

## Review

## Regulatory effect of traditional Chinese medicines on signaling pathways of process from chronic atrophic gastritis to gastric cancer

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## ABSTRACT

Chronic atrophic gastritis (CAG), a common disease of digestive system, is an extremely important cause of gastric cancer (GC). The occurrence and development of CAG involves the abnormality of multiple signaling pathways. Traditional Chinese medicines (TCMs) has the advantages of mild action, multi-target and small adverse reaction, etc., which broadens the way for the treatment of the disease, and TCMs can play a therapeutic role by regulating multiple signaling pathways. In this review, based on the related experiments of TCMs and Chinese herbal compounds in recent years, the related literatures were searched and 10 kinds of signaling pathways involved were summarized, in order to provide a reference for further research on reversing or delaying the progress of CAG and preventing gastric cancer.

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## 1. Introduction

Gastric cancer (GC) is the fifth most common cancer and the third most common cause of cancer death globally. Mortality rates for GC continue to be high, with survival rates around 30% worldwide. GC is a multifactorial disease, where many risk factors can influence its development, both environmental and genetic including *Helicobacter pylori* infection, age, high salt intake, and diets low in fruit and vegetables (Smyth et al., 2020). The most popular classification of GC displays as two subtypes, intestinal and diffuse. The intestinal subtype encompasses tubular and glandular elements, with multiple degrees of differentiation. The diffuse subtype displays poorly cohesive single cells without gland formation. Additionally, GC with signet ring cells is relatively prevalent, being classified as a “diffuse type”. Currently, signet ring cell carcinoma is described as a weakly cohesive type of cancer, consisting mostly of tumor cells with prominent cytoplasmic mucin and an eccentrically placed crescent-shaped nucleus (Eusebi et al., 2020; Machlowska et al., 2020).

Chronic atrophic gastritis (CAG) is a chronic condition characterized by the replacement of the original gastric glands by intestinal metaplasia (IM), pseudopyloric metaplasia, and/or fibrosis (Lahner et al., 2020). When CAG involves the corpus oxyntic glands, impaired gastric acid and intrinsic factor secretion may lead to iron and/or vitamin B<sub>12</sub> deficiency anemia as a consequence of micronutrient malabsorption (Botezatu & Bodrug, 2021). The histopathological cascade for the development of intestinal GC, also called Correa cascade of gastric carcinogenesis, is a stepped process: from normal gastric epithelium to chronic non-atrophic gastritis, CAG, IM, dysplasia and CG (Banks et al., 2019). Thus, patients with premalignant gastric lesions (CAG, IM and dysplasia) have a considerable risk of developing GC, early detection of these lesions being important for early treatment and screening for GC.

Communication between and inside cells as well as their response to external stimuli relies on elaborated systems of signal transduction. They all require a directional transmission across membranes, often realized by primary messenger docking onto external receptor units and subsequent internalization of the signal in form of a released second messenger (Oya, Hayakawa, & Koike, 2020). This in turn starts a cascade of events which ultimately control all functions of the living cells. Although signal transduction is a fundamental biological process realized by supramolecular recognition and multiplication events with small molecules, more elaborated systems step by step incorporate more elements of cell signaling, such as primary and secondary messenger or a useful cellular response such as cargo release (Bekus & Schrader, 2020). The development of CAG often involves the abnormality of multiple signal transduction pathways, involving immune and inflammation-related signaling pathways as well as regulating apoptosis-related signaling pathways. The signal will transmit extracellular information into the cell as cells exposed to external stimuli, thereby leading to the transcription of relevant target genes, and regulating the activities of the cells (Hu et al., 2021). Modulating signal transduction pathways plays a key role in the prevention of GC or reversal of CAG.

There is currently no specific medicine for gastric cancer, nevertheless, traditional Chinese medicines (TCMs) has obvious advantages in the treatment of CAG due to its characteristics including multi-component, multi-target and compatibility based on the treatment principle of syndrome differentiation and classification (Yang et al., 2020). In terms of clinical medication, TCMs lay more emphasis on the overall adjustment of patients' internal *qi* movement and viscera functions. While improving the clinical symptoms and enhancing the living quality of patients, TCMs can inhibit and reverse the continuous development of CAG into GC, and has a significant preventing effect on IM and DYS. Moreover,

studies have shown that the active components and compounds of TCMs have a reversal effect on multi-drug resistant cells of GC (Yang & Shu, 2013). We summarized the regulatory effects of TCMs on signal transduction pathways of CAG and GC (Table 1), which have been studied extensively in recent years.

We summarized regulation of the common signal transduction pathways of the CAG and GC as Fig. 1, providing a new basis for the treatment of CAG or the prevention of GC with TCMs. The development of more effective agents and the identification biomarkers that can be used for the diagnosis, prognosis, and therapy of patients who might benefit from specific targeted therapies can be elucidated.

## 2. Common signaling pathways involved in CAG and GC

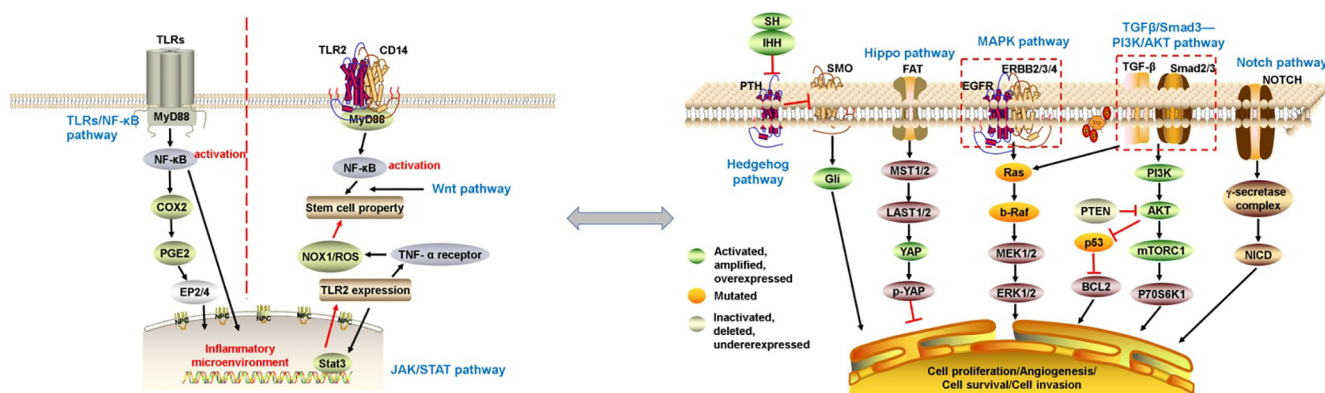
### 2.1. NF- $\kappa$ B signaling pathway

