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Review Article

Deciphering the Ras/MAPK Signaling Pathway in the Progression and Treatment of Hepatocellular Carcinoma

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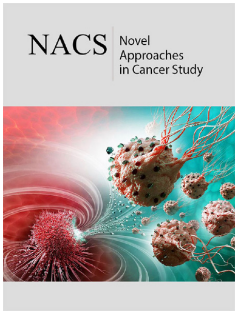

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Abstract

Hepatocellular Carcinoma (HCC) is a serious health issue and its frequency is rapidly escalating throughout the world therefore researchers have focused more attention to the Ras/MAPK signaling pathway. The signaling pathways are linked to develop tumors and the Ras/MAPK pathway is one of these pathways, activated in 60% of HCCs with poor prognosis. A number of different proteins causes the abnormal regulation of the MAPK pathway in HCC. Ras, a small GTPase and Raf are the most commonly mutated oncogene supports the critical function of this pathway in oncogenesis. The genetic mutations leading to effector molecule to permanently activated in the Ras/MAPK signaling cascades. The inappropriate activation of this pathway is primarily due to the downregulation of various Ras/MAPK pathway inhibitors including RASSF proteins, GAPs, DUSP1, Spred and Sprouty proteins. The post-transcriptional or epigenetic processes downregulate these cancer suppressor genes. The aim of current study on the primary mutations resulting in aberrant activation of Ras/MAPK pathway and their role on the initiation and progression of HCC. It also offers an update on the various inhibitors to target this central signaling pathway including various Ras, Raf, MEK inhibitors in the context of HCC. Finally, we evaluate the available options for treatment in this context.

Keywords: Hepatocellular carcinoma; Nonalcoholic steatohepatitis; Oncogenes; Tumor suppressor genes; Multikinase inhibitors; Immunotherapy

Introduction

Hepatocellular Carcinoma (HCC) is the most prevalent liver tumor affecting 85-90% of all patients [1]. The significant reason for HCC is cirrhosis, it affects the majority of patients [2]. It remains a significant public health issue due to its status as the second primary reason of cancer-related death and the fifth greatest prevalent cancer globally [3]. The occurrence of HCC is increasing fastly in emerging countries due to various reasons i.e., the rising prevalence of cirrhosis from numerous causes specifically Nonalcoholic Steatohepatitis (NASH), an increase in the survival rate of cirrhotic patients but steadily rising the risk of Hepatitis C Virus (HCV) infection and obesity [4]. Persons with chronic HBV or HCV infections, particularly those with liver cirrhosis, have a significantly extreme risk of HCC contrast to healthy people [5,6]. All of these risk factors contribute to persistent inflammation, which promotes hepatic fibrosis, hepatic cirrhosis, and ultimately HCC [7].

The multi-step process of HCC progression is controlled by the epigenetic and genetic changes to deactivate tumor suppressor genes and activate oncogenes therefore dysregulating the essential cellular functions. HCC is inherently diverse tumor and various molecular

