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Review Article

The Role of MAPK/p38 Signalling Pathway in Cancer

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Abstract

Cancer is one of the fatal diseases globally. It is unfortunate that despite many years of devoted studies towards finding a better therapeutic approach, the scourge of the disease has continued to rise with attendant mortalities. Many studies have been devoted to finding constructive clues to the pathways that are implicated in the onset and progression of cancer. Recently, increasing bodies of studies have identified the MAPK/p38 role in its pathological pathways. The current review effort explored different functions of MAPK/p38 in the onset and progression of cancer. This signaling pathway is crucial for the overall integrity of the cell and its regulation has been associated with tumorigenesis and cancer metastasis. Several scientific research have also identified its roles in the ability of cancer cells to resist chemotherapeutic interventions. However, to fully explore the MAPK, studies that will elucidate the various MAPK/p38 isoforms and their roles in tumorigenesis may proffer the next revolution in the fight against cancer incidences.

Keywords: MAPK/p38; Cancer; Signaling pathway; Metastasis; Tumorigenesis; Phosphorylation.

Introduction

Cancer is one of the deadly diseases globally and many attentions are focused to find suitable therapeutic options [1], contain designing new medicine to reduce this disease [2]. Advances in science and technology now make it possible to determine the genetic mutations that are responsible for different types of cancer [2]. Next generation sequencing is also here to identify various molecular pathways involved in tumorigenesis [2]. One of these important pathways in cancer onset is the MAPK signaling pathway [3].

A brief knowledge about the MAPK signaling pathway

The mitogen activated protein kinases are important mediators of many types of signals that take place intracellularly [4,5,3,6,7]. The signaling pathways they mediate are important in many cell events like cell

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survival, cell multiplication, apoptosis, cellular health, and the ability of normal cells to transform to cancer forms [4,5,3,6]. These mediators are actually serine threonine kinases [4,5,3], known to control all aspects of life and their alteration is always associated with different diseases like cancer [8]. MAPK pathway can modulate cancer resistance and sensitivity to therapeutic agents [9]. Three distinct kinases cascade in the MAPK signaling pathway with specific functions, namely the MAPKKK (termed the upstream kinase), the MAPKK (termed the middle kinases) and the MAPK [8]. These three protein kinases have been known to form the backbone of the MAPK signaling pathway whose phosphorylation and subsequent interactions with other pathways inform the uniqueness of the pathway [6]. They utilize G-protein as their input source to send signals for biological activities necessary for survival [10]. MAPK must undergo phosphorylation to become functional and one keyway of phosphorylating MAPK is inhibiting the upstream activating pathways, a form of negative feedback [2]. Physiological events such as hormonal imbalances, cytokinetic signals, endogenous and exogenous stressors like (exemplified by the extracellular signaling regulated kinases (ERK)) and stress activated responses [exemplified by Jun N-Kinases (JNK)) are responsible for the activation of MAPK [11]. Its alteration during diseases has made it an important subject for more than two decades now [3]. Extensive work has been done so far on designing new medicine to target different pathways of the MAPK in order to find treatment for different types of cancers [10,8] but the MAPK/p38 is going to be extensively discussed more extensively because of its modulating effects in the study of many diseases like cancer.

Diverse roles of the MAPK/p38 signaling pathways

Review by Bengal, et al., [12] identified the many impacts of the MAPK/p38 pathway in the regulation of many whole-body metabolisms such as the phosphorylation of glycogen synthase. The MAPK serves as the connecting point between different biological endogenous and exogenous signals crucial for biological functions. P38 kinase is one of the kinases from MAPK family and has been consistently reported to be implicated in the pathways of many diseases [13]. MAPK/p38 exist in four gene homologies namely MAPKs 11, 12, 13 and 14 each of which code for different orientations of the MAPK/p38 dependent genes. MAPK/p38α 14 are ubiquitously present in most cells while the other homologous forms of the gene are restricted to certain types of tissues such as the brain, skeletal muscles, Kidneys, pancreas, the testis, and the small intestinal tracts where they perform distinctive regulatory activities to enhance normal biological activities in those sections of the body [14,15]. p38α and the p38β play significant roles ranging from normal cardiac development, immunological responses by eliciting the generation of T cells to the enhancement of proper sex determinant [16,17]. While other forms of the MAPK/p38 genes like p38γ and the p38δ play regulatory roles in cell lines such as tissue regeneration and immunological reactions [18]. Interrelations between these MAPK/p38 subtypes have suggested the downregulatory functions of the p38α activate p38γ and p38δ [13].

