.	Ras inhibitor, regulating apoptosis, the Ras effector domain with RASSF2 to create an androgen complex to inhibit metastais	(Volodko et al. 2014; Zinatizadeh et al. 2019; Safa et al. 2020)
RASSF1C	62	Promoter methylation, LOH	Limit the transformation of Ras ability, inhibit tumor cell growth	(Guo et al. 2015; Donninger et al. 2016)
NORE1A/RASSF5	72.4	Methylation-based promoter silencing, LOH.	Growth-inhibiting properties regulate apoptosis. NORE1A, a second mediator of Ras, also referred to as Ras-binding protein binds to RAS by a GTP-dependent mechanism.	(Liu et al. 2014; Donninger et al. 2015; Barnoud et al. 2017).)
NORE1B	62	Methylation-based promoter silencing.	NORE1B and Ras regulate Ras and T-cell signaling in immune cells, RASSF1A and NORE1B interact to stop HCC	(Zinatizadeh et al. 2019)
Spred				
Spred1/2	68	Hypermethylation in the promoter region	Spred protein blocks GrB2, Raf activation	(Khan et al. 2020; Moon & Ro, 2021a)
DUSP1		Methylation-based promoter silencing, LOH, Post-transcriptional approach	Negative ERK regulator	(Chen et al. 2019; X. Chen et al. 2021; Zhao et al. 2021)
RKIP		Post-transcriptional approach	RKIP inhibits MEK from phosphorylating and activation by RAF	(Lin et al. 2022)

RAF kinase inhibitor protein (RKIP), which suppresses MEK phosphorylation through RAF, functions as an inhibitor of the MAPK signaling cascade (Wu et al. 2020). RKIP functions as an antagonist inhibitor of MEK stimulation by dissociating an RAF-MEK complex. Therefore, decreased RKIP expression had seen in a range of human malignancies, and loss of RKIP leads to aberrant initiation of the MAPK pathway. When comparing HCC tissues to non-tumor tissues, RKIP is typically downregulated, and this downregulation helps activate the MAPK pathway in HCC (Wong et al. 2011; Wu et al. 2020). The enzyme dual-specificity

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phosphatase 1 (DUSP1) inhibits ERK negatively. ERK activation directly induces the transcription of many DUSP family members, producing a negative regulatory loop (Chen et al. 2019). In HCC, a relationship between higher levels of ERK protein and lower DUSP1 was found. Reduced patient survival and increased tumor aggressiveness have been strongly connected with low expression of DUSP1 (Calvisi et al. 2008). GFs have a role in the autocrine and paracrine activation of the MAPK pathway. The ligands bind to EGFR and then initiate the MAPK signaling cascade downstream of the RTK, including epidermal growth factor (EGF) (Seshacharyulu et al. 2012; Sabbah et al. 2020). Increased production of TGF-α and EGF is often seen in HCC, particularly in the early phases of carcinogenesis, which may indicate that MAPK is involved in the neoplastic change of hepatocytes (Moon and Ro, 2021a). An example of a paracrine cellular mitogenic factor is HGF. It mostly targets epithelial cells and is released by mesenchymal cells. HGF binds to HGFR (c-Met) on the hepatocyte surface and is produced by hepatic stellate cells (HSC) in the liver (Wu et al. 2020). This interaction initiates MAPK signaling cascades and stimulates the propagation of parenchymal cells. The MAPK pathway is triggered by the interaction of FGF to FGFR and HGF to HGFR are expressed at considerably high in HCC (Dhanasekaran et al. 2016; Kamal et al. 2022). In humans, there are four FGFRs and 22 different kinds of FGFs. FGFRs are composed of a single transmembrane domain, heparan sulfate (HS)-binding domain, Ig-like extracellular ligand-binding domains, and cytoplasmic tyrosine kinase domains (Nandi et al. 2022; K. Qin et al. 2023). A number of FGFs including FGF1/2/8/7/19 are increased in HCC and act in an autocrine way to promote the growth and invasion of HCC cells. Similarly, HCC is associated with at least one elevated FGFR (Wang et al. 2021). In the liver, the insulin-like growth factor (IGF) pathway controls differentiation, proliferation, and death. Two ligands, IGF-1 and IGF-2, and IGF1R and IGF2R make up the IGF system (Adamek and Kasprzak 2018).