The NF- $\kappa$ B family mainly includes five members, including RelA (p65), c-Rel, RelB, NF- $\kappa$ B1 (p50) and NF- $\kappa$ B2 (p52), which could form stable homo- and heterodimeric complexes. As reported, NF- $\kappa$ B would be activated by certain factors to participate in the occurrence and development of diseases through various reactions, such as inflammation, apoptosis, and stress (Jiang, Liu, & Liu, 2021). Under the static state, NF- $\kappa$ B-p65 binds to the inhibitory protein I $\kappa$ B in the cytoplasm. When cells are stimulated, I $\kappa$ B degrades, whereupon p65 is released and transferred into the nucleus, combining with specific sites on DNA, promoting the release of inflammatory factors and gene expression, and accelerating the process of CAG (Yang, Cai, & Mao, 2004). It is reported that a direct contact of *H. pylori* with transformed gastric epithelial cells induced fast activation of NF- $\kappa$ B, nuclear translocation of p50/RelA and p50/p50 dimers, and strong accumulation of IL-8 mRNA. Further, a major role of NF- $\kappa$ B and a contributory role of AP-1 transcription factor in regulation of cancer progression was shown (Sokolova & Naumann, 2017). Key targets as well as upstream and downstream relationships in NF- $\kappa$ B signaling pathway are shown in Fig. 2.

Baicalein is one of the main active components of *Scutellaria baicalensis* Georgi, which belongs to phenolic antioxidant. Atractyloides lactone I is an effective monomer composition of *Atractylodes macrocephala* Koidz. These two components can inhibit the release of IL-8, reduce the NF- $\kappa$ B and COX-2 synthesis, improve HSP70 synthesis, and cut off the long-term and repeated damage of gastric mucosa caused by inflammatory factors and have a therapeutic effect on CAG (Li, Yu, Gao, & Liu, 2016; Tian, Wang, & Zhang, 2015). Paeoniflorin and clematolide were respectively extracted from *Paeonia lactiflora* Pall and *Clematis florida* Thunb, which can induce the apoptosis of tumor cells by inhibiting the expression and activity of NF- $\kappa$ B p65 protein in the nucleus, thus playing the preventive and therapeutic role of CAG (Dai, Fang, & Liu, 2010; Wu, Li, Ge, & Liu, 2008). XIAP, a sort of NF- $\kappa$ B-related regulatory genes, is the strongest endogenous apoptotic inhibitory protein. It was found that capsaicin can inhibit the occurrence and development of CAG by inhibiting the NF- $\kappa$ B pathway and down-regulating the expression of IKK $\beta$ , NF- $\kappa$ B and XIAP (Zhou & Zhang, 2015). Studies by Lin et al. (2016) showed that Weiweikang Granule (*Panax quinquefolii* Radix, *Atractylodes Macrocephalae* Rhizoma, *Paeoniae Radix Alba*, *Notoginseng Radix et Rhizoma*, *Corydalis Rhizoma*, *Fel Ursi*, *Glycyrrhizae Radix et Rhizoma*) inhibited the signal transduction mediated by NF- $\kappa$ B, thus preventing the release of IL-6 and increasing the release of IL-10, so as to prevent the damage caused by inflammatory cells to gastric mucosa and achieve the purpose of treating CAG. Anwei Decoction (*Coptidis Rhizoma*, *Zingiberis Rhizoma*, *Pinelliae Rhizoma*, *Lilii Bulbus*, *Paeoniae Radix Alba*, *Linderae Radix*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Coicis Semen*, *Aucklandiae Radix*, *Glycyrrhizae Radix et Rhizoma*) can signif-

**Table 1**  
Studies of TCMs on regulating signaling pathways of CAG and GC.

| Diseases                | Chinese herbal prescriptions/ medicinal materials/ active ingredients | Signaling pathways                | Target proteins                             | References                           |                            |
|-------------------------|---|-----------------------------------|---|--------------------------------------|----------------------------|
| CAG                     | Baicalein   | NF-κB                             | IL-8, NF-κB p65, COX-2, HSP70               | (Li, Yu, Gao, & Liu, 2016)           |                            |
|                         | Attractylodes lactone I   | NF-κB                             | NF-κB p65, COX-2, HSP70                     | (Tian, Wang, & Zhang, 2015)          |                            |
|                         | Paeoniflorin  | NF-κB                             | NF-κB p65                                   | (Dai, Fang, & Liu, 2010)             |                            |
|                         | Clematoside   | NF-κB                             | NF-κB p65                                   | (Wu, Li, Ge, & Liu, 2008)            |                            |
|                         | Weiwikang Ganule  | NF-κB                             | NF-κB p65, IL-6, IL-10                      | (Lin, Yu, Zhai, & Zhao, 2016)        |                            |
|                         | Anwei Decoction   | NF-κB                             | NF-κB p65, Bcl-2                            | (Wei, Zhu, Lin, & Cheng, 2014)       |                            |
|                         | Xiangsha Liujunzi Decoction   | NF-κB                             | NF-κB p65, IL-1, TNF-α                      | (Cheng et al., 2017)                 |                            |
|                         | Qinghuayin Decoction  | NF-κB                             | NF-κB, COX-2                                | (Huang et al., 2015)                 |                            |
|                         | Qizhu Erzhu Ercao Decoction   | NF-κB                             | NF-κB/p65, Cyclin E                         | (Li, Xu, & Shan, 2015)               |                            |
|                         | <i>Polygonum capitatum</i> Buch. Ham. ex D. Don                       | PI3K/AKT/mTOR                     | PTEN  | (Jiang et al., 2018)                 |                            |
|                         | Anwei Decoction   | PI3K/AKT/mTOR                     | PTEN, PI3K, PDK1, AKT, XIAP                 | (Wei et al., 2018)                   |                            |
|                         | Ershen Sancao Decoction   | PI3K/AKT/mTOR                     | AKT, ERK, PTEN                              | (Huang & Zhou, 2016)                 |                            |
|                         | Jianpi Yiqi Decoction   | Wnt/β-catenin                     | β-catenin, Wnt3a, c-myc, GSK-3β             | (Chen, 2017; Liu, 2017)              |                            |
|                         | Anwei Decoction   | JAK/STAT                          | JAK1, STAT3, c-myc, SOCS-3                  | (Wei et al., 2017)                   |                            |
|                         | Ganweibaihe Decoction   | JAK/STAT                          | IL-2, IFN-γ, IL-4, IL-10                    | (Mao, 2017)                          |                            |
|                         | Shuangpu Powder   | TGF-β/Smad                        | Bcl-2, P53, PCNA, Ag-NORs, EGF, TGF-β1      | (Yang et al., 2016)                  |                            |
|                         | GC  | Astragaloside                     | TLRs  | MyD88, TLR4, SOD                     | (Zhang, Zhou, & Liu, 2013) |
|                         |   | <i>Periplaneta americana</i>      | TLRs  | TLR4, MyD88, NF-κB p65               | (Zhou & Yuan, 2017)        |
|                         |   | <i>Polygonum capitatum</i>        | TLRs  | TLR2, TLR4, TLR5, TLR9, MyD88, TRAF6 | (Jiang et al., 2019)       |
|                         |   | Jianpi Qinghua Decoction          | TLRs  | TLR4, MyD88, NF-κB, COX-2            | (Huang et al., 2016)       |
| Banxia Xiexin Decoction |   | Notch                             | Notch1, Notch2, Hes1, Jagged1               | (Bai et al., 2019)                   |                            |
| curcumin                |   | PI3K/AKT/mTOR                     | PI3K, p-Akt                                 | (Chen, Huang, & Gao, 2016)           |                            |
| Celastrol               |   | PI3K/AKT/mTOR                     | miR-21                                      | (Liu, Tan, Fang, Zhan, & Wang, 2017) |                            |
| Dihydroartemisinin      |   | Wnt/β-catenin                     | Dvl2, p-GSK3β, β-catenin, Cyclin D1, GSK-3β | (Liu & Mei, 2018)                    |                            |
| Weipixiao Decoction     |   | Wnt/β-catenin                     | Lgr5, MMP-7, Wnt1, β-catenin                | (Zeng et al., 2016)                  |                            |
| Fufang Xiyi Pulvis      |   | Wnt/β-catenin                     | Wnt2 and β-catenin                          | (Li et al., 2015)                    |                            |
| Shenqi Yizhu decoction  |   | Wnt/β-catenin                     | p-GSK3β, β-catenin                          | (Xu & Lu, 2018)                      |                            |
| Zuojin Wan Pilula       |   | Wnt/β-catenin                     | MMP-7                                       | (Zhang et al., 2015)                 |                            |
| Curcumin                |   | JAK/STAT                          | HSP90                                       | (Li & Chen, 2019)                    |                            |
| Ursolic acid            |   | JAK/STAT                          | COX-2, procaspase-3                         | (Tang et al., 2012)                  |                            |
| Xinwei Granule          |   | JAK/STAT                          | STAT3                                       | (Xie, Sun, & Liang, 2013)            |                            |
| Astragaloside IV        |   | Hedgehog                          | Cyclin D1, Shh, Ptch, Gli-1                 | (Zhao et al., 2016)                  |                            |
| Ginsenoside Rg1         |   | Hedgehog                          | Shh, Ptch, Gli-1                            | (Zhao et al., 2017)                  |                            |
| Dihydrotanshinone       |   | Hedgehog                          | MMP2, MMP9, p53, FoxO3, STAT3               | (Cheng, Lou, Ge, Shi, & Zhang, 2017) |                            |
| Curcumin                |   | Hedgehog                          | Shh, Gli-1                                  | (Sun, & Liu, 2012)                   |                            |
| Silymarin               |   | MAPK                              | Bax, p-JNK and p-p38, Bcl-2, p-ERK1/2       | (Kim et al., 2019)                   |                            |
| Resveratrol             | MAPK  | IL-6                              | (Yang et al., 2018)                         |                                      |                            |
| Lycopene                | MAPK  | ROS, EGFR, COX2                   | (Han, Lim, & Kim, 2019)                     |                                      |                            |
| Triptonide              | Notch   | Notch1, RBPJ, IKKα, IKKβ, p-NF-κB | (Xiang et al., 2019)                        |                                      |                            |



