

## Review

# The Role of p38 $\gamma$ in Cancer: From review to outlook

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## Abstract

p38 $\gamma$  is a member of the p38 Mitogen Activated Protein Kinases (p38 MAPKs). It contains four subtypes in mammalian cells encoded by different genes including p38 $\alpha$  (MAPK14), p38 $\beta$  (MAPK11), p38 $\gamma$  (MAPK12), and p38 $\delta$  (MAPK13). Recent studies revealed that p38 $\gamma$  may exhibit a crucial role in tumorigenesis and cancer aggressiveness. Despite the large number of published literatures, further researches are demanded to clarify its role in cancer development, the tissue-specific function and associated novel treatment strategies. In this article, we provide the latest view on the connection between p38 $\gamma$  and malignant tumors, highlighting the function of p38 $\gamma$ . The clinical value of p38 $\gamma$  is also discussed, helping the translation into the remarkable therapeutic strategy in tumor diseases.

Key words: p38 $\gamma$ , molecular pathway, intestinal microbes, gene editing, immunotherapy

## Introduction

To date, the p38 $\gamma$ , the third mammalian p38, is initially described as a novel protein kinase from rats [1], known to assist local phosphorylation in the cell nucleus [2]. p38 $\gamma$  is a 43-kDa [3] and 367-amino acid protein [4] with a characteristic C-terminal motif KETXL. It can be docked with the PSD-95/Dlg/ZO-1 homology (PDZ) domain of additional proteins, such as  $\alpha$  1-syntrophin, PTPN3, SAP90/PSD95 and the scaffold protein SAP97/hDlg. p38 $\gamma$  binds its PDZ domain of these proteins and induces the phosphorylation [5, 6]. For instance, the environmental osmotic pressure changes trigger p38 $\gamma$  activation in the cytoplasm and concentrate in the nucleus, thereby increasing the binding of p38 $\gamma$  and nuclear hDlg and resultantly disassembly of the hDlg-PSF (protein-associated-splicing factor) complex [7, 8]. Due to its capacity to shuttle between cytoplasm and nucleus, p38 $\gamma$  might establish a link between two key procedures of gene expression and cytoskeleton reorganization to adapt to environmental changes.

Notably, p38 $\gamma$  can be activated by the stress and mitogenic signals, and further promote tumorigenesis and progression of cancer [9]. For example, p38 $\gamma$  is

activated by Ras and is indispensable for Ras transformation and invasion [2, 10, 11]. p38 $\gamma$  is located predominantly in the nucleus [3]. Meanwhile p38 $\gamma$  is capable of inhibiting cell migration, essential for oncogene-induced senescence [12]. These findings indicate that p38 $\gamma$  probably has tumor suppressive or carcinogenic effects (Table 1).

## Overview of MAPKs

Mitogen-activated protein kinases (MAPKs) are serine/threonine protein kinases that convert extracellular stimuli into a variety of cellular responses [13]. The RAS/RAF/MEK/ERK (MAPK) signaling cascade, one of the widespread signaling pathways, plays a vital role in cellular processes whose cell disorders relevant to carcinogenesis and cancer development, including differentiation, propagation, inflammation, apoptosis, survival and innate immunity [13]. In the early 80s, ERK1 appeared in the focus as the first MAPK core molecule to be discovered and identified in mammals [14]. Subsequently, the highly homologous ERK2 and ERK3 were cloned one after another, and the research

on the mammalian MAPK pathway began [14]. Currently, typical MAPKs mainly include ERK1/2, JNK1/2/3, p38 isoforms accompanied by in-depth studies [14]. Furthermore, each classic MAPK consists of a set of three kinases acting in sequence: a MAPK, a MAPK kinase (MAPKK) and a MAPKK kinase (MAPKKK), and the extensive functions they regulate are principally mediated by phosphorylation of members of the protein kinase family named MAPK-activated protein kinases (MAPKAPKs) [14].

## Overview of p38

The p38 MAPK family is one of the four major mitogen-activated protein kinases (MAPKs) cascades as a class of highly conserved proteins found firstly in studies of endotoxin-induced cytokine expression [10, 15-17]. It was reported to get involved in inflammation, cell growth, cell differentiation, cell death, and the cell cycle [10, 15, 18-21]. So far, there are four p38 isoforms respectively named p38 $\alpha$  (MAPK14), p38 $\beta$  (MAPK11), p38 $\gamma$  (SAPK3, ERK6 or MAPK12), and p38 $\delta$  (MAPK13) [5]. These kinases share extremely analogical protein sequences; p38 $\alpha$  and p38 $\beta$  have 75% identity, whereas p38 $\gamma$  and p38 $\delta$  have 62% and 61% identity with p38 $\alpha$ , respectively. Simultaneously, p38 $\gamma$  and p38 $\delta$  have 70% similarity with each other [22].

## p38 $\gamma$ and Cell cycle

Targetedly, cells are capable to dispose DNA damage by terminating the cell cycle process or performing procedural cell death [23]. Highly conservative DNA repair and cell cycle checkpoint pathways enable cells to cope with endogenous and exogenous DNA damage [23].