processes influence its growth [8,9]. The phosphatidylinositol 3-kinase/AKT/mammalian target of rapamycin (PI3K/AKT/mTOR), Janus Kinase/Signal Transducer Activator of Transcription factor (JAK/STAT), Hippo signaling pathways, p53 pathway, Hedgehog (HH), and the Wnt/β-catenin, are the major pathways associated to HCC [10]. The primary mechanism of liver cancer has notably the Ras/Raf pathway activation been identified as the deregulation of cell proliferation [11]. Several studies revealed the Ras/MAPK pathway is a crucial biological route involved in the progression of liver tumors in both preclinical as well as in humans [12]. It is reported that Ras/MAPK pathway is the most important in developing HCC among the other signaling pathways [13]. This route is activated in 50-100% of HCC patients as per studies [14]. The HBx and HCV core proteins mediate the initiation of the Ras/MAPK pathway to cause heptocarcinogenesis [15]. Sirtuin 1 (SIRT1) plays a critical role in HCC by promoting tumorigenicity through regulation of oncogenes, metabolic reprogramming, and enhancing cell survival [16,17]. SIRT1 modulates MAPK signaling, which is pivotal for cell proliferation, differentiation, and survival. By deacetylating key components of the MAPK pathway, SIRT1 can enhance tumorigenicity, promote metastasis through epithelial-mesenchymal transition, and contribute to chemoresistance. Targeting SIRT1-MAPK interactions presents a promising strategy for improving HCC treatment outcomes [18]. SIRT1 activators and inhibitors can significantly impact the effectiveness of drugs targeting the Ras/MAPK pathway in HCC by modulating cell proliferation and survival mechanisms, potentially enhancing or diminishing therapeutic outcomes [19]. This review reports the molecular cascades to activate the Ras/MAPK pathway in HCC and molecular inhibitors to block Ras/MAPK signaling cascades for treatment. Additionally, suggest current and effective treatment strategies to focus on the Ras/MAPK signaling pathway. The phosphorylation of MAPK and the expression of the proteins c-fos and c-jun reveal to determine the role of the signal transduction cascade in the development of hepatocarcinogenesis.

Ras/Raf Pathway

Members of the multigene families Ras, Raf, and MEK include the three members Ha-Ras, N, and Ki of Ras, the three members A, B and Raf1 of Raf, and the five members of the MEK gene family (MEK1-5) are responsible to regulate Ras/MAPK pathway [20]. The MAPK cascade are serine/threonine kinases change the extracellular molecules such as hormones and growth factors into intracellular signals to regulate differentiation, survival, and proliferation of cells [21]. G-Protein-Coupled Receptor (GPCR) or Receptor Tyrosine Kinase (RTK) mediates signaling from cell surface receptors to the nucleus is thought to activate cellular processes [22]. The superfamily of Ras/MAPK pathway consists of some members based on the degree of similarity and makes up seven groups: Extracellular signal-Regulated Kinase (ERK) 1/2, ERK ¾, ERK5, ERK 7/8, Nemo-Like Kinases (NLKs), p38 a/b/c/d and Jun N-terminal JNK 1/2/3 kinases [23]. Normally, the Ras/MAPK pathways interact with other pathways including the PI3K/Akt/mTOR, Rho/actin, Wnt/β-catenin, and TGFβ/Smads to regulate cellular functions [24].

The Ras protein is a GTPase protein and four isoforms expressed by three distinct genes; H, N, and K-Ras4A/4B [25]. Ras is the initial ERK 1/2 intracellular effector and activated by different extracellular stimuli as RTK's activation through different growth factors [26]. The stimuli switch the state of Ras from an inactive GDP bound form to GTP active form therefore trigger the various pathways associated with cell survival, growth, differentiation, and migration via means of several effectors [27]. GTP bound Ras activates the Raf-1 kinase, which further drives it to the cell membrane. Raf-1 activation phosphorylates the MEK 1/2 and subsequently phosphorylates ERK 1/2 accordingly, a number of proteins control the Ras/MAPK pathway. Activated ERK moves to the nucleus and stimulates several TF, the AP-1 family members as c-Fos and c-Jun [28]. These factors transcribe genes involved in cells progression or other biological activities by bind to promoter region specifically on AP-1 binding sites [29].