**Fig. 1.** Pathways that represent potential targets for the treatment of chronic atrophic gastritis and gastric cancer.

icantly reduce the expression of Bcl-2 and NF-κB in gastric mucosa and blood, regulate and promote cell apoptosis, and enhance the defense and repair function of mucosal barrier, so as to achieve the purpose of treating CAG (Wei, Zhu, Lin, & Cheng, 2014). Xiangsha Liujunzi Decoction (*Ginseng Radix et Rhizoma, Attractylodis Macrocephalae Rhizoma, Poria, Citri Reticulatae Pericarpium, Pinelliae*

*Rhizoma, Amomi Fructus, Aucklandiae Radix, Zingiberis Rhizoma Recens, Glycyrrhizae Radix et Rhizoma*) can protect gastric mucosal tissues and functions by down-regulating the expression of NF-κB p65 gene and protein, thereby inhibiting the abnormal secretion of pro-inflammatory factor IL-1 and TNF-α, and reducing the inflammatory cascade amplification (Cheng et al., 2017).

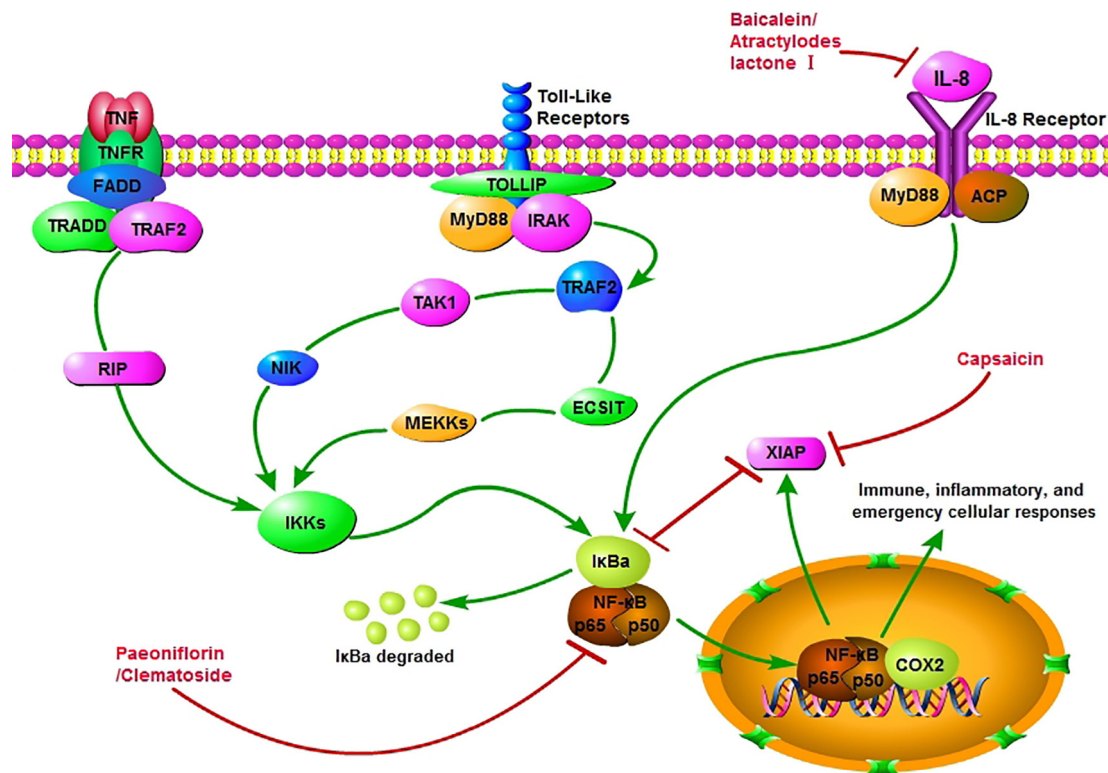


Fig. 2. Interaction of key factors upstream and downstream in NF-κB signaling pathway.