Table 2: The three domains of spred protein 1, 2, 3, EVE-3 and their specific functions

Domains	Functions	References
EVHI	Inhibits ERK activation. Targets proteins to specific sites of action Site of protein-protein interactions through which dimers are formed	(Bundschu et al. 2007; Zhao et al. 2018; Yan et al. 2020; Gong et al. 2020)
KBD	Inhibits ERK activation. Facilitates spred membrane to localization. Promotes the heterodimer formation	(Endo, 2020; Gong et al. 2020; Lorenzo and McCormick 2020)
SPR	Inhibition of ERK Required for spred1 and spred 2 formation	(Kato et al. 2003; Gong et al. 2020; Lorenzo and McCormick 2020)

The MAPK pathway is controlled by non-coding RNAs, including micro RNAs (miRNAs) and long non-coding RNAs (lncRNAs). It is shown that miRNAs regulate MAPK signaling in HCC (Tasharrofi and Ghafouri-Fard 2018). For instance, by directly inhibiting RAS/RAF respectively, miR-30a and miR-4510 lower the function of the MAPK pathway, whereas miR-330-5p and miR-487 have the opposite effect by focusing on Sprouty and SPRED, negative regulators of the MAPK pathway (Zhou et al. 2017; Moon and Ro 2021a). MiR-330-5p and miR-487 are overexpressed, while miR-4510 and miR-30a are downregulated in HCC, per reports (Xiao et al. 2018; Xu et al. 2018). BRAF-initiated non-coding RNA (BANCR) is a lncRNA that, when overexpressed, activates the MAPK pathway in a variety of tumors, including HCC. Notably, MARK/ERK signaling in HCC cells was deactivated by downregulating BANCR by shRNA-mediated knockdown, which inhibited cellular migration and proliferation (Burke et al. 2020). Other lncRNAs that are known to promote liver carcinogenesis by triggering MAPK signaling include URHC, LL22NC03-N14H11.1, IGF2AS, and others that are increased in liver cancer (Xu et al. 2014; Bao et al. 2017). lncRNAs RUNX1-IT1 and CASC2, on the other hand, drastically downregulate their expression in HCC and deactivate the MAPK pathway (Yan et al. 2019).

Cell-released exosomes carry numerous biomolecules such as DNA, proteins, mRNAs, lncRNAs and miRNAs. Exosomes are becoming increasingly recognized as essential to intercellular communication in normal and diseased conditions (Zhu et al. 2020; Kim 2022). Neoplastic cells communicate with the tumor microenvironment via exosomes, promoting tumor development, invasion, and metastasis. Additionally, tumor cells may communicate via exosomes, which carry numerous signal molecules (Maia et al. 2018). Cancer cells produce exosomes that trigger MAPK signaling in the targeted cells by transferring GFRs and miRNAs. Numerous studies indicate that HCC-derived exosomes activate the MAPK pathway in recipient cells (Fares et al. 2020).

HBV and HCV infection are important HCC risk factors. HBV/HCV infection increases the risk of HCC via many molecular processes, such as genomic incorporation of viral DNA and apoptotic pathway inactivation. Recent studies indicate HBV may activate this pathway (Levrero and Zucman-Rossi 2016; DuShane and Maginnis 2019). HBV core antigen protein (HBcAg) stimulates IL-6 synthesis in hepatocytes by activating the MAPK pathway, which drugs may inhibit. Additionally, studies suggest that the HCV core protein greatly activates the MAPK

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protein (Chen et al. 2017). MEK1-specific inhibitor inhibited MAPK signaling via the HCV core protein, indicating the viral protein works at MEK1 or elements upstream of it (Du et al. 2021).