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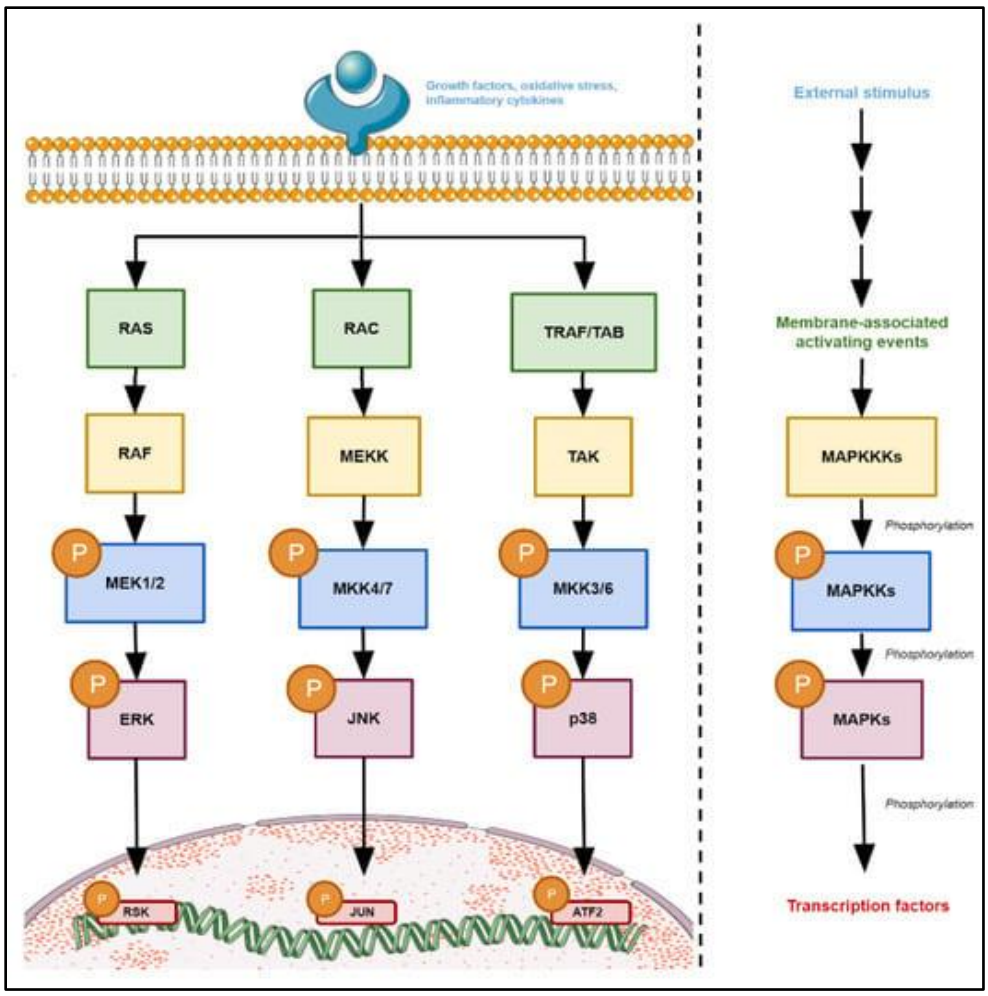

Figure 1: The figure represents a schematic representation of the various members of the MAPK and how they are phosphorylated. The intersections between the various components are represented with arrows. Several events act as external stimuli creating different activities at the plasma membrane under the influence of different activating agents like the RAS. All these lead to the phosphorylation of the MAPK and all the various components that are associated with them [13].

The MAPK/p38's other roles in neurotransmission have been reported using mouse models. For instance, MAPK/p38 has been implicated in the efficiencies of synaptic transmissions in the brain and loss of MAPK/p38 regulation are associated with the onset of many neurodegenerative diseases like Alzheimer's diseases (AD) [3,19-21]. This revelation in current research efforts is indispensable considering the ubiquity of this pathway in the brain [21], thereby providing insights into possible therapeutic measures against many neurological diseases like cancer of the brain. The pathway also regulates the development of the testis (including sex determination) and its deactivation upon exposure to lethal chemicals have been linked to many cases of infertilities in males [17].