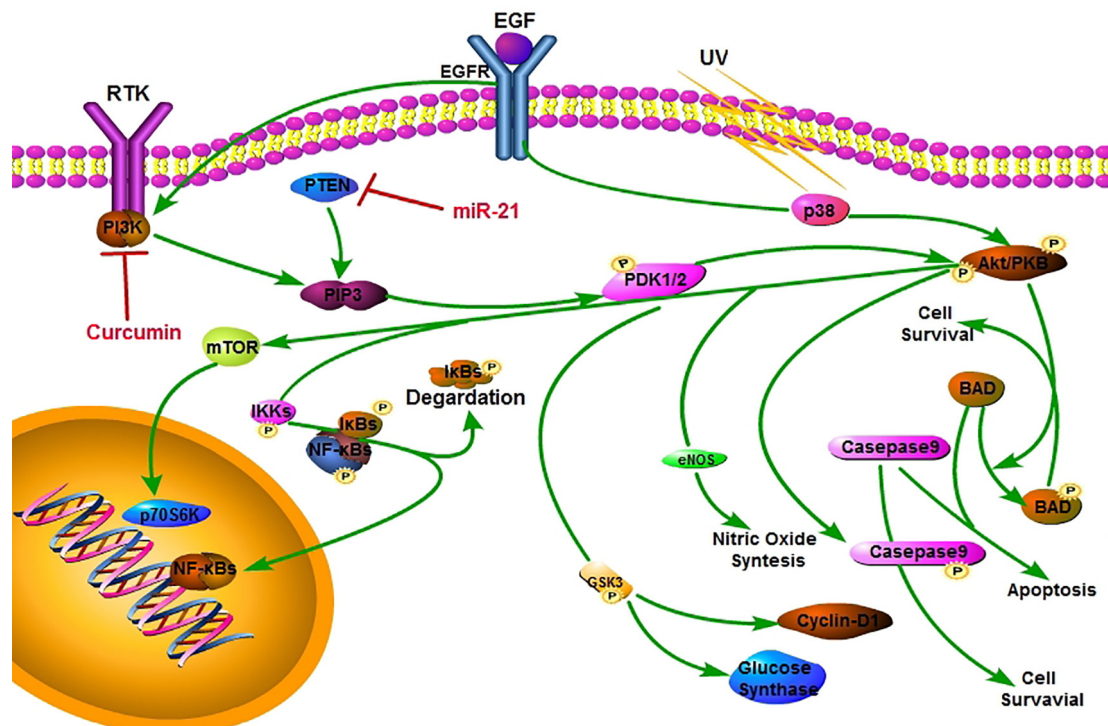


Fig. 3. Interaction of key factors upstream and downstream in PI3K/AKT signaling pathway.

Qinghuayin Decoction (*Artemisiae Scopariae Herba*, *Atractylodis Rhizoma*, *Coptidis Rhizoma*, *Magnoliae Officinalis Cortex*, *Paeoniae Radix Rubra*, *Pogostemonis Herba*, *Amomi Fructus Rotundus*, *Coicis Semen*) regulated the abnormal immune response in the gastric mucosa

of CAG and promoted the recovery of the gastric mucosal barrier via inhibiting the activation of NF-κB, down-regulating the high expression of COX-2, reducing the release of pro-inflammatory factors, and thereby blocking and reversing the process of gastric



mucosal gland atrophy and canceration (Huang et al., 2015). Moreover, Qizhu Erzhu Ercao Decoction (*Astragali Radix*, *Polygonati Odorati Rhizoma*, *Ophiopogonis Radix*, *Atractylodis Macrocephalae Rhizoma*, *Pinelliae Rhizoma*, *Coicis Semen*, *Scutellariae Radix*, *Agrimoniae Herba*, *Fritillariae Thunbergii Bulbus*, *Curcumae Rhizoma*, *Hedyotidis Diffusae Herba*) has also been shown to reverse the precancerous lesions of atrophic gastritis, and its mechanism may be to inhibit the expression of NF- $\kappa$ B/p65 and Cyclin E, so as to prevent the occurrence and development of tumors (Li, Xu, & Shan, 2015).

## 2.2. PI3K/AKT/mTOR signaling pathway

PI3K/AKT/mTOR pathway exerts a vast number of functions in different diseases and cancer progression. It is implicated in apoptosis, autophagy, and survival of many types of cancer including gastric cancer (GC). PI3K/AKT/mTOR pathway is a major negative regulator of autophagy. Activation of this pathway through activation of the mammalian target of rapamycin (mTOR) can promote cell proliferation by inhibiting autophagy (Cao et al., 2019). PI3K/AKT signaling is of crucial importance for chemoresistance, and contributes to epithelial-mesenchymal transition (EMT) which occurs in drug-resistant and metastatic human cancer cells. Mounting evidence has shown so far some micro RNAs (miRNAs) showed different expression pattern between GC chemoresistant cell lines and controls, and can therefore be involved in chemotherapy resistance (Wang, Shen, & Hu, 2018). Histone modification, DNA methylation, and non-coding RNAs are three main epigenetic players that act on PI3K-AKT-mTOR pathway, and have been associated with cell invasion, autophagy, and apoptosis regulation in GC (Fattahi et al., 2020). Key targets as well as upstream and downstream relationships in PI3K/AKT signaling pathway are shown in Fig. 3.

Studies have found that curcumin can reduce the expression levels of PI3K and p-Akt mRNA, suggesting that curcumin inhibited proliferation and induced apoptosis of gastric cancer cells by down-regulating the PI3K/AKT signaling pathway (Chen, Huang, & Gao, 2016). *Polygonum capitatum* Buch.-Ham. ex D. Don, mainly containing flavonoids, is a kind of ethnodrug from the Miao nationality in China, which can inhibit the activation of PI3K/AKT pathway via upregulating the expression of PTEN protein, thereby improving the gastric mucosa inflammation caused by *H. pylori* (Jiang et al., 2018). Celastrol can down-regulate the expression of miR-21 in gastric cancer cells, inhibit the PI3K/AKT-NF- $\kappa$ B signaling pathway, and induce the apoptosis of gastric cancer cells (Liu, Tan, Fang, Zhan, & Wang, 2017). In addition, some reports pointed out that dihydroartemisinin, baicalin, ginsenoside Rg<sub>3</sub>, gallic acid, resveratrol can suppress the growth of gastric cancer cells as well, the mechanism of which may be related to the regulation of the PI3K/AKT signaling pathway (Nian, Wang, Fu, & Yang, 2019; Ma & Li, 2020). Anwei Decoction can improve the expression of PTEN gene and protein, down-regulate the expression of PI3K, PDK1, AKT and XIAP, inhibit the PI3K/AKT signaling pathway and promote the apoptosis of gastric mucosal cells in CAG rats (Wei et al., 2018). Ershen Sancao Decoction (*Pseudostellariae Radix*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Agrimoniae Herba*, *Hedyotidis Diffusae Herba*, *Glycyrrhizae Radix* et *Rhizoma*, *Astragali Radix*, *Atractylodis Macrocephalae Rhizoma*, *Coicis Semen*) can restrain the expression of oncogene-AKT, ERK and up-regulate the expression of tumor suppressor gene-PTEN, induce the apoptosis of precancerous cells, inhibit the overgrowth of cells, improve the state of cell proliferation, reverse atrophy and intestinal metaplasia, and restore the normal gastric mucosa, so as to prevent precancerous lesions of CAG from going forward to gastric cancer (Huang & Zhou, 2016). Jianpi Yiqi Decoction (*Codonopsis Radix*, *Atractylodis Macrocephalae Rhizoma*, *Poria*, *Glycyrrhizae Radix* et *Rhizoma*, *Citri*