1.4. Therapeutic Focus: Exploiting MAPK Signaling in HCC

Molecular-targeted treatments are gaining interest in inhibiting oncogenic signaling pathways. Both fundamental academics and physicians are focusing on RTK as a therapeutic target for HCC therapy (Jindal et al. 2019). The majority of TKIs compete with ATP-catalytic domain binding of several oncogenic Tyrosine kinases (TKs). Type I, II, and III inhibitors alter the target enzyme's structure, preventing kinase action (Hojjat-Farsangi 2014). Sorafenib, the first licensed treatment for HCC patients, targets RAF and other RTKs, including PDGFR-β, VEGFR2/3, and KIT (Tian et al. 2020; Habiba et al. 2022). In advanced HCC patients, sunitinib, a multi-kinase inhibitor that targets PDGFR, and TK 3, showed less favorable results compared to sorafenib (Wang et al. 2021). In research, HCC cases in the sorafenib group had a median overall survival (OS) of 10.2 months, whereas those received sunitinib had 7.9 months (Raoul et al. 2018; Dawson et al. 2020). A phase II study of metastatic HCC patients found erlotinib, a potent EGFR inhibitor (Zhu et al. 2014). A Phase III research indicated that HCC patients getting sorafenib plus erlotinib had a mOS of 9.5 months, whereas those receiving placebo had 8.5 months (Table 3) (Zhu and Sun 2019; Coffman-D'Annibale et al. 2023). Lenvatinib beats sorafenib for liver cancer. Lenvatinib improved OS in HCC patients who were not eligible for surgery of tumor excision. Lenvatinib diminishes angiogenesis and lympho-angiogenesis by targeting VEGFR, FGFR, PDGFR, and KIT (Yamamoto et al. 2014). Combination treatment with golvatinib has been used to address acquired resistance to lenvatinib (Guo et al. 2022). Regorafenib similarly targets to sorafenib, repressing STAT3 signaling by activating SHP1, and also inhibits V600-mutated B-RAF (Moon and Ro 2021b). Refractory sorafenib patients received regorafenib or placebo in a phase III study. Regorafenib therapy resulted in a longer mOS contrast to placebo (10.6 months vs. 7.8 months) (Bruix et al. 2013). Orally bioavailable cabozantinib targets VEGFR, RET, MET, and AXL and is authorized for HCC patients. Cabozantinib, a dual VEGFR/MET blocker, targets the MET pathway which is commonly started after blocking VEGFR (Cochin et al. 2017; Schöffski et al. 2017). Phase III research compared Cabozantinib to a placebo on OS in advanced HCC patients, previously undergone sorafenib. Cabozantinib had a median PFS of 5.5 months and mOS of 10.2 months, compared to 1.9 months and 8 months with placebo, respectively (D'Angelo et al. 2020; D'Alessio et al. 2021). A Phase II study indicated that tivantinib, an oral MET inhibitor, improved OS and PFS in high-MET-expressing HCC patients who had undergone sorafenib. A phase III research found that tivantinib did not enhance OS in patients with MET-high HCC, received systemic treatment, contrast to placebo (Rimassa et al. 2018). In the phase III REACH-2 study, sorafenib-treated patients had a mOS of 8.5 months in ramucirumab vs 7.3 months with placebo. Ramucirumab survival benefit is strongly correlated with blood AFP levels (Vogel and Saborowski 2020).

Table 3: Phase III clinical trials evaluating molecular-targeted therapies for hepatocellular carcinoma (HCC)

Drugs	Therapeutic targets	Median OS (months)	Median PFS (months)	References
Sorafenib	RAF, VEGFR, PDGFR, KIT	10.6	NR	(Terashima et al. 2016)
Erlotinib	EGFR	9.5	NR	(Thomas et al. 2018)
Sunitinib	PDGFR, VEGFR, KIT, RET	7.9	3.5	(Bertino et al. 2014)
Lenvatinib	VEGFR, PDGFR, FGFR, RET, KIT	13.6	7.4	(Wang et al. 2022)
Regorafenib	B-RAF, PDGFR, VEGFR, GFR, RET, KIT	10.6	3.1	(Yan et al. 2023)
Cabozantinib	MET, VEGFR, AXL, RET	10.2	5.2	(D'Alessio et al. 2021)
Ramucirumab	VEGFR2	8.5	2.8	(Llovet et al. 2022)
Tivantinib	HGFR	8.4	2.1	(Bertino et al. 2014)
Atezolizumab and Bevacizumab	PD-L1 and VEGF-A	19.2	6.9	(D'Alessio et al. 2021)
Nivolumab	PD-1	16.4	3.7	(Zhu and Sun, 2019)
Pembrolizumab	PD-1	13.9	3.0	(Rinaldi et al. 2021)

Targeting the immunological checkpoint is a promising new technique for treating HCC. Targeting the immune checkpoint is justified by the experiment that cancer cells expressing PD-L1 may evade the immune system by interacting with PD-1 on activated B, T, natural killer, and myeloid cells (Pinato et al. 2020; Naimi et al. 2022). The human monoclonal antibody nivolumab blocks the contact between PD-1 and PD-L1, hence suppressing immune checkpoint signaling (Pandey et al. 2022). The phase III CheckMate 459 trial assessed the safety and effectiveness of nivolumab + sorafenib as first-line treatment for advanced HCC patients. While nivolumab therapy resulted in clinically significant OS improvements (16.4 vs. 14.7 months), the difference was not significant (Yau et al. 2022). KEYNOTE-240, a phase III research, examined the effectiveness of pembrolizumab, a humanized monoclonal Ig targeting PD-1, as second-line therapy for HCC patients received sorafenib (Zhu and Qin 2022; Nikoo et al. 2023). The pembrolizumab group had no significant OS or PFS improvements over the placebo group. In HCC patients,

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blocking both the immune checkpoint and VEGF had different therapeutic advantages than targeting either alone (Qin et al. 2023). A multinational, open-label phase III research randomly assigned unresectable HCC patients without systemic therapy to receive atezolizumab (PD-L1), bevacizumab (VEGF-A), or sorafenib as treatment (Tella et al. 2022; Yang et al. 2022). Atezolizumab with bevacizumab increased OS and PFS over sorafenib. A recent research found a mOS of 19.2 months for atezolizumab + bevacizumab and 13.4 months for sorafenib after 12 months of evaluation. The longest survival rate in a phase III trial with HCC supports the effectiveness of atezolizumab + bevacizumab. Most advanced HCC patients now get combinational treatment as the standard of care (Finn et al. 2021).

