Advances in Research Related to the p38 MAPK/PTGS2 Signaling Pathway and Pathogenesis of Laryngeal Cancer: A Review

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Laryngeal cancer is a malignant tumor of the head and neck with clinical features of high recurrence and metastasis and a poor prognosis. The pathogenesis of laryngeal cancer is not clearly understood, but it is undoubtedly a complex developmental process involving multiple pathways and genes. Finding new ways to treat laryngeal cancer is particularly important as it is the second most common cancer of the head and neck, with many post-operative complications, poor quality of life and poor outcomes for patients with mid to late-stage laryngeal cancer. The pathogenesis of laryngeal cancer is currently a hot topic of research. p38 mitogen-activated protein kinase/prostaglandin-endoperoxide synthase 2-related targets and signalling pathways have repeatedly been shown to play an important role in the development of tumours, including laryngeal cancer. With the continuous development of immunology, biochemistry and experimental techniques, it has become a current research trend to investigate the pathogenesis of laryngeal cancer at the molecular level. p38 mitogen-activated protein kinase and prostaglandin-endoperoxide synthase 2 have repeatedly been shown to play an important role in tumorigenesis and are also closely associated with the development of laryngeal cancer. This paper explores the potential association of p38 mitogen-activated protein kinase/prostaglandin-endoperoxide synthase 2 related targets and pathways with the development of laryngeal cancer in the context of the mechanisms of action of these pathways in a variety of tumors, with the aim of predicting possible targets for drug treatment of laryngeal cancer.

Key words: Laryngeal cancer, p38 mitogen-activated protein kinase, prostaglandin-endoperoxide synthase 2, matrix metalloproteinase

Head and neck tumors are the sixth most common malignant tumors in the world, in which Squamous Cell Carcinoma (SCC)[1] predominantly, accounting for approximately 90 % of cases. Laryngeal cancer ranks second among head and neck malignancies[2] and is also predominantly SCC, with an age of onset among the middle-aged and older men, due to many causative factors, including smoking, alcohol consumption, laryngopharyngeal reflux, radiation, HPV infection in the oropharynx and hormonal disorders. The treatment of laryngeal cancer focuses on surgery, including radiotherapy and chemotherapy, etc. Although the 5 y survival rate for patients with early-stage laryngeal cancer is high, reaching about 80 % to 90 %, patients with mid to late-stage laryngeal cancer have a poor survival prognosis and a high recurrence rate[3-5]. Overall, patients with laryngeal cancer have a wide range of fluctuating 5 y survival rates[6] and common complications such as hoarseness and dysphagia[7], which seriously affect their quality of life. In recent years, the incidence of laryngeal cancer has been increasing year by year[8] and a more in depth exploration of the pathogenesis of laryngeal cancer is to find more optimal treatment options to improve the prognosis of laryngeal cancer patients has become a key issue in the current treatment. The study of p38 Mitogen-Activated Protein Kinase (p38 MAPK)/Prostaglandin-Endoperoxide Synthase 2 (PTGS2) related targets and signaling pathways can help to elucidate and refine the biological characteristics of laryngeal cancer, and provide guidance for the diagnosis and treatment of laryngeal cancer and the development of laryngeal cancer drugs.

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p38 MAPK/PTGS2 SIGNALING PATHWAY:

p38 MAPK:

MAPK is an intracellular serine-threonine protein kinase that is activated by a variety of factors, including cytokines, neurotransmitters, cellular stress and cell adhesion. The MAPK signaling pathway is a three-step enzymatic cascade signaling pathway, in the order MAP Kinase Kinase Kinase (MEKK or MKKKK), MAP Kinase Kinase (MEK or MKK) and MAP Kinases (MAPKs). The MAPK signaling pathway is one of the major pathways in the integrated cell signaling network and is widely involved in the proliferation, differentiation and apoptosis of tumor cells. p38 kinase is one of the four classical signaling pathways of the MAPK pathway. The other three signaling pathways, c-Jun N-terminal Kinase (JNK), Extracellular Signal Regulated Protein Kinase (ERK) and large MAPK like Big MAP Kinase 1 (BMK1)/ERK5), can also be involved in the activation of p38 kinase.