*Reticulatae Pericarpium*, *Pinelliae Rhizoma*, *Aucklandiae Radix*, *Amomi Fructus*, *Curcumae Rhizoma*, *Hedyotidis Diffusae Herba*, *Muscovite*, *Curcumae Radix*), derived and modified from Xiangsha Liu-Junzi Decoction, can significantly improve gastric mucosa atrophy in CAG rats, which is closely related to the suppression of PI3K/AKT signaling pathway (Yan et al., 2019).

## 2.3. Wnt/ $\beta$ -catenin signaling pathway

The Wingless-related integration site (Wnt)/ $\beta$ -catenin signaling pathway regulates crucial cellular processes including cell fate determination, organogenesis during embryonic development, normal adult homeostasis, motility, polarity and stem cell renewal. The unbalance of physiological signaling pathways due to the acquisition of mutations in tumour cells is considered the most common cancer driver (Koni, Pinnarò, & Brizzi, 2020). The Wnt/ $\beta$ -catenin pathway is crucial for tissue development and homeostasis in all animal species and its dysregulation is one of the most relevant events linked to cancer development and dissemination. The Wnt cascade has been subdivided into different branches due to its complexity. The canonical and the non-canonical Wnt/ $\beta$ -catenin pathways are known to control both physiological and pathological processes, including cancer (Echizen, Hirose, Maeda, & Oshima, 2016). Key targets as well as upstream and downstream relationships in Wnt signaling pathway are shown in Fig. 4.

Studies showed that artemisinin (ART) exerts anti-tumor effects via inducing cell apoptosis, anti-angiogenesis and oxidative stress. Dihydroartemisinin (DHA, ramification and active metabolites isolated from artemisinin) can down-regulate the expression of Dvl2, p-GSK3 $\beta$ ,  $\beta$ -catenin, Cyclin D1, and up-regulate the expression of GSK-3 $\beta$  protein, thereby reducing the proliferation, invasion and migration of gastric cancer cells (Liu & Mei, 2018). Wogonin is the main active component of *S. baicalensis* with antioxidative, anti-inflammatory and immunomodulatory effects. It can significantly reduce the protein levels of  $\beta$ -catenin, c-myc and Cyclin D1 and restrain proliferation, migration, and invasion of gastric cancer cells (Wang, Wei, & Cheng, 2016). Jianpi Yiqi Decoction down-regulated the level of  $\beta$ -catenin, Wnt3a, c-myc, and up-regulated the level of GSK-3 $\beta$ , thus promoting the differentiation and apoptosis of gastric mucosal cells and affecting the formation of gastric mucosal atrophy (Chen, 2017; Liu, 2017). Weiwei Decoction combined with cimetidine and Rongwei Liqi Decoction (*Cyperii Rhizoma*, *Amomi Fructus*, *Citri Reticulatae Pericarpium*, *Pinelliae Rhizoma*, *Pseudostellariae Radix*, *Atractylodis Macrocephalae Rhizoma*, *Glycyrrhizae Radix* et *Rhizoma*, *Corium Erinacei*) combined with joint gecko can effectively improve the pathological state of gastric mucosa atrophy in CAG model rats, promote gastric mucosa microvascular neogenesis, suppress gastric mucosa oxidative stress reaction, restore the impaired gastric mucosa and ameliorate gastric mucosal acid function. The mechanism may be connected with regulating the abnormal expression of GSK-3 $\beta$ ,  $\beta$ -catenin, Cyclin D1 and COX-2 in gastric mucosa, thus blocking the abnormal activation of the Wnt pathway (He, 2017; Li & Li, 2019). A study indicated that dysregulation of Wnt/ $\beta$ -catenin pathway might be involved in the pathogenesis of the process from CAG to GC. Weipixiao Decoction (*Astragali Radix*, *Pseudostellariae Radix*, *Atractylodis Macrocephalae Rhizoma*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Hedyotidis Diffusae Herba*) inhibited expressions of Lgr5, MMP-7, Wnt1,  $\beta$ -catenin and aberrant activation of Wnt/ $\beta$ -catenin pathway, which might be one of mechanisms involved in suppressing or reversing gastric carcinogenesis (Zeng et al., 2016). Fufang Xiyi Pulvis (*Eremias multiocellata*, *Astragali Radix*, *Mume Fructus*, *Paeoniae Radix Alba*, *Salviae Miltiorrhizae Radix* et *Rhizoma*, *Scutellariae Barbatae Herba*) different particle combination agent can effectively reduce the positive expression of Wnt2 and  $\beta$ -catenin, regulate cell proliferation and apoptosis, reverse