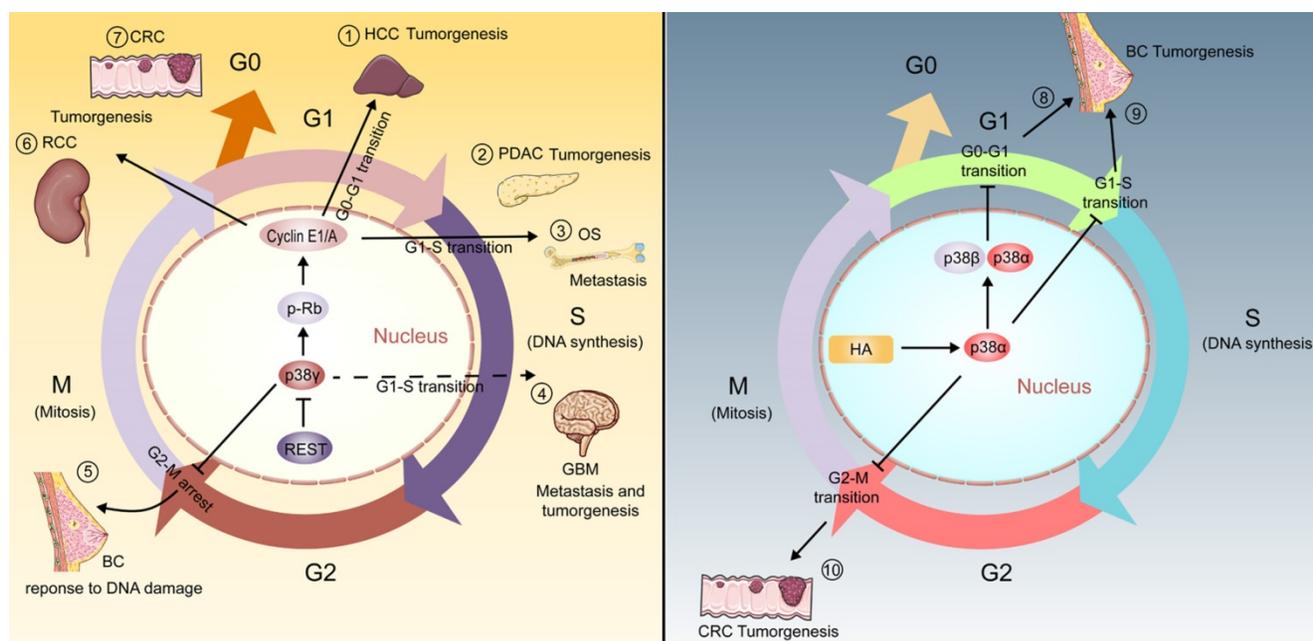
In the past decade, p38 pathway has been emphasized as a core part of cell cycle regulator in cancer which principally manifested as the effect of p38 $\alpha$ / $\beta$ / $\gamma$  instead of p38 $\delta$  (Figure 1). For example, in human breast cancer MDA-MB-231BO cells, hyaluronan activates p38 $\alpha$ / $\beta$  and up-regulates the expression of p21<sup>cip1</sup>, leading to the decrease of Cyclin D1 level, prolonging the conduction in G0-G1 phase and slowing the growth of breast cancer cells [24]. p38 $\alpha$  can also phosphorylate Rb, down-regulate the expression of E2F transcription factor, delay the progression of G1-S phase and reduce tumor cell proliferation in MCF7 breast cancer cells [25]. Likewise, the activation of p38 $\alpha$ -dependent p53 promotes the expression of GADD45 $\alpha$ , inhibits the activity of the Cdc2/Cyclin B1 complex, and achieves the function of inhibiting the growth of HCT116 human colorectal carcinoma cells by blocking the G2-M phase [26]. A study has reported that circTNFRSF21 is the upstream of p38 $\delta$ , and its

expression enhancement can promote the transition of endometrial carcinoma cells from G0/G1 to S phase. However, the mechanism by which p38 $\delta$  regulates the cell cycle is still unclear [27].

**Table 1.** The carcinogenic and anticancer effects of p38 $\gamma$

Type	Observation	Species	References
<b>Tumors promoted by p38<math>\gamma</math> signaling</b>			
BC	p38 $\gamma$ is related to the aggressiveness and metastasis of BC	Human	11, 40,41, 42,43,45
	Alcohol selectively stimulates phosphorylation of p38 $\gamma$ in breast cancer cells	Mouse	43
	Increased p38 $\gamma$ expression is related to a decrease in overall survival rate of BC patients	Human	41
	PFD acts as a targeted inhibitor of p38 $\gamma$ and can inhibit the development of TNBC in cells and/or mice	Mouse	48
SCC	SCC incidence and tumor lesion number per mouse were lower in p38 $\gamma$ - mice than that in WT mice	Mouse	21
	There is a conspicuous correlation between the expression of p38 $\gamma$ and the clinical stage of tumor, tumor volume and lymph node metastasis in ESSC	Human	49
	The expression extent of p38 $\gamma$ is related to HNSCC	Human	20
HCC	In HCC cases, the excessive expression of p38 $\gamma$ is highly indicative of its carcinogenicity and unfavorable prognosis	Human	31
	In mice with absent p38 $\gamma$ , HCC is strongly inhibited, and survival time is prolonged	Mouse	31
	p38 $\gamma$ inhibitor PFD is able to prevent the occurrence of HCC induced by DEN	Mouse	31
CRC	Highly expressed p38 $\gamma$ boosts the growth, proliferation, cell migration and apoptosis resistance of CRC cells in human CRC tissues	Human	34
	Mice with IEC-specific p38 $\gamma$ deletion in the AOM/DSS model have reduced colon tumor formation	Mouse	51
PDAC	p38 $\gamma$ is involved in the spread of PDAC and aggressive behavior	Mouse	16
	The pharmacological p38 $\gamma$ inhibitor PFD inhibits carcinogenesis effect and tumor growth in PDAC	Mouse	16
Glioma	p38 $\gamma$ is related to the proliferation and apoptosis of glioma, and p38 $\gamma$ is positively correlated to the differentiation grade of glioma	Human	55
CTCL	High level of p38 $\gamma$ is related to CTCL and is fundamental for viability of cancer	Human	4, 57
OS	p38 $\gamma$ may play an indispensable part in the proliferation, migration and invasion of OS cells	Human	58, 36
RCC	Overexpression of p38 $\gamma$ is capable to encourage RCC cell development, proliferation and migration	Human	35, 60
	The expression of p38 $\gamma$ mRNA and protein in RCC tissues are higher than those in normal tissues adjacent to the carcinoma	Human	35
	High p38 $\gamma$ levels are detected in FeNTA-induced renal cancer development and maintenance	Human	60
NSCLC	Compared with the control group, the markedly elevated level of p38 $\gamma$ is related to the germination of NSCLC disease	Human	61
Bladder cancer	The outcome of patients with high expression of p38 $\gamma$ is worse	Human	62
<b>Tumors suppressed by p38<math>\gamma</math> signaling</b>			
NSCLC	In xenograft models, p38 $\gamma$ is able to lessen the tumor initiation ability and tumor growth of NSCLC cells	Mouse	12