The p38 MAPK was first discovered in 1993[9] and is a 38 kDa protein consisting of 360 amino acids in a specific order. p38 MAPK can be activated by hormones, cytokines and cellular stressors and plays a major role in inflammation, immune response and tumorigenesis[10]. There are four isoforms of p38 MAPK namely, p38 alpha (α) (MAPK14), p38 beta (β) (MAPK11), p38 gamma (γ) (MAPK12) and p38 delta (δ) (MAPK13). Among the four isoforms, p38α and p38β are widely distributed and significantly expressed *in vivo*, while p38δ is mainly located in tissues such as testis, pancreas and kidney, and p38γ is mainly expressed in muscle[11,12]. Of these, p38α is the best characterized and most studied. It is considered as a potential therapeutic target for the treatment of inflammation and cancer[13]. When cells are stimulated by external factors, Intracellular Apoptosis Signal-Regulating Kinase 1 (ASK1) is activated, which in turn activates MKK3 and MKK6. p38 MAPK can be further phosphorylated by upstream activated MKK3 and MKK6 kinases, thereby activating the p38 MAPK pathway[14,15]. Sometimes p38 can also be activated by MKK4, the activator of JNK. Activated p38 MAPK is translocated from the cytoplasm to the nucleus to regulate transcription and messenger Ribonucleic Acid (mRNA) expression of genes such as ETS like-1 protein (Elk-1), p53, Activating Transcription Factor-2 (ATF2) and other factors in the nucleus[16].

The p38 MAPK pathway can receive extracellular stimuli and translate them into cellular responses such as apoptosis, proliferation and differentiation. The effects of p38 MAPK phosphorylation status on some tumor cells are shown in Table 1 [17-21]. For example, rhodopsin and huperzine can induce apoptosis in hepatoma cells by activating the p38 MAPK pathway[17]; total alkaloids from *Phyllostachys* spp. can activate the JNK/p38 MAPK pathway leading to apoptosis in Adenocarcinomic Human Alveolar Basal Epithelial (A549) cells[18]; aloe rhodopsin can inhibit tumor angiogenesis, cell migration and invasion by activating the p38 MAPK pathway[19]. Meanwhile, it has also been shown that the p38 MAPK pathway can also be inhibited to play a therapeutic role in the disease, as per the study explained by Yan *et al.*[20], which concluded that the level of p38 MAPK phosphorylation in gastric cancer cells was significantly reduced and the motor growth of gastric cancer cells was inhibited after treatment with citicoline; Zhang[16], who concluded that the activation of the p38 MAPK/ Nuclear Factor kappa B (NF-κB) pathway could be inhibited and the levels of inflammatory factors could be downregulated to ameliorate radiation lung injury; and researcher Liao, who found that Heme Oxygenase-1 (HMOX1) knockdown decreased phosphorylated p38 (p-p38) MAPK expression and caused increased apoptosis in glioma neutrophils[21]. In conclusion, p38 MAPK has completely opposite effects on tumors in terms of promotion or inhibition, the exertion of which depends on the type and stage of cancer development[22], and plays an important role in the regulation of apoptosis, growth inhibition and differentiation, and cell cycle arrest.

PTGS2:

PTGS, also known as Cyclooxygenase (COX), is divided into two isozymes, PTGS1 and PTGS2, the former structurally expressed and the latter inducibly expressed, which are widely distributed in the body and play a key role in prostaglandin biosynthesis. Inducible expression of PTGS2 (also known as COX2), a membrane-bound, rate-limiting, short-lived enzyme whose expression is mainly induced by inflammation[23], is often considered as a target for the treatment of inflammation and pain[24]. PTGS2 is expressed at extremely low and almost negligible levels in normal tissues, but is stimulated by cytokines, inflammatory mediators, hormones and growth factors, and is overexpressed in a variety

of tumors and cancers including adenocarcinoma, SCC, metastatic cell carcinoma, Hepatocellular Carcinoma (HCC), Cholangiocarcinoma (CCA) and Endometrial Cancer (EC)[25-29]. Studies have shown that prostaglandin, the major product of PTGS2, has proproliferative, angiogenic, anti-apoptotic and inhibitory effects on immune surveillance[30].