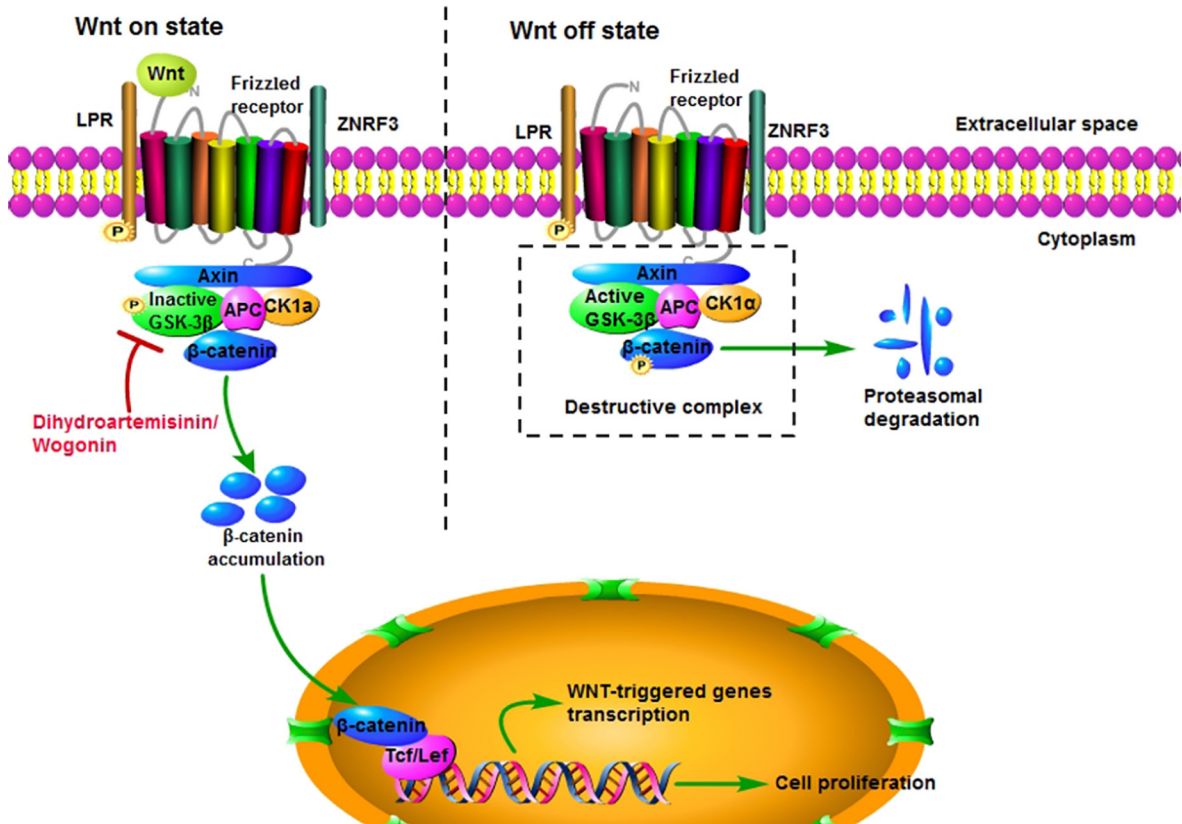


Fig. 4. Interaction of key factors upstream and downstream in Wnt signaling pathway.

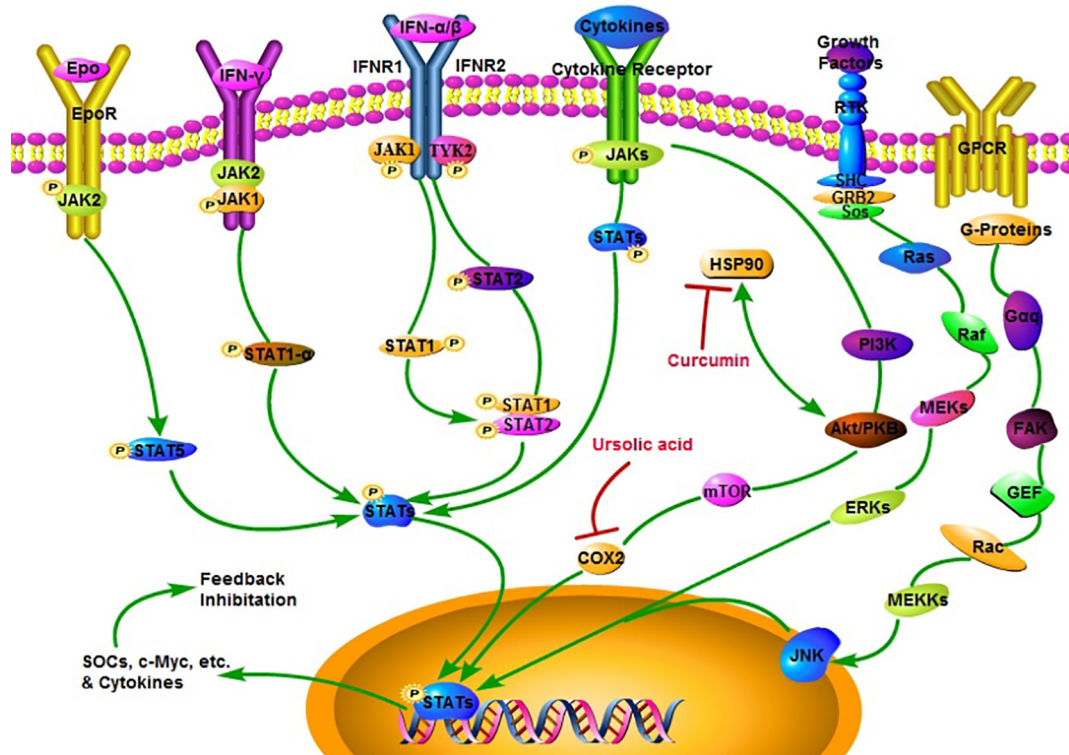


Fig. 5. Interaction of key factors upstream and downstream in JAK/STAT signaling pathway.

gastric mucosal hyperplasia and intestinal metaplasia in PLGC model rats, and better intervene the carcinogenesis process (Li et al., 2015). Shenqi Yizhu Decoction (*Codonopsis Radix*, *Glycyrrhizae Radix et Rhizoma*, *Atractylodis Macrocephalae Rhizoma*, *Curcumae Rhizoma*, *Coicis Semen*, *Poria*, *Astragali Radix*) could significantly inhibit the expression of p-GSK3 $\beta$ ,  $\beta$ -catenin and Vimentin, the key proteins of Wnt/ $\beta$ -catenin pathway, and inhibit the development of gastric cancer by regulating the Wnt/ $\beta$ -catenin signaling pathway (Xu & Lu, 2018). Zuojin Pilula (*Coptidis Rhizoma*, *Euodiae Fructus*), a traditional Chinese herbal formula, can prevent and treat gastric cancer cell metastasis induced by *H. pylori*, and the mechanism may be related to the inhibition of MMP-7 expression via Wnt/ $\beta$ -catenin signaling pathway (Zhang et al., 2015).

#### 2.4. JAK/STAT signaling pathway

JAK/STAT cascade is a principal signal transduction pathway in cytokine and growth factor signaling, regulating various cellular processes such as cell proliferation, differentiation, migration and survival. Numerous *in vivo* and *in vitro* studies have shown that dysregulated JAK/STAT signaling is a driving force in the pathogenesis of various solid cancers as well as hematopoietic malignancies. Interestingly, aberrant activation of the JAK/STAT pathway has also been described to contribute to the process of gastric tumorigenesis (Khanna, Chua, Bay, & Baeg, 2015). Inhibition of STAT3 has consistently resulted in a significant decrease in the levels of the anti-apoptotic protein Survivin, leading to a decrease in gastric cancer cell survival (Bockerstett & DiPaolo, 2017). There is crosstalk between the NF- $\kappa$ B and JAK/STAT signaling pathways. The transcription factors NF- $\kappa$ B and STAT3 are activated by cytokines and regulate (sometimes jointly) the transcription of genes involved in apoptosis, proliferation, and other cellular processes. In GC, NF- $\kappa$ B and STAT3 act as oncogenes, enhancing the metastatic potential of tumor cells and contributing to the development and progression of the tumor (Kipkeeva et al., 2020). Key targets as well as upstream and downstream relationships in JAK/STAT signaling pathway are shown in Fig. 5.