In endocrinology, the production of glucocorticoids remains an important

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reaction of endocrines to stressors usually activated by glucocorticoids receptors and this remains a focal target of the MAPK/p38 [8]. However, the interrelatedness between glucocorticoids and the MAPK/p38 has been documented to impact the expression of many genes, which can also be targeted for therapeutic purposes [8].

Current studies are therefore being utilized to explore the synergistic and antagonistic relationships between these MAPK/p38 subtypes and how they are linked to certain diseases like neurodegenerative diseases, skeletal muscle dystrophy, type 2 diabetes [12], and many types of cancer [13].

Activation and regulation of MAPK/p38

The mechanisms behind the activation and limitation of MAPK/p38 is an interesting signaling pathway to study [13]. Exposure to high radiation like UV, low oxygen conditions and ischemic stroke can induce different levels of stressful conditions to the cells to release the cytokines [13]. All these events are facilitating p38 phosphorylation in MAPK signaling pathway. Studies have shown that the attachment of TAK1-binding protein to the p38 isoforms c-brings about conformational changes which enhance the activation of the p38 [22]. These are facilitated by the GTPase which are found upstream of the MAPK pathway. Nevertheless, the mechanistic processes involved in the pathway is yet to be fully understood. The MAPKKs are found at the downstream of the pathway where a subclass of the MAPKKs namely MKK4 have been reported to enhance the phosphorylation of the p38 and the JNK [22]. There are other means of activating the p38 which is often found in thymus cells through thymus cell receptors [13]. There is the need to understand the role of some protein in their regulations of the proper expressions and activities of the p38 [13]. These proteins ensure that the p38 is specific in their signaling roles by enhancing the changes in its conformations necessary to ensure that it is activated and rightly located within the cell [23].

Various activators of the MAPK/p38 pathways

Phosphates regulate the activation of the MAPK/p38

Two phosphorylation agents, namely Thr180 and Tyr182 are associated with the phosphorylation of p38 [13]. These are the dual specificity phosphatases (DUSP) known to be important biomarkers or indicators of cancer [13]. This infers that the dephosphorylating these residues will deactivate p38 activities [13]. Many studies have shown that the DUSP4 plays different types of roles in oncogenesis. The possibility is that it suppresses the activities of tumor suppressing genes [24]. Different concentrations of the DUSP4 have been observed to be associated with some cancer types like breast and colorectal cancer [25]. Downregulated concentration of the DUSP4 causes those types of cancer. However, scientific reports have made it clear that there is a strong association between DUSP4 concentrations and the onset of different tumor types. Lower DUSP4 concentrations leads to poor cancer prognosis [26,27].

There are other phosphatases that are associated with the inactivation of p38. One such phosphatases include members of the PP2 family. PP2C inactivates the p38 by

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working on the PAT2Ks and by the direct dephosphorylation of the Thr180 [26]. Another member of this family, the PP2A interacting with the p38 also causes its inactivation but its activities depend on the cell types and the nature of stimulation [28].

Micro RNA regulates the activation of MAPK/p38

Conserved non-coding RNAs like the microRNAs have their special regulatory functions. Studies associating them with the regulation of the p38 pathways have been documented. When the Argonaute proteins are assembled on the micro-RNA induced silencing complex (miRISCs), complimentary mRNAs are silenced [29]. This is of homeostatic importance which are often characterized in different cases of cancer and inflammatory responses [13]. Typically, a type of miRNAs known as miRNA-17-92 whose upregulation is associated with several tumor types like gastric, breast and colon cancer [30]. Another member of the miRNA known as the miR-200 with the p38 have been associated with significant role of reactive oxygen species production which are linked to the development of liver cancer by promoting apoptosis [7]. Recently, it was discovered that another family of the miRNA known as the miR-139-5p, plays important roles in the regulation cell to cell migration and its expression has been associated with the phosphorylation of the MAPK/p38 leading to the uncontrolled movement of cells [31].

Different types of miRNAs are important in the regulation of these pathways in the study of various cancers, But the use of the miRNAs as biomarkers is currently in the stage of model studies and not many clinical studies have been conducted to assess the role of the miRNAs in the activation or dephosphorylation of the activities of the MAPK/p38 pathway [13].