1.5. Drug Resistance in MAPK-Targeted Therapy for Cancer Cells

Drug resistance may occur from targeted therapy targeting RTKs regardless of their great efficacy and selectivity (Karoulia et al. 2017). Mutations or differentiations in downstream RAS, RAF, MEK, or ERK may reactivate MAPK signaling in cancer (Lee et al. 2020). The development of a resistant mutation inside the RTK may also result in resistance to RTK inhibitors, reducing the drugs efficacy (Nagano et al. 2018). B-RAF inhibitors provide some early therapeutic advantages. However, long-term use of these drugs leads to drug resistance (Healy et al. 2022). For instance, recurrence of the MAPK signaling was induced by ATP-competitive RAF inhibitors such as dabrafenib, vemurafenib, and sorafenib, either by causing structural changes in RAF or by obtaining an active mutation in the down MEK and ERK (Zhao and Luo, 2022). Other RAF inhibitors, including TAK-580, PLX8394, BGB283, and LXH254, have recently been discovered and are now going through clinical studies in HCC to overcome first-generation inhibitor drug resistance (Lee et al. 2020; Yuan et al. 2020). Furthermore, RAF and MEK or RAF and ERK dual inhibition has been investigated for decreased cancer recurrence. MEK inhibitor-treated cancers also become resistant to the drugs as a result of the MAPK pathway being reactivated (Caunt et al. 2015). Mutations or changes to upstream molecules like RAS, RAF, RTKs, or NF1 may cause reactivation, which increases the signaling pathway. A mutation in MEK that results in poor drug binding to MEK may also cause resistance to MEK inhibitors (McCubrey et al. 2012).

Reactivation may happen when upstream molecules like RAF, NF1, RTKs, or RAS change or mutate, increasing the signaling pathway. A mutation in MEK that results in poor drug adhesion to MEK may also cause resistance to MEK inhibitors. Cancers may resist MAPK-based target treatment by activating an alternate pathway to promote the proliferation of cells. Activation of the PI3K and YAP pathways are key mechanisms for MAPK signaling resistance (Kun et al. 2021). In colorectal cancer cells, a mutation in K-RAS led to resistance to EGFR and MEK inhibition via activating PI3K (Vitiello et al. 2019). Melanoma cells exhibited resistance to MEK inhibition by upregulating AKT and YAP, leading to increased oncogenic activity. Additionally, lung carcinomas resistant to MEK inhibitors were extremely responsive to YAP inhibitor therapy, preventing the development of resistant cells (Lin et al. 2015).

Epigenetic processes and chromatin remodeling have a crucial role in pharmacological tolerance to MAPK regulation. The BRAFV600E mutation in melanoma cells makes them resistant to RAF suppression (dabrafenib) and MEK inhibition (trametinib) due to SIRT6 downregulation. Interestingly, only SIRT6 haploinsufficiency increased H3K56 acetylation at the IGFBP2 gene, resulting in IGF activation and downstream signaling, conferring resistance to RAF or MEK inhibition (Strub et al. 2018). Genetic and epigenetic alterations in malignancies strongly impact medication resistance and sensitivity. Efficient MAPK signaling-targeted treatment for diverse human malignancies requires understanding resistance mechanisms.

2. CONCLUSION AND PERSPECTIVES

Clinical decision-making may be significantly affected by the ability to predict a patient's response to targeted therapy based on a detailed knowledge of the molecular mechanism leading to tumorigenesis. The complicated, multi-step process of HCC development occurs due to changes in many signaling cascades. Among the diverse oncogenic signals, initiation of the MAPK pathway is evaluated in around 50% of patients in the initial stages of HCC and is prevalent in the majority of individuals with HCC. Several investigations have demonstrated the pivotal and central involvement of MAPK signaling in the progression of HCC. Mutations in the cellular effectors in signaling are uncommon in HCC patients, although the MAPK signaling pathway is commonly shown to be upregulated in HCC patients. It implies that the signaling system in HCC should be activated by a different method. Currently, the most preferred biological targets for HCC therapy are RTKs, which are upstream elements of the MAK/ERK signaling cascade. Combinational therapy with additional target therapies has been explored for the treatment of HCC because of the unsatisfactory clinical results from RTK inhibitors alone, as shown by sorafenib. Target therapies for cancer-based on MAPK signaling have, up to now, been attentive to the central molecules in the signaling. The signaling pathway has a wide variety of positive modulators. A possible strategy should be to inhibit new targets that are essential for the stimulation of this pathway. We are interested in seeing how well the

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new target treatments work in preclinical HCC contexts utilizing transgenic animal models that have active MAPK signaling, as well as in clinical trials.

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