Guanine Nucleotide Exchange Factors (GEFs) and GTPase-Activating Proteins (GAPs) regulate the activation of Ras. GEFs convert GDP to GTP although GAPs hydrolyse the GTP-Ras [30]. Anti-apoptotic and Ras proliferative Signals are regulated by members of the Ras Association domain Family (RASSF) which consists of NORE1A, NORE1B, RASSF1A, RASSF1C, RASSF2-10 [31]. The Spred family protein prevents Raf activation, and the Raf kinase inhibitor protein (RKIP) prevents MEK from phosphorylation by Raf-1, so are further controllers of the Ras/MAPK system [28]. Sprouty proteins control the Ras/MAPK pathway either by blocking Raf or the growth factor receptor bound-2 (GRB-2)-SOS complex [28]. Ras not only activates Raf and the MAPK pathway but a different additional effectors interact with Ras through the Ras-Binding Domain (RBD) [32]. The primary ones are the Phospholipase C epsilon (PLCe), Ral Guanine Nucleotide Dissociation Stimulator (RalGDS), and PI3K [33]. Ras stimulates these effectors to activate a number of pathways including the PI3K pathway involved in survival, growth, proliferation, angiogenesis, also the control of glucose and lipid metabolism [34]. The intracellular mechanisms linked to the regulation of MAPK pathway in HCC were addressed in more detail in behind paragraphs and shortly discussed the influence of crosstalk involving Ras with other pathways as well as the function of certain other Ras effectors in cancer development (Figure 1).