**Abbreviations:** BC, breast cancer; TNBC, triple-negative breast cancer; SCC, squamous cell cancer; HNSCC, head and neck squamous cell carcinoma; ESSC, esophageal squamous cell carcinoma; CRC, colorectal cancer; HCC, hepatocellular carcinoma; PDAC, pancreatic ductal adenocarcinoma; RCC, renal cell carcinoma; CTCL, cutaneous t-cell lymphoma; OS, osteosarcoma; NSCLC, non-small cell lung cancer; GBM, glioblastoma; WT, wild type; IEC, intestinal epithelial cell; PFD, pifrenidone; AOM/DSS, azomethane/dextran sodium sulfate; DEN, diethylnitrosamine.



**Figure 1. p38 $\gamma$  participates in the biological process of various cancers by regulating the cell cycle process.** (1) p38 $\gamma$ /p-Rb/Cyclin (E1/A) pathway could encourage tumorigenesis and proliferation of hepatocellular carcinoma by promoting G0-G1 phase transition; (2) p38 $\gamma$ /p-Rb/Cyclin (E1/A) pathway could promote the transition of the cell cycle from G1 to S phase, and is affiliated to tumorigenesis, proliferation, and motility of pancreatic ductal carcinoma; (3) p38 $\gamma$ /p-Rb/Cyclin (E1/A) pathway could promote the transition of the cell cycle from G1 to S phase, connected with tumorigenesis, proliferation, and invasion of osteosarcoma; (4) As a downstream target of transcription factor REST, p38 $\gamma$  can be restrained by REST and may promote the transition of G1-S phase, resulting in the proliferation and migration of glioblastoma; (5) p38 $\gamma$  causes G2-M phase arrest and maintains breast cancer cell survival under conditions of DNA damage; (6) p38 $\gamma$ /p-Rb/Cyclin (E1/A) pathway may play a crucial part in the proliferation, development and migration of human renal cell carcinoma cells; (7) p38 $\gamma$ /p-Rb/Cyclin (E1/A) pathway may play a vital role in the proliferation, development and invasion of human colorectal cancer cells; (8) Hyaluronan-dependent p38 $\alpha$ / $\beta$  activation induces G0-G1 phase arrest, leading to growth inhibition of breast cancer; (9) Blocking G1-S phase conduction by p38 $\alpha$  also inhibits the tumorigenesis of breast cancer; (10) p38 $\alpha$  blocks G2-M phase transmission and weakens the tumorigenesis of colorectal cancer.

As early as 1999, p38 $\gamma$  has been found to inhibit cell proliferation by down-regulating cyclin D1 during adrenal cell hypoxia [28]. Moreover, it is proved that the activation of ATM/MKK6/p38 $\gamma$ /Cds1 pathway is essential for the correct regulation of G2 checkpoints in mammalian cells [29]. In line with this, it has been proved that *Xenopus* p38 $\gamma$  can promote the meiosis of *Xenopus* oocytes treated with progesterone, while p38 $\alpha$  or p38 $\beta$  have no effect [30]. On this basis, fully grown *Xenopus* oocytes are blocked in prophase of meiosis I and are induced to pass through meiosis by progesterone stimulation [30]. In human cells, it has also been found that the presence of p38 $\gamma$  can cause cell cycle changes, and this may be essential for the proliferation, invasion and carcinogenic activity of numerous cancers [16, 31]. Similarly, the ectopic expression of p38 $\gamma$  may contribute to a significant arrest of the cell cycle in G2/M phase, which may be a mechanism of breast cancer cells to survive established on DNA damage [32, 33].

Taken together, p38 $\gamma$  participates in the regulation of the cell cycle, contributing to a variety of cancers [16, 31, 32, 34-37] (Figure 1). Considering the prominent position of p38 $\gamma$  in regulating the cell cycle process, the role of p38 $\gamma$  in cell cycle regulation in more cancers is worthy of further investigation.

## Breast Cancer

Estrogen receptor (ER) is a transcription factor related to BC, which has the paradoxical effect of promoting proliferation and resisting invasion [11, 38, 39]. It has been reported that p38 $\gamma$  can integrate the invasive antagonism of Ras and ER without affecting the proliferative activity of BC, thereby promoting the invasiveness of BC [11]. Involvement in cellular metabolism is another mechanism by which p38 $\gamma$  increases BC invasiveness. Using a novel metabolomics approach to demonstrate the role of p38 $\gamma$  in apoptosis, invasion, and migration, Chen et al. showed the potential to promote cancer metastasis, particularly altering the enrichment of certain metabolites and metabolic pathways, which may bring potential to the evolution of novel therapeutic strategies for BC [40].

Another study based on a particular kinetic cell movement analysis method further certifies that p38 $\gamma$  can control cell movement by regulating the metastasis-associated small GTPase-RhoC ubiquitination and lysosomal degradation, as well as regulate diversifications in cell structure and cell form of BC [41]. This evidence suggests p38 $\gamma$  may possess a fundamental effect in the metastatic properties of BC. Apart from that, there is pertinence between

enhance expression of p38 $\gamma$  and the decline in the overall survival rate of BC patients [41].

In ethanol-induced mice, loss of p38 $\gamma$  can alleviate BC development and metastasis, and knockdown of p38 $\gamma$  can block alcohol-aroused RhoC activation, cell spread, invasion and migration [42]. Correspondingly, there is a significant positive correlation between the expression of p38 $\gamma$  and RhoC in clinical BC samples [41]. Alcohol has also been reported to augment the invasiveness of BC cells in another study. It stimulates the phosphorylation of p38 $\gamma$  by activating ErbB2 and promotes the interaction of p38 $\gamma$  with the substrate SAP97/DLG as well as the phosphorylation of SAP97/DLG, thus leading to the activation of CSCs (cancer stem cells) [43].