One study found high expression of PTGS2 in oesophageal adenocarcinoma and it was shown to be an independent predictor of poor prognosis[31]. In endometrial cancer cells, PTGS2 is overexpressed and confers cellular resistance to apoptosis[32]; targeted knockdown of PTGS2 promotes apoptosis against hepatic astrocytes[33], among others. Currently, several studies[34-37] have demonstrated that COX2 is highly expressed in Laryngeal Squamous Cell Carcinoma (LSCC) tissues and its expression is closely related to and inversely correlated with the prognosis, pathological stage, and lymph node metastasis of LSCC.

p38 MAPK/PTGS2 SIGNALING PATHWAY AND LARYNGEAL CANCER:

The p38 MAPK signaling pathway plays an important role in promoting proliferation, invasion and metastasis of head and neck tumors and is highly expressed[38,39]. Members of the MAPK family induce PTGS2 expression and p38 MAPK is an upstream signaling molecule of COX2[40,41]. Our group also found that the MAPK signaling pathway in the preliminary network pharmacological analysis is one of the main pathways in the regulation of Head and Neck Squamous Cell Carcinoma (HNSCC) by the tonic formula, and PTGS2 is one of the top five key target proteins in the pharmacological mechanism of the network regulation of HNSCC by the tonic formula[42]. Matrix Metalloproteinase 9 (MMP-9) is a member of the MMP family involved in angiogenesis. Kang reported that Hepatocyte Growth Factor (HGF) can upregulate COX-2 expression through the p38 MAPK pathway, which leads to increased MMP-9 expression and induces breast cancer cell invasion[43]. Yang *et al.* found that microRNA (miR) may be an upstream regulatory molecule of the p38 MAPK/COX2 pathway in cardiovascular diseases[44]. COX2 overexpression in tumor cells increases prostaglandin production, induces high downstream B-cell lymphoma 2 (Bcl-2) expression and low Transforming Growth Factor (TGF)-beta (β) type II Receptor (TβRII) expression, and ultimately leads to enhanced tumor aggressiveness. COX2 promotes tumor cell proliferation, metastasis, increases cancer recurrence rate and even correlates with cancer cell resistance to radiotherapy drugs[45], which is highly significant in the development of tumor cancer. In recent years, clinical Immune Checkpoint Inhibitors (ICI) using Programmed Death-1 (PD-1) antibodies has shown breakthrough improvements in the treatment of a variety of cancers, but most patients with HNSCC have had little success. Research into the pathogenesis of LSCC, the discovery of new target genes and the development of targeted drugs for HNSCC has become urgent issues.

Intercellular signaling is cross-coupled and complex, and AKT Serine/Threonine Kinase 1 (AKT1) can phosphorylate Inhibitor of NF-κB kinase subunit beta (IκB) and release the pro-inflammatory transcription factor NF-κB, leading to NF-κB activation. The p38 MAPK can act both directly on PTGS2 and indirectly by activating downstream NF-κB, thereby activating PTGS2[46,47]. At the same time, NF-κB can bind to the NF-κB consensus element in the upstream promoter region of PTGS2 to counteract PTGS2 and promote its transcription[48]. The upstream and downstream regulatory relationships of the p38 MAPK/PTGS2 signaling pathway is shown in fig. 1.

TABLE 1: EFFECT OF p38 MAPK PHOSPHORYYLATION STATUS ON TUMOR CELLS

p38 MAPK phosphorylation status	Effects on tumor cells	Reference
Activation	Promoting apoptosis of liver cancer cells	[17]
	Promoting apoptosis of lung cancer cell A549	[18]
	Inhibiting of angiogenesis, migration and invasion of colorectal cancer cells	[19]
	Inhibiting the growth and movement of gastric cancer cells	[20]
Inhibition	Promoting apoptosis of neutrophils in glioma	[21]