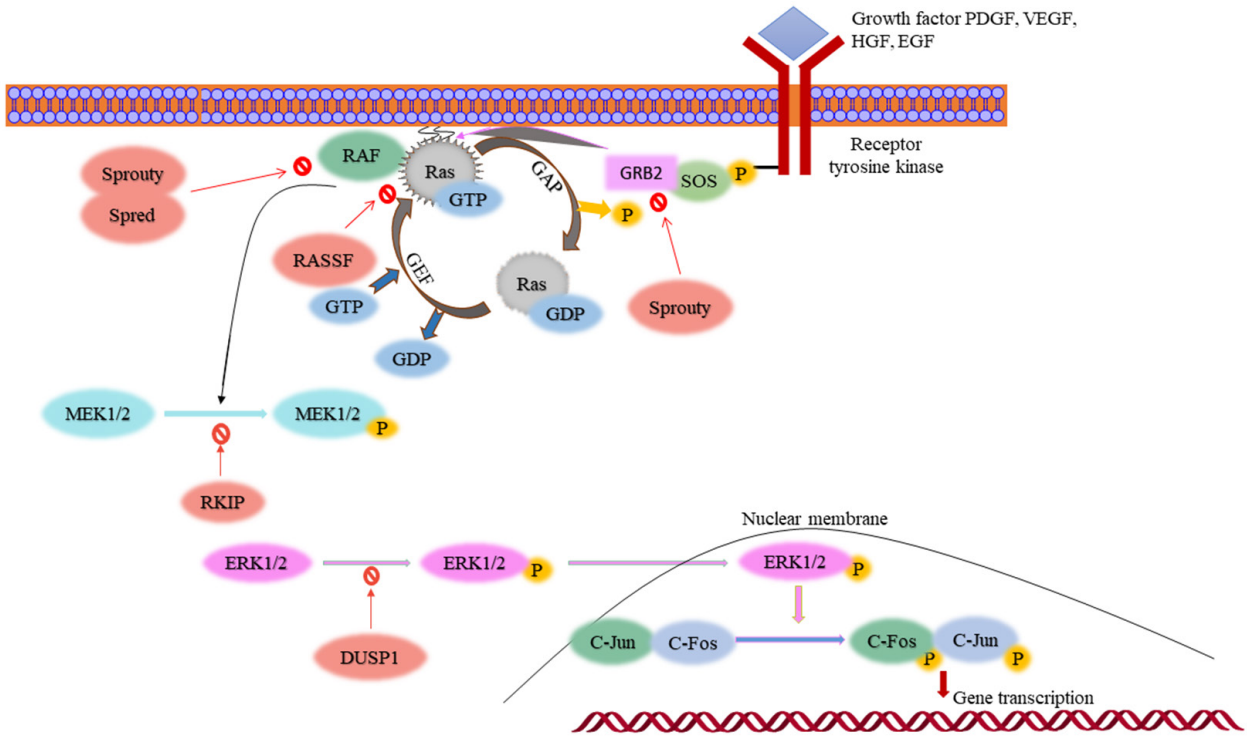

Figure 1: Schematic representation of MAPK/ERK signaling pathway and its regulation. MAPK/ERK signaling pathway is initiated by the binding of growth factors to receptor tyrosine kinases (RTKs) on the cell surface. Activation of RTKs leads to the recruitment of the adaptor protein GRB2 and the guanine nucleotide exchange factor SOS, which facilitate the exchange of GDP for GTP on Ras, activating it. Active Ras (Ras-GTP) then activates RAF, which in turn phosphorylates and activates MEK1/2. MEK1/2 phosphorylates ERK1/2, leading to its activation. Activated ERK1/2 translocate to the nucleus, where it phosphorylates transcription factors such as C-Fos and C-Jun, promoting gene transcription. The pathway is negatively regulated by several mechanisms: Sprouty inhibits GRB2 and RAF; Spred inhibits RAF; RASSF promotes the hydrolysis of GTP to GDP on Ras, inactivating it; RKIP inhibits MEK1/2; and DUSP1 dephosphorylates ERK1/2, inactivating it. These regulatory mechanisms ensure precise control over cell signaling events.

The Ras/MAPK Pathway in Hepatocellular Carcınoma

Current considerations on signaling pathway in hepatocarcinoma

Ras/MAPK pathway dysregulation is linked to cancerous transformation and development, including liver cancer as it performs a decisive role to regulate the important cellular functions such as the survival and proliferation of cells [35]. Liver cancer exhibits higher levels of MEK 1/2 and ERK 1/2 expression than the surrounding nonneoplastic liver tissue [36]. Additionally, a strong relation between expression of MAPK and c-Fos protein, c-Fos and the cyclin D1, MAPK and cyclin D1 is found in human HCC [37]. The MAPK pathway is implicated in tumor growth where the therapy of HCC cells with a particular Ras/MAPK inhibitor suppresses the tumor growth and causes apoptosis [38].

Ras mutations

The Ras gene mutations reported about 20-30% in all human tumors and a high incidence in the colon (40-50%), pancreas (57%), salivary gland (15%) and skin cancer (17%) [39]. The point mutations linked to cancer are in Ras protooncogene primarily affect codons 12, 13 and 61 [40]. These mutations make the Ras protein active, allowing it to trigger downstream processes [41].

Suppression of Ras Inhibitors

Ras GTPase-activating proteins

The Ras family consists of 150 members and are usually categorized into Ras, Ran, Rho, Rab, and Arf families. Ras GAPs convert the Ras-GTP activated form to the GDP-inactivated by increasing the Ras GTPase activity, this results to convert the GTP to GDP. Inhibiting GAP activity triggers accumulation of the activated Ras, allowing it to activate downstream effectors [42]. RAS GAPs are categorized into a number of different families, such as RASA1 or p120GAP, GAP1 proteins (RASAL1, RASA2-4), NeuroFibromin (NF1), the SynGAPS (RASAL2/3, SynGAP1, DAB2IP A/B), and the IQGAP family (IQGAP1-3) [43]. Ras GAPS family members like RASAL1, DAB2IP and hDAB2IPA are persistently downregulated in a number of human HCC cell lines including HepG2, SK-Hep-1, Hep 3B, PLC/PRF/5 probably with hypermethylation in the promoter [28]. DAB2IP, RASAL1, and NF1 expression levels were significantly suppressed in patients and was primarily due to promoter hypermethylation [44].

The siRNA-mediated inhibition of RASAL1, PITX1 (a RASAL1 upstream inducer) and DAB2IP expression results in improved cell survival, partially as a result of increased RAS GEF activity [45]. The re-expression of RASAL1, PITX1 and DAB2IP results in a substantial decrease proliferation and an increased apoptosis in HCC cells [46]. Several GAPs can stimulate apoptosis in cancer cells to defend the individual. The five GAPs are Deleted in Liver Cancer 1 (DLC1), Regulator of G-protein Signaling 3 (RGS3), DOC-2/DAB2 interacting protein (DAB2IP), p120 RasGAP (RASA1) and STARD13 affect the number of pro-apoptotic and anti-apoptotic proteins or the associated signaling pathway lead to apoptosis [47]. The hDAB2IPA expression is discovered to be much lower in HCC with promoter hypermethylation found in >80% of liver tumors. DAB2IP downregulation is linked to a poor overall survival. The gene and protein expression of IQGAP1 is highly expressed in 84% of tumors whereas IQGAP2 are significantly suppressed in 78% of patients hence IQGAP1 has an oncogenic role and IQGAP2 maintains a tumor suppressor function [48] (Table 1).