Epithelial cell-mesenchymal transition (EMT) refers to the biological process of epithelial cells transforming into cells with mesenchymal phenotype through specific procedures and helps cancer cells spread from solid tumors and form detectable metastasis [44]. It was previously shown that p38 $\gamma$  could facilitate EMT and CSCs in BC cells, as evidenced by reductive E-cadherin expression and incremental Vimentin level [45]. In this course, ErbB2 and ErbB4 act as the major upstream receptor kinases. Both are capable to activate p38 $\gamma$  through ubiquitin-proteasome-dependent degradation and the degradation of GATA3 is caused subsequently. This suppression causes the up-regulation of miR-200b and down-regulates the expression of Suz12, eventually leading to EMT and invasiveness of BC [45].

Distinguishingly, among all types of BC, triple negative BC (TNBC) tends to have the worst prognosis due to the lack of therapeutic targeting of ER, progesterone receptor (PR), and epidermal growth factor receptor 2 (HER-2) [46]. Meanwhile TNBC is prominently heterogeneous but abundant among the CSCs population [47]. Qi et al. point out p38 $\gamma$  activates Nanog transcription by forming a polyprotein complex with c-Jun/Hsp90 on the Nanog promoter and activates the expression of transcription factors such as Sox2 and Oct3/4 to stimulate CSCs amplification in TNBC cells. These consequences further suggest that the coalescence of Hsp90 inhibitors with the non-toxic p38 $\gamma$  inhibitor PFD may even be more efficacious in treating TNBC by destroying functional protein complexes, thereby co-consuming the CSCs population [48].

## Squamous Cell Carcinoma

Lack of p38 $\gamma$  makes the incidence and number of tumors per mouse lower than that of wild-type mice [21]. Researchers demonstrated that p38 $\gamma$  and p38 $\delta$  are concerned with the production of cytokines such

as IL-6, STAT3, and TNF- $\alpha$  in the skin, contributing to skin tumor evolution. The loss of p38 $\gamma$  versus p38 $\delta$  abrogated tumorigenesis in human epidermoid carcinoma A431 cells [21].

In the case of esophageal squamous cell carcinoma (ESCC), stable down-regulation of p38 $\gamma$  can prevent tumorigenesis in a nude mouse model of ESCC cell xenotransplantation [49]. In addition, p38 $\gamma$  can promote the movement and proliferation, and prevent the apoptosis of ESCC cells *in vitro* [49]. Similarly, higher p38 $\gamma$  expression is also observed in head and neck squamous cell carcinoma cells [20].

## Hepatocellular Carcinoma

p38 $\gamma$  is immediately related to the expression of ACTA2 and COL1A [31]. Both these two genes encode actin and collagen respectively, which are fibrotic markers that commonly used before liver cancer develops, indicating the HCC with p38 $\gamma$  elevation is easier to migrate and deteriorate [31].

Experiments by Tomas-Loba et al. showed that p38 $\gamma$  staining in human HCC biopsy tissues is much stronger than in non-tumor tissues and p38 $\gamma$  knockdown weakened proliferation and colonization in HCC cell lines [31]. In addition, HCC in mice lacking p38 $\gamma$  in hepatocytes (AlbCre-p38 $\gamma$  mice) is observed to be strongly controlled. Compared with control (AlbCre+/-) mice, their tumors were smaller, fewer, and survived longer [31]. Albcre-p38 $\gamma$  mice additionally showed the ability to prevent liver cancer induced by carbon tetrachloride or high-fat diet [50]. As a cyclin-dependent kinase (CDK)-like kinase, p38 $\gamma$  exhibits a sort of substrate specificity and inhibition sensitivity analogical to conventional CDKs, which is manifested as phosphorylate the C terminus of retinoblastoma tumor suppressor protein (Rb) to promote liver proliferation [16, 31]. p38 $\gamma$  may stand for a unique kinase that activates the non-classical CDK pathway in a cell cycle protein-independent manner when the CDK-cyclin complex is low, thus initiating the cell cycle and allowing the cells to escape from quiescence under stress stimulation. Collectively, these evidences undoubtedly confirm that p38 $\gamma$  is necessary for Rb-dependent cell cycle progression and liver tumorigenesis, supporting the potential of p38 $\gamma$  as a target for HCC treatment.

## Colorectal Cancer

Loss of p38 $\gamma$  significantly inhibits cell growth, proliferation, and migration in HT3-29 cells and primary human CRC cells, while suppressing apoptosis. In particular, p38 $\gamma$  standards are observably increased in human CRC tissues in terms of the surrounding normal epithelial tissues [34]. Consistent with previous research, p38 $\gamma$  deletion also

results in decreased Rb phosphorylation and cyclin (E1/A) expression, both of which are augmented as p38 $\gamma$  highly expressed in CRC cells [34].

As an important regulatory factor, p38 $\gamma$  promotes CRC tumorigenesis by transmitting exogenous and endogenous signals. For example, conditional p38 $\gamma$  knockout of intestinal epithelial cells (IECs) reduces the expression of proinflammatory cytokine and  $\beta$ -Catenin/Wnt pathway activity in colon tissues, successfully linking inflammation with CRC [51]. Chronic application of PFD can alleviate CRC induced by inflammation in mice, but no effect in mice with conditional p38 $\gamma$  knockout in IECs [51]. In addition, in the AOM/DSS mouse model, p38 $\gamma$  deficiency also attenuates the generation of CRC [51].

The Ras-dependent mechanism is an important part of the occurrence of CRC [52]. PTPH1 acts as an exclusive p38 subtype-specific phosphatase known to interact through PDZ binding [53]. Hou et al. found through experiments that p38 $\gamma$  can directly phosphorylate PTPH1 to promote the growth of Ras conversion and Ras-dependent CRC [52]. In human CRC tissues, the transcription factor c-Jun was activated by phosphorylated p38 $\gamma$  through its C-terminus, and then the activated c-Jun recruited p38 $\gamma$  as a cofactor to the matrix metalloproteinase 9 (MMP9) promoter, inducing its transactivation and ultimately promoting CRC cell invasiveness [3].