Curcumin significantly inhibited the mRNA transcription and protein expression levels of HSP90 in gastric cancer cells, suggesting that curcumin could inhibit the activation of Hsp90-JAK/STAT3 signaling pathway to limit the invasion and migration of gastric cancer cells (Li & Chen, 2019). Ursolic acid (widely found in *Hedyotis diffusa* Willd., *Ligustri Lucidi Fructus*, *Prunus mume* (Sieb.) Sieb. et Zuce and *Prunella vulgaris* L.) inhibited the proliferation and induced apoptosis of gastric cancer cells by blocking the STAT3 pathway and down-regulating the expression of COX-2 or procaspase-3 (Tang et al., 2012). In addition, extracts from some Chinese traditional herbs (*Zanthoxylum nitidum* (Roxb.) DC., *Sophora flavescens* Alt. Hort. Kew ed., *Indigofera tinctoria* L. and *Anemone raddeana* Regel) can also prohibit the combination of STAT3 and target genes, so as to suppress the proliferation of gastric cancer cells and promote cell apoptosis (Liang, Dai, Zhou, Zhang, & Yu, 2017; Nie, Wang, & Yang, 2017; Xue & Nie, 2014; Xue, Zou, Zhou, & Wang, 2017). Anwei Decoction may prevent CAG and alleviate inflammation by regulating the expression of JAK1, STAT3, c-myc, and SOCS-3, which are key factors of JAK/STAT signaling pathway (Wei et al., 2017). Ganweibaihe Decoction (*Lilii Bulbus*, *Bupleuri Radix*, *Curcumae Radix*, *Linderae Radix*, *Toosendan Fructus*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Paeoniae Radix Alba*, *Taraxaci Herba*, *Glycyrrhizae Radix et Rhizoma*) down-regulated the expression of JAK/STAT protein in tissues, inhibited the excessive secretion of inflammatory factors-IL-2 and IFN- $\gamma$ , promotes the secretion of anti-inflammatory factors-IL-4 and IL-10, and thereby regulating the balance between Th1/Th2 cells, prompting the normal immune response, alleviating the injury of inflammatory factors to gastric mucosa and accelerating the repair of gastric mucosa (Mao,

2017). Xinwei Granule (*Astragali Radix*, *Glehniae Radix*, *Dendrobii Caulis*, *Sparganii Rhizoma*, *Curcumae Rhizoma*, *Scutellariae Barbatae Herba*) down-regulated the expression of STAT3 and p-STAT3 in gastric mucosal tissues of PLGC rats, which effectively intervened the further development of PLGC (Xie, Sun, & Liang, 2013). Xiangsha Liujun Pilula can regulate blood lipid, fight against oxidative stress, inhibit abnormal activation of JAK2/STAT3 signaling pathway, so that prevent abnormal proliferation and differentiation of gastric mucosal cells (Chen et al., 2017).

#### 2.5. Hedgehog signaling pathway

Hedgehog (Hh) signaling has been implicated as a critical factor in gastric gland organogenesis and differentiation during embryonic development. The central components of the Hh signaling pathway are three Hh ligands (Sonic hedgehog [SHH], Indian hedgehog [IHH], and Desert hedgehog [DHH]), the transmembrane receptor Patched1 (PTCH1), and the transcription factors GLI1, GLI2, and GLI3. Although all three Hh ligands activate identical signaling cascades by binding to PTCH1, the distribution of these ligands exhibits tissue specificity. SHH and IHH are most highly expressed in the gastrointestinal tract (Merchant & Ding, 2017). In the adult stomach, the Hh pathway not only regulates gastric epithelial cell differentiation and maturation but also is essential to the physiology of the stomach. Hh ligands (typically SHH in the stomach) secreted by the epithelial cells are recognized by receptors on stromal cells, which initiates the Hh signaling cascade in stromal cells and increases transcription of downstream target genes (Wessler, Krisch, Elmer, & Aberger, 2017). In the chronic inflammatory setting, expression of SHH is downregulated in inflamed tissues, mainly because of the loss of parietal cells and epithelium atrophy. However, with gastric lesion progression, increasing expression of SHH is accompanied by epithelial regeneration and proliferation, which underline the important role of SHH and Hh signaling in gastric epithelial repair and regeneration. Furthermore, GC cells show not only elevated SHH expression but also increased PTCH1 receptor expression. Thus, excess SHH stimulates Hh signaling and promotes GC cell proliferation and progression (Xu, Song, Wang, & Ajani, 2019). Furthermore, the insulinlike growth factor/phosphoinositide 3-kinase (PI3K)/Akt pathway shows a reciprocal relationship with Hh-dependent tumor formation during GC cell migration. It is reported that the Hh pathway promotes GC progression and metastases through activation of the PI3K/Akt pathway. Akt, in turn, stabilizes full-length GLI2 through phosphorylation of S230, thereby amplifying the transcriptional output of Hh signaling (Ishaku Akyala, & Peppelenbosch, 2018). Key targets as well as upstream and downstream relationships in Hedgehog signaling pathway are shown in Fig. 6.

Astragaloside IV and ginsenoside Rg1 are the active components of *Astragalus propinquus* Schischkin and *Panax notoginseng* (Burk.) F.H.Chen, respectively. Studies showed that astragaloside IV and ginsenoside Rg1 can increase the expression of SHH, Ptch, Gli-1 gene and protein content, and astragaloside IV can enhance the expression of Cyclin D1. Both of them have a certain activation effect on the key factors of the signaling pathway, which increase the positive feedback factors in the signaling pathway, reduce the expression of negative feedback factors, further maintain the dynamic balance of cell apoptosis and proliferation, so as to protect the gastric mucosa (Zhao et al., 2016; Zhao et al., 2017). Dihydroshinone (DHT) is one of the main lipid-soluble compounds from *Salvia miltiorrhiza* Bge. DHT could inhibit the capability of migration and induce cell apoptosis of gastric cancer cells. The potential molecular mechanism may be related to the inhibition of MMP2, MMP9, evaluation of p53 up-regulated modulator of apoptosis, up-regulation of p53 and FoxO3 signaling pathways,



and down-regulation of STAT3 and Hedgehog signaling pathways (Cheng, Lou, Ge, Shi, & Zhang, 2017). Curcumin can inhibit the proliferation of gastric cancer cells *in vitro* and may induce cell apoptosis by inhibiting the expression of SHH, Gli-1 in Hedgehog signaling pathway (Sun & Liu, 2012).