Table 1: An overview of key components related to Ras signaling pathway regulation and downstream effects in the context of HCC.

Component	Description
Ras GTPase-Activating Proteins (Ras GAPs)	Ras GAPs convert the Ras-GTP activated form to the GDP-inactivated form by increasing the Ras GTPase activity.
	Inhibiting GAP activity leads to the accumulation of activated Ras, activating downstream effectors.
	Ras GAPs include RASA1 (p120GAP), GAP1 proteins (RASAL1, RASA2-4), neurofibromin (NF1), SynGAPS (RASAL2/3, SynGAP1, DAB2IP A/B) and IQGAP family (IQGAP1-3).
	RASAL1, DAB2IP and hDAB2IPA are downregulated in HCC cell lines, possibly due to promoter hypermethylation.
	Suppression of RASAL1, PITX1 and DAB2IP expression improves cell survival, partly due to increased RAS GEF activity. Re-expression of these proteins decreases proliferation and increases apoptosis in HCC cells.
RASSF Class of Ras Inhibitors	RASSF1A and NORE1A activate MST1 kinase and BAX, leading to apoptosis. Promoter hypermethylation silences RASSF1A and NORE1A in many malignancies.
	RASSF1A binds to plasma membrane calcium pump (PMCA) 4 proteins to inhibit MAPK pathway.
	Serum DNA from HCC patients shows irregular methylation of RASSF1A gene promoter, potentially for early diagnosis.
	NORE1B is epigenetically inactivated in 62% of HCC cases.
	RASSF4 may occasionally be silenced epigenetically.
Downstream Ras Signaling Pathway: Raf Kinase	Raf kinases (A-Raf, Raf-1, B-Raf) are upstream regulators of the Ras/MAPK pathway.
	B-Raf mutations, particularly V599E are common in various cancers, leading to increased kinase activity.
	RKIP blocks Ras/MAPK pathway activity; its downregulation is associated with cancer progression, including HCC.
	RKIP downregulation in HCC is linked to epigenetic transcription and promoter methylation.

RASSF1A and NORE1A are the two key players activate the Macrophage Stimulating 1 (MST1) kinase and BAX to cause both caspase dependent and caspase-independent apoptosis after coupled to Ras. RASSF1A and NORE1A must heterodimerize to start Ras-associated pro-apoptotic proteins [49]. The RASSF1A binds to Plasma Membrane Calcium Pump (PMCA) 4 proteins to inhibit MAPK pathway [50]. The function of inhibitors in proliferation describes readily why their dysregulation significantly contribute to the Ras/MAPK pathway initiation in a variety of malignancies. RASSF1A and NORE1A typically exhibit promoter hypermethylation in many types of human malignancies [51]. The promoter hypermethylation is thought to be the primary mechanism for RASSF1A silencing, although post-translational mechanisms involving downregulation of microRNA also contribute to RASSF1A inactivation in HCC [52]. The serum DNA from HCC patients show irregular methylation of the RASSF1A gene promoter in patients indicating this genetic modification eventually used for early diagnosis in individuals with a significant risk to develop liver cancer [53]. The human HCC about 62% exhibit epigenetic inactivation of NORE1B [51] and an additional RASSF1A silencing is seen in 50-92% of these cases [54]. HCC samples do not exhibit any hypermethylation of the RASSF1C promoter [55] while RASSF4 may occasionally have abnormal epigenetic silencing [56].