### Pancreatic Ductal Adenocarcinoma

p38 $\gamma$  has been reported to link K-Ras signaling and the Warburg effect by means of phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) and glucose transporter 2 (GLUT2). It's crucial for aerobic glycolysis and pancreatic tumorigenesis [16]. The p38 $\gamma$  activation-dependent phosphorylation and stabilization of PFKFB3 and its interaction with GLUT2 constitute a ternary complex, which can effectively boost the occurrence of aerobic enzymes and pancreatic ductal adenocarcinoma (PDAC) via their regionally elevated concentrations. The course of cell cycles from the G1 to S phase in p38 $\gamma$  silenced pancreatic ductal epithelial cells (KPC) cells has been found to be blocked compared with KPC and associated with lower levels of CDK6 (cyclin dependent kinase 6) and p-Rb proteins [16]. The function of p38 $\gamma$  in the G1/S transition may be critical for stimulating cell proliferation and cell motility, activating glycolysis, promoting inflammatory responses as well as the development and growth of PADC [16, 54]. In addition, a novel therapeutic strategy established by PFD and the PFKFB3 inhibitor PFK15 can inhibit glucose uptake, reduce lactic acid secretion, and suppress PDAC growth [16].

### Glioma

p38 $\gamma$  defect results in lessened proliferation and enhance apoptosis of glioma cells [55]. With the decrease of p38 $\gamma$ , the expression of human telomerase reverse transcriptase (hTERT) and telomerase show a corresponding decline, while the expression of Caspase-3/9 increases [55]. Glioblastoma (GBM) is the most malignant and common glioma [56]. Previous studies have shown that the transcription factor REST (repressor element 1-silencing transcription factor) may be present as a cancer gene in GBM [37]. As a downstream gene of REST, p38 $\gamma$  can be inhibited by the complex formed by REST and its cofactors, which may trigger the transition of G1-S phase in cell cycle. The inhibition of p38 $\gamma$  by REST may eventually lead to the proliferation and migration of GBM cells, which partially proves the tumor suppressor effect of p38 $\gamma$  [37]. In glioma of the entire nervous system, the controversial results shown by p38 $\gamma$  so far may be due to different experimental conditions and experimental designs. Therefore, appropriate experiments are needed to verify the fundamental role of p38 $\gamma$  in glioma next.

### Cutaneous T-cell Lymphoma

p38 $\gamma$  is likely to be an important breakthrough in improving the level of CTCL diagnosis and treatment in the future. It selectively increases its expression to promote cell activity in CTCL patients and cell lines [4]. Meanwhile multi-kinase inhibitor F7/PIK75 could efficaciously restrain p38 $\gamma$  enzymatic activity and the production of its phosphorylated substrate pDLDH1 in CTCL cells and mouse xenografts [4].

Sézary syndrome (SS) is a form of CTCL that appears on the skin. Based on different investigations *in vitro*, for instance, the expression of p38 $\gamma$  is higher in CD<sup>+</sup>T cells in patients with Sézary syndrome than in healthy blood donors [57]. In 2018, a private non-profit clinical research center and hospital called City of Hope filed for a patent, which included a new p38 $\gamma$  inhibitor and its application in the treatment of CTCL [57]. The lead compound inhibitor in this patent has ATP competitive inhibitory effect on p38 $\gamma$ , and this compound shows dose-dependent inhibitory effect on tumor growth in CTCL xenograft model [57]. The additional library of EMD Biosciences screens 260 kinase inhibitors, including two novel potential p38 $\gamma$  inhibitors, and shows a typical-I p38 inhibitor binding schema to determine that p38 $\gamma$  is a potential objective for the therapy of CTCL [57].

### Osteosarcoma

miR-187 is confirmed to be the direct upstream molecule of p38 $\gamma$  in osteosarcoma cells [58]. The low

level of miR-187 is significantly related to staging, lymph node metastasis and deep stromal infiltration. By inhibiting p38 $\gamma$ , it reduces the biological behaviors of osteosarcoma cells like cell proliferation, migration and invasion. Correspondingly the reverse expression of miR-187 and p38 $\gamma$  in specimens of OS patients further confirmed this process [58].

Notably, the main cause of OS abnormal growth is the uncontrolled cell cycle and cell division [59]. p38 $\gamma$  can also play a cancer-promoting part in OS by stimulating Rb phosphorylation and cyclin E1/A expression and regulating G1-S phase transition [36]. Accordingly, present study shows that mRNA and protein expression of p38 $\gamma$  in human OS tissue and primary OS cells were significantly higher than that in human primary osteoblasts and OB-6 osteoblastic cells [36].

### Renal Cell Carcinoma

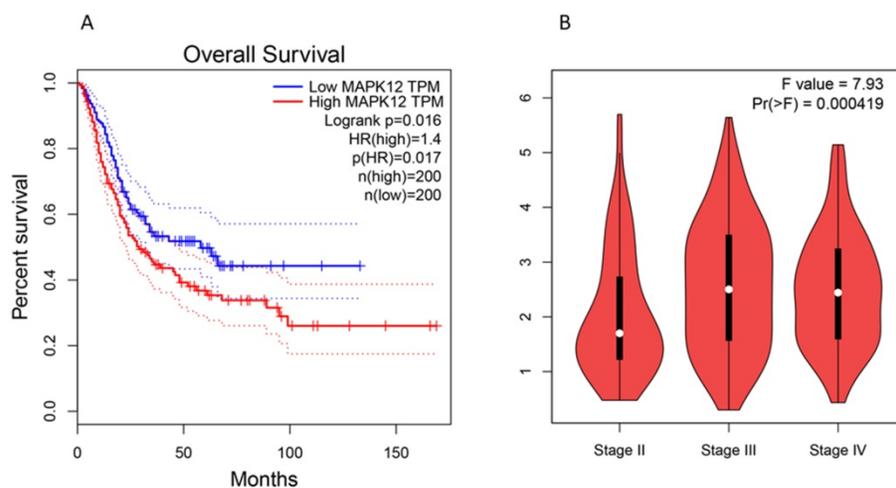
p38 $\gamma$  can analogously serve as a novel cyclin dependent kinase (CDK)-like kinase, which can phosphorylate Rb at the molecular level and regulate the cell cycle protein cyclin E1/A expression, ultimately promoting the progression of RCC cells [35]. Correspondingly, ectopic overexpression of p38 $\gamma$  promoted the growth, proliferation and migration of 786-O cells and primary RCC cells [35]. Besides, it manifested an increase of p38 $\gamma$  mRNA and protein degree in human renal cell carcinoma instead of adjacent tissues [35]. The results of Aguilar et al. showed that the level of p38 $\gamma$  in the kidney increased gradually after 1 and 2 months of cancer induction with ferric nitrilotriacetate (FeNTA) [60]. In this case, with the evolvement of cancer, the level of p38 $\gamma$  in the tumor even reached more than 30 times of that in the normal kidney [60].