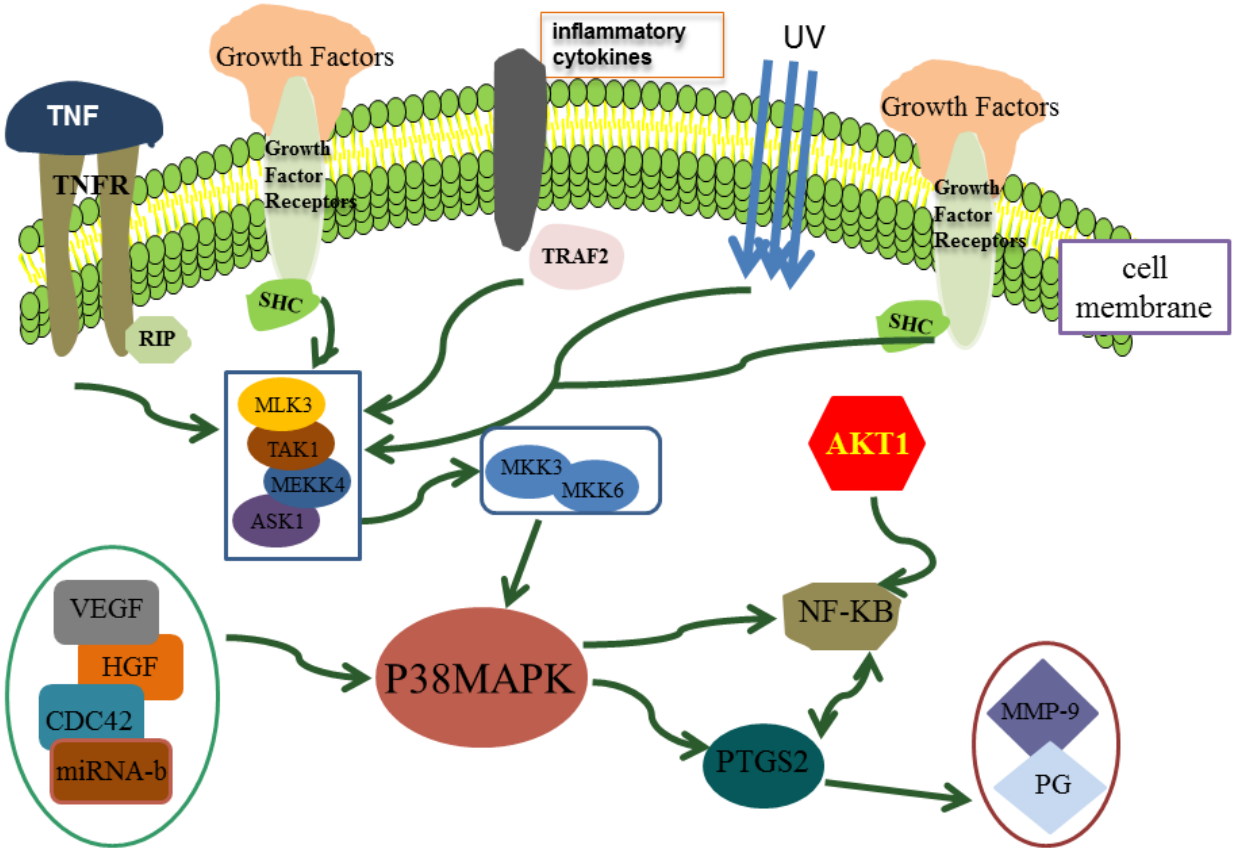

Fig. 1: Diagram of upstream and downstream regulation of p38 MAPK/PTGS2 signaling pathway

The interaction between p38 MAPK and PTGS2 not only facilitates angiogenesis and promotes invasiveness of cancer cells[49], but is also associated with the resistance of cancer cells to apoptosis[50]. According to this study, the p38 MAPK/PTGS2 signaling pathway plays a direct role in the proliferation, invasion and apoptosis of laryngeal cancer cells. Although its mechanism of action in the development of laryngeal cancer has not been fully elucidated, studies such as its upstream and downstream regulatory relationships in other cancers can still provide ideas and directions for the study of laryngeal cancer in this pathway.

CONCLUSION

Modern medicine focuses not only on efficacy, but also on humanistic care for patients, putting people first and respecting life. Therefore, it has become a major challenge for otolaryngologists to improve the clinical outcome of patients with mid to late-stage laryngeal cancer, to reduce the complications associated with surgery in laryngeal cancer patients and to improve their quality of life. p38 MAPK and PTGS2 are highly expressed in laryngeal cancer cells and are closely associated with proliferation, invasion and apoptosis of laryngeal cancer cells. This study has initially described the potential associations between the p38 MAPK/PTGS2 pathway and the development of laryngeal cancer, but experimental validation is still lacking. Further studies will be carried out in the future with the aim of understanding the pathogenesis of laryngeal cancer at the molecular level, which will provide a basis for overcoming the difficulties in developing targeted drugs for laryngeal cancer and finding targeted drugs for laryngeal cancer as soon as possible.

Conflict of interests:

The authors declared no conflict of interest.

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