Localization of the MAPK/p38

To understand MAPK/p38 signaling specificity, it is necessary to identify its location in the cell. Studies have identified the cytoplasm and the nucleus as the two locations of the p38MAPK signaling pathway [13]. When cells are in their resting inactive forms, most of the p38 is localized in the cytoplasm but upon activation or phosphorylation, some of the p38 forms get pulled into the nucleus while some are left in the cytoplasm [13]. An experimental study using UV light as the activation agent discovered the movement of the p38 to the nucleus [32].

MAPK/p38 and cancer

The P38α plays significant roles in different types of cancer via cell death or apoptosis. It can have also been associated with implicating the activities of different cancer cell types such as their ability to invade and proliferate as well as inflammatory responses [33]. Other isoforms such as p38γ and p38δ have also been reported to be associated with a number of diseased conditions like tumor but the specific regulatory functions of the latter are yet to be fully elucidated [34].

The role of MAPK/p38 in cancer proliferation

One of the important characteristics of tumor cells lies in the fact that they can multiply and invade other cells. The unique role of the

MAPKp38 in cell cycle regulation and transcription makes it a suitable candidate for studies that will help in the understanding of various molecular pathways that are implicated in tumorigenesis [13]. Different expression levels of the p38 MAPK can greatly determine how cells survive, differentiate, and undergo apoptosis thereby determining the potentials for tumorigenesis and metastasis [35]. One of the important subsets of the p38 MAPK, p38α, has been reported to exert a negative effect on the progress of the cell cycle at different phases. One study stated that the mechanism behind this stemmed from the fact that that subset of the p38 downregulates the activities of cyclins while at the same time upregulates the activities of cyclin dependent kinases inhibitors [13]. Similarly, tumor suppressor p53 is modulated. It can also positively induce the prevention of tumor proliferation by inducing cellular senescence [36]. Different cell lines in the body have found the conserved functions of the p38α isoforms, playing different roles in the modulation of different cancer pathways [35]. It is important to note the interrelation between the p38α and ROS production. Studies have hypothesized the possibility of the latter's ability to utilize p38α to induce programmed cell death which have been recognized to be important in the prevention of the initiation of cancer cells. Conversely, the other isoform of the p38α namely p38β is found to antagonize the apoptotic destruction of apoptotic cells thereby enhancing cancer genesis and proliferation [37]. Significant studies have shown that two isoforms namely p38γ and p38δ play the dual roles of either enhancing the oncogenesis or preventing oncogenesis leading to different outcomes of cancer and their expressions are variously affected by different types of epigenomic methylations that either silence or upregulate their expression [38,39].

Role of MAPK in cancer metastasis

One of the inflammation keys especially in the chronic situation is enhance in the invasive ability of the cells, cancer metastasis. Numerous reports implicating the multifunctional roles of the MAPK/p38 in the association with inflammation and tumor metastasis [40]. The tumor micro-environment is characterized by the presence of different types of cells, channels of blood delivery to the tumor and some cytokine and chemokine. The blood vessels serve as the channel of blood delivery to the tumor to ensure that the tumor is fed with the appropriate nutrients [41]. Another point to note is the fact that p38α has been shown to have activating cyclooxygenase 2 which has been shown to cause inflammatory activities with great impact on the ability of cancer to progress and spread into other cells. This is associated with some cancer cells like skin and breast cancer [41]. It is also discovered that the P38α enhances the synthesis of cytokines which also tend to favor inflammation and survival of the cell. The other isoform, p38β is not involved in this process [42].

p38α can also cause the formation of matrixes and distortion of cancer cells to improve the progression of tumor forming cells [13]. Angiogenesis in cancer involves the formation of new vessels near the cancer cells and spreading these cells [43]. Emerging studies also have shown that the upregulation of the p38MAPK often triggers the formation of hypoxia to elicit the formation of

angiogenesis. Therefore, infer that the p38MAPK is involved in both tumorigenesis and metastasis [44].

The p38 and two subsets of the MKK genes, MKK3 and MKK6 were knocked out in some model of studies, and it was surprisingly shown that the p38 gene is involved in the induction of hypoxic conditions via HIF that also enhance the activities of angiogenic factors [45]. While the other subsets of the p38β have been implicated in the initiation of tumor via lipocalin 2 activities and studies that aim to show the effect of the elevation of the LCN2 on cancer metastasis showed a positive correlation (that is, elevated levels of the LCN2 increased the likelihood of cancer spread to other parts of the cells in cancer metastasis) [46]. Thus, the two isoforms of the MAPK/p38 play different functions in tumorigenesis and metastasis [47]. It is also suggested that the downstream activation of the p38MKK6 is possibly not going to enhance cancer metastasis. But the postulation is that for this premise to hold, the model used must be different [48].