### Non-Small Cell Lung Cancer

Cancer stem cells (CSCs) are the main source of tumorigenesis and recurrence and participate in p38 $\gamma$ -mediated inhibition of NSCLC. Activated p38 $\gamma$  can mediate the ubiquitination and degradation of stem cell proteins such as Sox2, Oct4 and Nanog by means of activating the downstream kinase MK2 to phosphorylate Hsp27, thereby inhibiting the tumor stem cell characteristics and tumor initiation ability of NSCLC cells [12]. Conversely, a significant increase in p38 $\gamma$  is associated with carcinogenicity of NSCLC, but not with stage, tumor, or response to treatment [61]. As of yet, the research of p38 $\gamma$  in NSCLC is limited, especially when the current opinions are contradictory without the specific role and mechanism of p38 $\gamma$ .

### Bladder Cancer

Kaplan Meier analysis shows that the expression of p38 $\gamma$  in bladder cancer is significantly different ( $P < 0.05$ ), and the prognosis of patients with high expression of p38 $\gamma$  is often gravely unfavorable [62]. p38 $\gamma$  may have the ability to become a prognostic marker and therapeutic target of bladder cancer. We used GEPIA (Gene Expression Profile Interactive Analysis): <http://gepia.cancer-pku.cn/> to conduct a correlation analysis and found that the high expression of p38 $\gamma$  in bladder cancer was negatively bound up with the overall survival of patients. Additionally, p38 $\gamma$  expression in different pathological stages (stage II, stage III, and stage IV) of bladder cancer had conspicuous significance (Figure 2). However, the mechanism of p38 $\gamma$  in bladder cancer is still obscure in experiments, consequently p38 $\gamma$  may be used as a potential research target.



**Figure 2. Expression of p38 $\gamma$  in different survival rates and different stages of bladder cancer.** (A) Correlation analysis between p38 $\gamma$  and overall survival in bladder cancer ( $p = 0.017$ ); (B) The expression of p38 $\gamma$  in different clinical stages of bladder cancer ( $p = 0.000419$ ).

## The latent clinical value of p38 $\gamma$ in human carcinoma

The early detection and diagnosis of cancer is crucial for patients. Sensitive tumor biomarkers are capable of reflecting the molecular differences of certain exceptional cancers when they occur at an early stage, which is not only propitious to inchoate diagnosis, but also advantageous to the screener and prognostic judgment of synthetical treatment tactics. Coincidentally, relevant studies have shown that the expression of p38 $\gamma$  is closely bound up with the depth of invasion, clinical stage, metastasis, and chemosensitivity. This section summarizes reports of p38 $\gamma$  as a biological marker for cancer diagnosis and prognosis and also summarizes the effect of p38 $\gamma$  on the sensitivity of tumor chemotherapy.

Literatures have demonstrated the value of p38 $\gamma$  in diagnosis. For example, researchers use immunohistochemistry with tissue microarray and performed a statistical analysis of its clinicopathological significance [49]. The expression of p38 $\gamma$  in ESCC is significantly different between clinical stage ( $P = 0.017$ ), lymph node metastasis ( $P = 0.008$ ) and tumor volume ( $P = 0.017$ ) [49]. In terms of prognosis, no conspicuous discrepancy is observed between patients with different levels of p38 $\gamma$  expression ( $P = 0.667$ ) in ESCC [49]. In a HCC cohort composed of 372 HCC patients, the Kaplan-Meier survival curve of patients stratified by p38 $\gamma$  expression shows that p38 $\gamma$  overexpression is associated with poor prognosis of HCC patients [31]. Among 43 samples of BC patients whose molecular subtypes are analyzed by PAM50 before, high expression of p38 $\gamma$  is accompanied by the obvious enrichment of BC basal-like subtypes ( $P = 0.018$ ) [41]. The expression of p38 $\gamma$  is also analyzed in 118 BC patients, including survival data. The results show that there is a consanguineous correlation between the higher expression of p38 $\gamma$  and the lower overall survival rate ( $P = 0.013$ ), suggesting that the expression of p38 $\gamma$  is of great significance for the prognosis of BC patients [41].

Chemotherapy still consists of the mainstay in cancer treatment. It has been reported that p38 $\gamma$  can transduce signals related to three widely used chemotherapy drugs, cisplatin, etoposide and tamoxifen [63].

## Outlook

A series of studies showed the impact of p38 $\gamma$  on carcinogenesis, invasion, maintenance and resistance to chemotherapy. The p38 $\gamma$  signal pathway leads to incremental expression of multiple downstream targets including transcriptional regulators. The transcription targets regulated by p38 $\gamma$  may be either

oncogenes or tumor suppressors, determined by different organs and tissue. Among the associated research of p38 $\gamma$  in cancer, conflicting data in specific cancer types indicate that the full role of p38 $\gamma$  is unclear, and further research is required to adequately comprehend the ponderance of p38 $\gamma$  in human pathology. This section summarizes the update and the prospect of p38 $\gamma$  in life sciences.