Spread family of MAPK inhibitors

Sprouty-Related Protein EVH1 Domain (SPRED) interacts with Ras to prevent activation of Raf and translocate to the cell membrane, consequently acting as a negative mediator of the Ras/MAPK pathway and acts as a tumor suppressor [57]. The SPRED family consists of four members in mammals: SPRED1-3 and EVE-3. Spred1 is mostly expressed in embryonic tissues and adult brain and less in other tissues; While Spred2 is frequently present in adult tissues and is hardly ever found in embryonic tissues; Spred3 is in the liver; EVE-3 in the liver and the brain [58]. The SPRED expression reduces the ERK phosphorylation and suppresses tumor cell proliferation [59]. Spred-2 overexpression in HCC cell line SMMC-7721 causes apoptosis of cells via downregulation of anti-apoptotic protein Mcl-1 and the caspase pathway [58]. Finally, reduced Spred expression is linked to serious HCC as intrahepatic metastases and tumor proliferation [28].

SPRED proteins can no more prevent ERK activation upon the removal of EVH1 region [60]. The EVH1 domain target proteins at certain locations for action by specifically binding to proline-rich sequences involved in processes like synaptic transmission, skeletal control, cytoskeletal remodeling and cell proliferation [58]. The SPR domain has multiple roles in different SPRED

proteins [61]. SPR deletions in the proteins SPRED1 and EVE-3 can still suppress ERK activation, whereas a comparable mutation in SPRED2 cannot [62]. The SPR domain of SPRED1 and SPRED2 encourages the development of heterodimers, which can respond to various stimuli in a temporal and spatial manner to carry out specific inhibitory functions [63]. SPRED3 has a lesser inhibitory activity than SPRED1 and SPRED2 but can still prevent ERK from being activated [64]. This shows the KBD domain is missing from SPRED3 that involve to suppress ERK activation. The KBD domain is thought to be necessary for SPRED1 and 2 phosphorylation and its existence improves the SPRED function [58].

Sprouty family of MAPK inhibitors

The Sprouty family of signal transduction protein contains 4 regulators i.e. Platelet-Derived Growth Factor Receptor (PDGFR-β), Vascular Endothelial Growth Factor Receptor (VEGFR), Fibroblast Growth Factor Receptor (FGFR) and Epidermal Growth Factor Receptor (EGFR) to change downstream cellular responses caused by GPCR and RTK [65]. Sprouty proteins primarily acting as modulators of the Ras/MAPK pathway and its dysregulation has linked to the metastasis and progression of many cancer types including lung, breast, colon and prostate cancer [66]. Sprouty homologues are differently expressed in HCC [28]. The expression of Sprouty 2 prevents ERK activation and HGF-induced proliferation [67] and the downregulation of Sprouty 2 promote cell proliferation hence the Sprouty family received the most attention in the field of HCC as a result of unrestricted activity of Ras/Raf pathway [68]. Moreover, the MAPK pathway is quickly activated by Sprouty 2 inactivation in association with AKT to cause hepatocarcinogenesis [28]. The downregulation of sprouty 2 is more significant in HCC with a poor prognosis [69].

The Downstream Ras Signaling Pathway

Raf kinase

The Raf kinase is a downstream regulator of Ras molecule [70]. The three Raf kinases A-Raf, Raf-1, and B-Raf all are upstream regulators of the Ras/MAPK pathway [71]. The more cancer-causing isoform, the B-Raf gene is mutated in many human cancers including 66% of skin cancers and a lower rate in papillary, colon, thyroid, and ovarian cancer [39]. The majority of B-Raf gene mutations (almost 90%) change valine to glutamic acid at position 599 (V599E), thereby increasing the kinase activity and triggers the activation of the MAPK cascades. Raf-1 mutations are extremely uncommon while A-Raf mutations have never reported [72].