The loss of function model also indicated that the p38α may also play other roles that enhance the suppression of tumor. This has been shown via genetic studies that indicated that the MKK4 which is included in the JNK pathways are associated with tumor suppression which has been found in some types of cancer like colon, breast, and prostatic cancers [13]. Conversely however, the loss of function model has also been identified to contribute to tumor initiation [49]. When the p38α undergoes high level of phosphorylation, the possibility of malignant cancer initiation was reported to take place in some cancer types such as the cancer of the thyroid gland [50]. This role is also played by p38β [50]. p38γ and p38δ are other isoforms of the p38 which their roles in tumorigenesis have been focused on studies [13]. These studies have been carried out using mouse models hence not many clinical studies have been carried out so far [13]. Knock down studies of these two isoforms showed that the reduction in their number could actually trigger the expression of cancer cells and subsequently lead to cancer metastasis [13]. But this is location dependent because another study also showed that the reduced level of the p38γ in the fibroblast lead to increase in cell multiplication and subsequent tumor initiation. These studies were conducted both *in vivo* and *in vitro* [51]. The two isoforms were also implicated in inflammatory functions and were found to also contribute to inflammations. This was because the various chemokines and cytokines which are needed for inflammatory activities were found to be lower in expression coupled with the recruited neutrophils which have been discovered to play a part in the formation of tumor microenvironment [52].

Based on the types of cells being studied, reports have shown that interactions between different signaling pathways may be involved in the crucial roles of regulating cellular activities [13]. For instance, the MAPK/p38 and JNK pathway may have some cross signaling patterns that play crucial roles in cancer initiation and metastasis [53]. They work together to initiate cancer genesis and metastasis and sometimes they play antagonistic roles between each other depending on the type of cancer [13]. Therefore, in choosing any therapeutic option, the cancer type, stage, and the cell where it is occurring coupled with

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interactions between different signaling pathways must be taken into consideration [13].

Targeting the MAPK/38 in the treatment of cancer

Of the various MAPK pathways that have been discovered to be implicated in cancer prognosis, the MAPK/38 pathways show promising results for therapeutic options [13]. This pathway is crucial for the proper activities in the cell in some cases while in some cases contributes to cellular abnormalities, we can say that targeting these pathways can help in the design of better cancer therapies for the treatment of cancer. Hence studies are gradually building up around targeting these pathways in radio and chemotherapy as better options in addressing cancer treatment [13].