Drugs that directly target DNA topoisomerase II  $\alpha$  (Topo II $\alpha$  or Topo II) represent a vital class of anti-tumor drugs in clinic. It has been proved that p38 $\gamma$  can actively regulate the signal transduction of the drug-Topo II and can improve the therapeutic activity of Topo II drugs [9]. In this process, p38 $\gamma$  is specifically activated by Topo II drugs, and thereafter activated p38 $\gamma$  phosphorylates Topo II at Ser-1524, resulting in stronger stability and growth inhibition. The combination of p38 $\gamma$  and Topo II drugs may have clinical value for tumor disease. So far, one p38 $\gamma$  inhibitor PFD was applied in clinical. It has been experimentally proven *in vivo* that its inhibitory effect on p38 $\gamma$  requires a high daily dose (500 mg/kg/day in drinking water) [51], which raises doubts about its clinical value in anti-cancer fields. Conversely, among more than 20 p38 family candidates in clinical trials [57], for instance, combined p38 $\gamma$  and p38 $\delta$  inhibitor (BIRB796) against IFN- $\gamma$  [64], multi-kinase inhibitor F7/PIK75 which effectively against p38 $\gamma$  for CTCL treatment [4], pirfenidone is the exclusive drug targeting p38 $\gamma$  clinically for anti-fibrosis [16]. Additionally, the Drugbank platform showed that the current experimental and investigational drugs targeting p38 $\gamma$  include Phosphonothreonine, Phosphoaminophosphonic Acid-Adenylate Ester, CEP-1347 and KC706 [65]. A number of pre-clinical and clinical trials were needed to explore more effective p38 $\gamma$  inhibitors.

The relationship between intestinal microbes and cancer is attracting immense attention in gastrointestinal cancer and cancers of other metabolic organs [66-68]. Imidazole propionate is a histidine-derived metabolite produced by microorganisms. In 2018, research by Ara Koh et al. showed that imidazole propionate could activate p38 $\gamma$  to promote the phosphorylation of p62 and activate the mechanical target of rapamycin complex 1 (mTORC1). The demonstration of this impairs insulin signal transduction at the level of insulin receptor substrates. This interaction between the intestinal flora metabolites and p38 $\gamma$  will eventually lead to the development of metabolic diseases, and potentially linked to the pathological conditions of cancer caused by the continuous activation of mTORC1 [68]. On the other hand, the signal adapter p62 is a multi-domain protein concerned with the activation of the

transcription factor NF- $\kappa$ B; the activity of p62 is closely related to the external apoptosis pathway, as well as autophagy, a key factor in tumorigenesis [69]. In 2020, further research by Ara Koh et al. found that the microbial metabolite imidazole propionate can reduce the effectiveness of metformin by interacting with the p38 $\gamma$ /AKT/AMPK metformin signaling pathway [70]. Although metformin is a major impactful drug for the treatment of type 2 diabetes, epidemiological studies have demonstrated a correlation between the application of metformin and the beneficial effects of cancer therapy [71]. In summary, p38 $\gamma$  may play as a key molecule in microbial metabolism that affects the effect of metformin on cancer. We hypothesize that the intestinal flora may regulate the pathogenesis of cancer by influencing p38 $\gamma$ .

Given that cancer is a genetic disease, gene therapy is expected to fight cancer from within with minimal side effects, and there is evidence that CRISPR-Cas9 can correct cancer-causing genome aberrations and induce the expression of tumor suppressor genes to achieve cancer gene therapy [72]. Using CRISPR-Cas9 inhibits oncogenes such as p38 $\gamma$  gene in some tumors, which may become a promising anti-cancer strategy. Researchers have used CRISPR-Cas9-induced p38 $\gamma$  knockout to inhibit the *in vitro* progression of human OS cells and the growth, proliferation and migration of human CRC cells and human RCC cells and induce significant apoptosis [34-36]. On the other hand, it is reported that CRISPR-Cas9 can be used as a powerful tool to manipulate epigenetic regulation to treat cancer and reshape abnormal epigenetic patterns and can selectively and genetically alter gene expression [73]. For example, nuclease-inactivated dCas9 is coalesced with certain epigenetic modifiers such as acetyltransferases to shape a compound, which enters the target site under the lead of a single guide RNA (sgRNA), and finally exerts an epigenetic regulation effect. This process is also known as epigenome editing [74, 75]. p38 $\gamma$  serves as the part of the corresponding gene expression product of epigenetic modification, may also be adaptive for epigenome editing therapy.

Immunotherapy has become a considerable part that cannot be ignored, including immunosuppressants targeting PD-1 for T cells and PD-L1 for tumor cells in recent years. The most cutting-edge Car-T therapy is also getting more attention. The efficacy of immunotherapy varied in individual patients and cancer diseases. The level of PD-L1 is the most influential factor to affect the anti-tumor effect of immunotherapy. Immune checkpoint inhibitors (ICIs) targeting PD-1 or PD-L1 have already greatly improved the prognosis in different cancer types and

prolong the patients' survival as well as quality of life. The approach that uses a panel of biomarkers to guide patient selection may provide an opportunity to improve patient outcomes relative to a single biomarker such as PD-L1 [76]. Based on the studies above, it may be feasible to combine the ICIs prediction biomarker represented by PD-L1 with p38 $\gamma$ .

One of the focus of anti-tumor immunotherapy is to activate CD8<sup>+</sup>T cells and maximize the function of CD8<sup>+</sup>T cells. CD8<sup>+</sup>T cells play a tumor-specific killing effect with the assistance of CD4<sup>+</sup>T cells. As CD8<sup>+</sup>T cells continues to function, immune checkpoints gradually appear on the surface of cell membranes, and bind to receptors from cancer cells, which eventually leads to the death of CD8<sup>+</sup>T cells. This is an immunosuppressive process and is also a major cause of immune escape from tumors. p38 $\gamma$  plays a basic role in the development and differentiation of T lymphocytes. The deletion of p38 $\gamma$  can facilitate the positive selection of thymocytes from CD4<sup>+</sup>CD8<sup>+</sup> double-positive cells to CD4<sup>+</sup> or CD8<sup>+</sup> single-positive cells [77]. Therefore, the clinical use of p38 $\gamma$  inhibitors may coalesce T cell immunotherapy with p38 $\gamma$  itself as an oncogene to develop more effective anti-cancer methods.