This is in accordance with the evidence that prolonged expression of c-Raf-1 and Raf-1 play a carcinogenic effect in a number of tumors [73]. The RKIP is yet another element contributing to Raf-associated hepatocarcinogenesis. RKIP is a protein to blocks the activity of the Ras/MAPK pathway for cellular proliferation and progression [74]. Raf-MEK complexes interrupt up upon binding of RKIP to either Raf-1 or MEK under vigorous conditions to prevent downstream signaling of MEK [75]. Raf is improperly activated whenever RKIP-mediated inhibition of Raf is disrupted, it leads to upregulate MAPK pathway [76]. Human prostate, ovarian, breast, melanoma, and colorectal cancers have linked to reduced RKIP activity [77]. RKIP downregulation has been demonstrated in liver cancer and helps to activate the MAPK pathway [78]. The epigenetic transcription and promoter methylation within the RKIP coding sequence are the two primary factors causing the reduction of RKIP expression in cancers [76]. The RKIP protein expression is downregulated in HCC tissue in contrast to noncancerous liver samples [28].

MEK/ERK proteins

ERK 1/2 are the chief substrates of MEK 1/2 [79]. Activated ERK1/2 activates cytosolic and nuclear substrates such as Transcription factor AP-1 perform a fundamental role in regulating the survival and proliferation of cells [80]. Hence the high ERK activity has been seen in a different cell lines and tumors as lung, pancreas, kidney, colon, and ovary cancer [81]. The main isoform associated with normal hepatocyte proliferation is ERK ½ [82]. The MEK/ERK pathway activated by a number of mechanisms to favour the advancement of liver cancer by enhancing cellular survival, proliferation, tumor growth, cell motility, invasiveness, and angiogenesis [83]. The frequency of ERK activation affects how specifically ERK and DUSP1 interact [84]. The initiation of ERK 1/2 dysregulates the DUSP1 through ubiquitin-mediated proteasome degradation pathway to degrades DUSP1 and activate ERK 1/2 for prolonged period [85].

Crosstalk Signalling of Ras/MAPK Pathway in Tumorigenesis

It is stated in the introduction, the Ras/MAPK pathway frequently interacts with other signalling pathways to regulate cellular processes both in healthy and in pathological conditions like liver cancer [10]. The Ras protein to activate Raf, a number of additional signaling molecules such as the PI3K, TIAM1, RalGDS and the PLCe proteins is activated to the interaction across pathways [86]. Moreover, TIAM1 stimulates cancer metastasis and is associated with poor prognosis in HCC patients [87]. The MAPK and PI3K/Akt/mTOR pathways interact at different levels which can have either a positive or negative effect on one another. Both mechanisms collaborate to encourage the survival and development of tumor cells, and favours carcinogenesis [88]. Consequently, the Ras/Raf, Wnt/β-Catenin, Rho/actin, and TGFb/Smads pathways make up a complicated network of interactions to promote tumor cell's differentiation, proliferation, and tumor invasion [89].

Therapeutic Implications

The field of molecular therapeutics in primary liver cancer treatment was introduced by the various effectors of MAPK pathway, which include several therapeutic targets due to their significance in hepatocarcinogenesis. Sorafenib is a strong multikinase inhibitor primarily inhibits Raf kinases, PDGFR-α, VEGFR-2/3, and c-kit and is the initial systemic treatment authorized for advanced HCCs [90]. A variety of Ras/MAPK pathway inhibitors have developed over the past few years, and at the meantime, specific inhibitors for many of the pathway's essential elements are being defined [28]. Small compounds like lonafarnib or tipifarnib block the MAPK pathway in an efficient manner. These compounds prevent the farnesyltransferase enzyme from catalyzing Ras protein farnesylation, a critical step