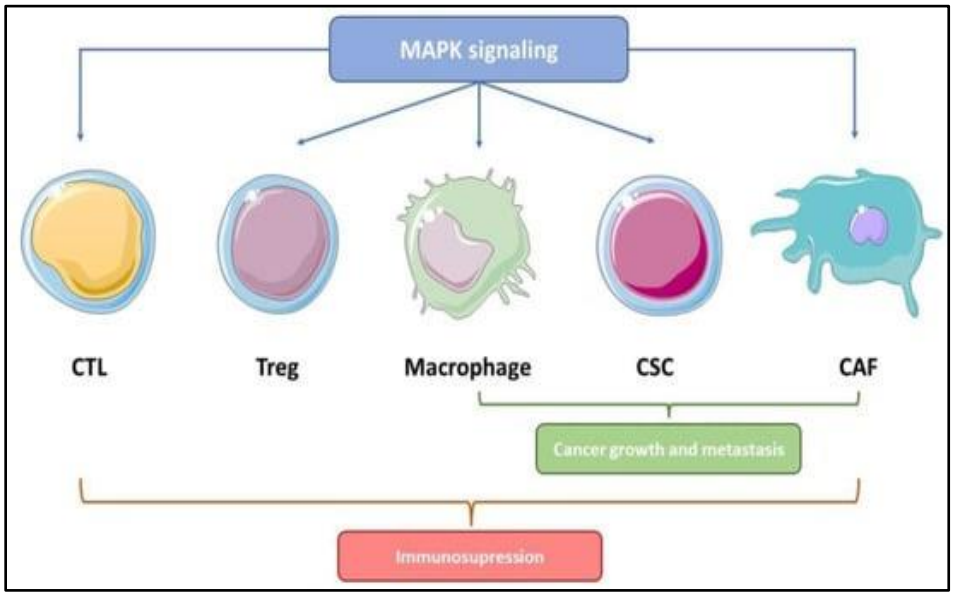

Figure 2: P38 in Radiotherapeutic Studies: Radiotherapy has been used in the management of cancers for decades now all over the world. Different outcomes treatments with radiotherapy have been examined to a large extent in different scientific and medical studies [13]. For decades of radiotherapy use, the specific molecular pathways that are involved were not clearly demonstrated until recent times via studies that are suggesting that the p38 MAPK signaling pathways are associated with different changes in cancer patients receiving radiotherapy [13]. Clinical studies involving humans showed that this pathway is involved in different apoptotic processes that are involved in the treatment of cancer using radiotherapy [54]. It plays significant pro-inflammatory roles such as the production of cytokines and also contributes to the progressive reduction in the vitality of cells (known as cellular senescence).

MAPK/p38 and chemotherapeutic studies

Programmed cell death is one of the processes occur during cancer cells chemotherapies. This usually occur as a response of cancer cells to medication. MAPK/p38 has been significantly reported to regulate the effects of chemotherapeutic agents against cancer cells. These have been shown to occur in the treatment of cancers of the breast and the colon [55]. P38 for instance, makes cancer cells resistant to different antitumor therapies like doxorubicin and other therapeutic options that are aimed at destroying the DNA.

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This stems from the fact that the p38 are involved in cancer cells survival in the absence of another subset named p53. One model study involving the use of mouse model discovered that positive effects of therapeutic agents when the p38 was downregulate showing the rate dependence of p38 in the cancer cells response to cancer drugs like cis platinum [56].

Effects of p38 pathways in cancer cells response to medication is largely dependent on cancer types and the tumor micro-environment. Sometimes, more than one type of cells is involved in the tumor microenvironment so that scientists have been able to discover that the formation of blood vessels within the tumor microenvironment can be arrested by inhibiting the p38 pathway. This has been confirmed using mouse models and it was discovered that arresting the p38 can actually pave way for the reduction of angiogenesis and the arrest of cancer spread to other cell lines [57]. One of the dilemmas of successful cancer therapy programs is the presence of intrinsic and or acquired resistance to therapeutic agents. This is often the case for cancer patients expressing the epidermal growth receptor and the human epidermal growth receptor gene [58]. A comprehensive understanding of the entire mechanisms of resistance to chemotherapeutic agents have not been unraveled even though certain events such as MAPK upregulations [58]. Ren, et al. [59] reported the signaling transduction pathways that are altered while using paclitaxel as a chemotherapeutic agent on the CHMm cell lines and reported programmed distortion of the CHMm cell lines via MAPK activation and converse deactivation of another pathway known as the P13K/AKT signaling pathway. However, whether similar signaling transduction in other cancer cell lines and tissue types occur is yet to be largely explored [60].

Conclusion and suggestions for the future

The MAPK pathways have been portrayed to be associated with different types of regulations on tumorigenesis and metastasis of cancer. It has also been shown to be an important target for cancer types of alleviations. The study of the numerous roles of the MAPK in cancer have been enhanced via different types NGS tools. The use of gene editing using the CRISPR cas9 has shown great potential. However, a lot still needs to be done to be able to understand the roles of the different isoforms of the MAPK pathways in cancer prognosis. Once this is achieved, the development of specific anti-cancer agents that are tailored towards each cancer type will be possible. It is therefore suggested that more studies still need to be carried out to be able to understand the roles of each of the MAPK isoforms in tumorigenesis and cancer metastasis. The affordability of cancer therapeutic agents is one of the greatest barriers to successful cancer treatment regimens. Recent efforts at the exploration of natural products such as flavonoid rich plants are being considered. Wholesome assessment of the roles of plant flavonoids in the regulation of the MAPK and other relevant pathways that are involved in tumorigenesis may help in the future.

Author's contributions

Maryam Bahjat (MB) conceptualized the topic while Monday Chukwudi (MC) developed the line of thought by gathering relevant literature needed for the review.

Both MB and MC participated in the rigorous study and review of literature that enhanced the review effort.

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Competing interests

The authors clearly indicate that there was no conflict of interest throughout the process of conceiving and writing this article.

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