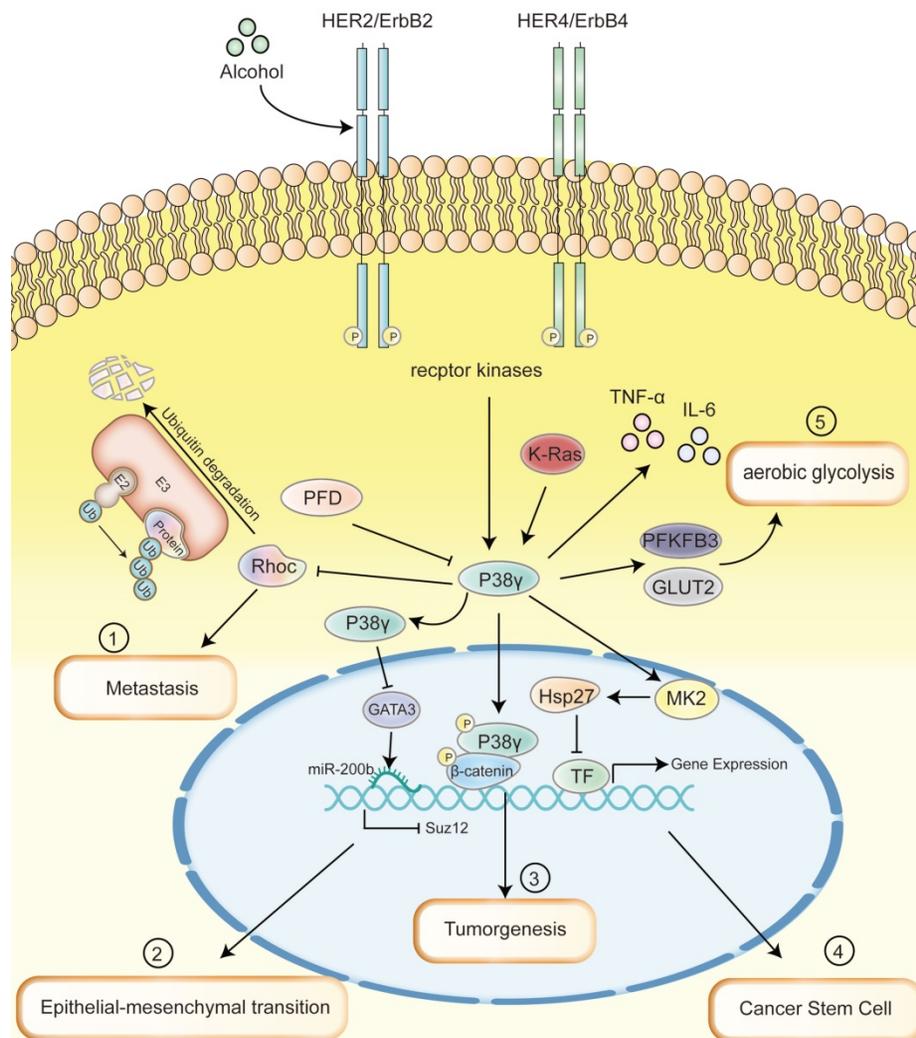
## Conclusion

While the past decade has witnessed the rapid development of cancer researches, cancer treatment methods are nothing new. Ample evidence proved that p38 $\gamma$  possesses a basic function in the oncogenesis and cancer development, including proliferation, EMT, invasion, metastasis. This heralds that p38 $\gamma$  may play an excellent function in diagnosis, treatment, and prognostic indicators in related tumor types. Despite the role of p38 $\gamma$  inhibitors in clinical tumors is not prominent, there is plenty of room for perfection. We summarized the primary impact of p38 $\gamma$  at different stages of a variety of tumors through several classic signal transduction pathways (Figure 3), besides foremost expectations. The future research orientation of p38 $\gamma$  may be based on large-scale clinical trials and further in-depth mechanisms. p38 $\gamma$  will definitely elicit audacious threads for comprehending and treating cancer.

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### Authors' contributions

HW and WTX design work, article analysis and key revisions, graphics and table design. WTX, RL, YD and SCH drafted the manuscript, review the related articles. WTX, RL, YD, SCH and HKD analyzed of final approval.



**Figure 3. Multiple signaling pathways that p38 $\gamma$  mainly involved in a range of cancer diseases.** (1) p38 $\gamma$  regulates the ubiquitination of RhoC related to metastasis to control cell movement and promote the metastasis of BC. (2) ErbB2/ErbB4/p38 $\gamma$ /GATA3/miR-200b/Suz12 pathway promotes the acquisition of the EMT phenotype, which may mediate the aggressiveness of BC. (3) The silencing of p38 $\gamma$  in intestinal epithelial cells can reduce the expression of pro-inflammatory cytokines and the activity of  $\beta$ -Catenin/Wnt pathway in colon tissue, thereby successfully linking inflammation with CRC, leading to tumorigenesis of CRC. (4) Upregulated p38 $\gamma$  can phosphorylate Hsp27 protein by activating the downstream kinase MK2, which binds to transcription factor proteins such as Sox2, Oct4, and Nanog to cause ubiquitination and degradation, thereby inhibiting the cancer stem cell characteristics and tumor initiating ability of NSCLC. (5) As the upstream of p38 $\gamma$ , K-Ras promotes the activation of p38 $\gamma$ , increases the expression of PFKFB3 and GLUT2, thus encourages aerobic glycolysis and facilitates the occurrence of PDAC. Throughout the process, cytokines such as TNF- $\alpha$  and IL-6 produced by p38 $\gamma$  link the inflammation and cancer; PFD is able to specifically inhibit the phosphorylation of p38 $\gamma$ .

## Competing Interests

The authors have declared that no competing interest exists.

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