that binds Ras to the cell membrane [91]. Regorafenib (SCH66336), a multikinase inhibitor, blocks BRAF, PDGFR-β, VEGFR-2/3, CSF-1R, RET, c-Kit, and Flt3 [92]. Clinical trials, systemic drugs, and a number of widely recognized immunotherapy approaches all contribute to the advancement of innovative drug development. The Food and Drug Administration (FDA) approved a number of drugs between 2017 and 2020 for the treatment of HCC including immune checkpoint inhaibitors (pembrolizumab, nivolumab, durvalumab, tremelimumab, ipilimumab), multikinase inhibitors (sorafenib, lenvatinib, cabozantinib, ramucirumab, regorafenib and atezolizumab in combination with bevacizumab) [93]. The FDA for the treatment of HCC expressly approved multiple immune checkpoint inhibitors and antiangiogenic therapies and numerous other medications are now being tested in clinical studies. First, second, and third-line therapy has significantly changed the course of HCC with a cure rate of over 90%, nevertheless few studies have reported a concerning increase in the recurrence of HCC. The most frequently changed mediators (the TERT promoter, CTNNB1, and TP53) and dysregulated pathways (Ras/MAPK, β-catenin/Wnt, and PI3K/mTOR) associated with HCC have all been identified using molecular characterizations. The right anti-tumor activity and toxicity need to be balanced through the use of innovative drugs and therapies. A number of drugs are currently available to prolong their lives for individuals with advanced HCC. It is still unclear which HCC patients respond best to a certain drug and what the ideal therapeutic strategy (Table 2).

Table 2: A comprehensive overview of various drugs used in the treatment of hepatocellular carcinoma (HCC).

Drugs	Therapeutic Targets	Median OS (Months)	Median PFS (Months)
Sorafenib	RAF, VEGFR, PDGFR, KIT	10.6	NR
Regorafenib	B-RAF, PDGFR, VEGFR, FGFR, RET, KIT	10.6	3.1
Cabozantinib	MET, VEGFR, AXL, RET	10.2	5.2
Ramucirumab	VEGFR2	8.5	2.8
Tivantinib	HGFR	8.4	2.1
Regorafenib	B-RAF, PDGFR, VEGFR, FGFR, RET, KIT	10.6	3.1
Sunitinib	PDGFR, VEGFR, KIT, RET	7.9	3.5
Lenvatinib	VEGFR, PDGFR, FGFR, RET, KIT	13.6	7.4
Atezolizumab and Bevacizumab	PD-L1 and VEGF-A	19.2	6.9
Nivolumab	PD-1	16.4	3.7
Pembrolizumab	PD-1	13.9	3

Future Perspectives

The future perspectives for this review are multifaceted and promising. As the understanding of hepatocarcinogenesis and the function of the Ras/MAPK pathway expands, individualized therapy based on the particular molecular patterns of each patient may become a reality. Early diagnosis and prognosis may be improved by the identification of certain biomarkers linked to Ras/MAPK pathway dysregulation in HCC. Novel therapeutic drugs that target this pathway could appear, possibly developing therapy approaches. The study of immunological responses and Ras/MAPK deregulation may lead to the development of new immunotherapies. The validation and improvement of Ras/MAPK-targeted drugs depends on clinical trials, translational research, and ongoing monitoring of patient outcome. A more thorough knowledge of HCC will be possible with the integration of multi-omics data and the encouragement of multidisciplinary cooperation. Additionally, addressing the expanding problem of HCC on a global scale requires taking into consideration the effects on global health and establishing ways for early identification and universal availability of current drugs.

Conclusion

A thorough understanding of the abnormal molecular mechanisms leading to carcinogenesis will feasibly allow to predict the patient's response to targeted therapy which might have a significant influence on clinical decision-making. Hepatocarcinogenesis, a multistep process results in the genetic and epigenetic change to activate oncogene, and inactivate tumor suppressor gene followed by changes in different signalling cascades. A number of intracellular processes in HCC like Ras/MAPK pathway is important for the growth and progression of HCC are dysregulated and lead to survival, differentiation, and proliferation of cells. The Ras/MAPK is the most effective signalling pathway that manages malignancy and controls apoptosis in cancer. The upregulation of the Ras/MAPK pathway has largely changed these cellular processes. This review discussed the several modulators to regulate the Ras/MAPK.

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