### 2.6. Hippo signaling pathway

The Hippo tumor suppressor pathway is critical for balancing cellular differentiation and proliferation in response to cell-cell contact, mechanical signals and diffusible signals such as lysophosphatidic acid. Hippo pathway signaling is frequently dysregulated in GC, as well as many other kinds of solid tumors, contributing to multiple aspects of malignant progression including unchecked cell division and metastasis (Li, Lu, & Xie, 2019). The activation of the Hippo pathway will eventually lead to phosphorylation on multiple serine residues of Yes-associated protein (YAP). Phosphorylated YAP can be sequestered in the cytoplasm by interacting with 14-3-3 protein and then degraded by the ubiquitin-proteasome system. Dephosphorylated YAP/TAZ enters the nucleus and promotes the transcription of genes that mediate proliferation and migration. Only moderate YAP expression was observed in the hyperplasia area of the normal gastric epithelium, while the YAP expression and nuclear localization were continuously observed to increase significantly in both primary and metastatic GC. The most upstream of Hippo pathway, MST1/2 and LATS1, is frequently showing downregulation in GC compared with its expression in normal gastric epithelium or adenoma (Yong, Li, Lin, Wang, & Xu, 2021). As the core downstream effector of Hippo pathway, the expression of YAP1 both in the cytoplasm and nucleus was first described to be dramatically upregulated in high-grade dysplasia, gastric adenocarcinoma, and metastatic gastric disease (Qiao, Li, Zheng, & Wang, 2018). Key targets as well as upstream and downstream relationships in Hippo signaling pathway are shown in Fig. 7.

Ursolic acid (UA) suppressed the proliferation and metastasis of gastric cancer cells and inhibited the tumorigenesis of gastric cancer *in vivo* in xenograft animals through the activation of the Hippo pathway, which suggests that UA can be used as a potential

chemopreventive and therapeutic agent for gastric cancer (Kim et al., 2019). *Pinus koraiensis* is a medicinal plant, and pinecone, an important organ of *Pinus koraiensis* is rich in essential oil. Essential Oil from *Pinus Koraiensis* Pinecones (PEO) may exert anti-tumor activity on gastric cancer cells via the Hippo/YAP signaling pathway, which is useful for the development of natural anti-tumor drugs (Zhang, Xin, Qiu, & Wang, 2019). CL-6, a curcumin derivative, shows better bioavailability than curcumin, which has shown anti-cancer effects in gastric cancer. Studies have found that CL-6 exerts anti-tumor effect in gastric carcinoma cells by inducing apoptosis through Hippo-YAP signaling pathway, which could inhibit YAP protein and mRNA expression, while inducing the expression of Lats and p-YAP. Furthermore, CL-6 can also increase levels of pro-apoptotic protein Bax, decrease levels of anti-apoptotic protein Bcl-2, and increased the Bax/Bcl-2 ratio (Ye et al., 2019). Huazhuo Jiedu Decoction (*Artemisiae Scopariae Herba, Scutellariae Radix, Hedyotis Diffusae Herba, Isatidis Radix, Lobeliae Chinensis Herba, Pogostemonis Herba, Scutellariae Barbatae Herba, Sophorae Flavescentis Radix, Coptidis Rhizoma, Fiveleaf Gynostemma Herba, Eupatorii Herba*) ameliorate the pathological condition of gastric mucosa by Hippo/TAZ signaling pathway in CAG rat model, whose mechanism is that the formula could inhibit the expression of TAZ and promote the expression of LATS2 and MST1 in gastric mucosal tissues (Wang, Hao, Yu, & Tian, 2019).

### 2.7. MAPK signaling pathway

Various studies have demonstrated that the ERK/MAPK pathways are involved in the regulation of cell motility both in GC and in normal epithelia. Indeed, ERK regulates the activity of MMPs in GC, thus influencing cell migration and invasiveness. Moreover, the secreted protein angiopoietin-like-4 (ANGPTL4), which is induced by hypoxia, exerts various effects on the neoplastic progression in scirrhous gastric carcinoma. GC cells may acquire resistance to anoikis through the activation of ANGPTL4-mediated FAK/Src/PI3K-Akt/ERK signaling, inducing the development of peritoneal metastases (Magnelli et al., 2020). The p38 pathway turns out to be deregulated in many cancers as well. p38 signaling is involved in the regulation of the epithelial-to-mesenchymal transition (EMT) and in the production of reactive oxygen species (ROS) triggered by EMT which are significantly generated in GCs. One of the targets activated by ROS is EGFR whose overexpression has been linked to lymph node diffusion and consequently to a worse prognosis in GC. These studies have demonstrated the involvement of the EGFR/Ras/MAPK signaling pathway in the activation of NF-κB, in the induction of the cyclooxygenase-2 (COX-2) and in the proliferation of GC cells. It is evident how the EGFR/Ras/MAPK signaling pathway is involved in the activation of NF-κB, through COX-2 induction, and in the stimulation of GC cells proliferation. On the other hand, a large number of studies on GC have shown that the MAPK pathway is associated with apoptosis and autophagy (Spirina et al., 2020). Key targets as well as upstream and downstream relationships in MAPK signaling pathway are shown in Fig. 8.

Silymarin is a kind of flavonolignans extracted from the fruit and seeds of *Silybum marianum* (L.) Gaertn. It has been found that silymarin could increase the expression of Bax, p-JNK and p-p38, and decrease the levels of Bcl-2 and p-ERK1/2 in a concentration-dependent manner, which indicated that silymarin induces inhibition of growth and apoptosis through adjustment of the MAPK signaling pathway in gastric cancer cells (Kim et al., 2019). Resveratrol (3, 4', 5-trihydroxystilbene) is most notably in *Reynoutria japonica* Houtt., *Mori Fructus* and many other Chinese medicines. The studies showed that IL-6 inducing gastric cancer cells invasion depends on the Raf/MAPK pathway activation. Nevertheless, resveratrol could preclude IL-6 from invading through the

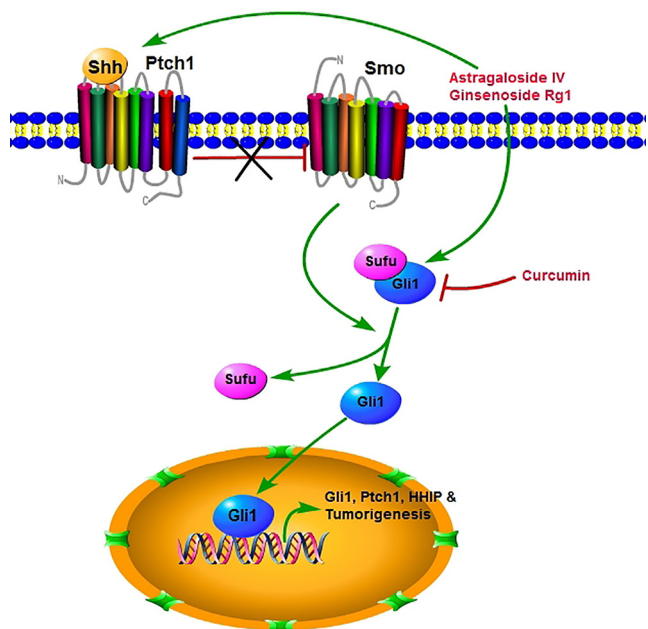


Fig. 6. Interaction of key factors upstream and downstream in Hedgehog signaling pathway.



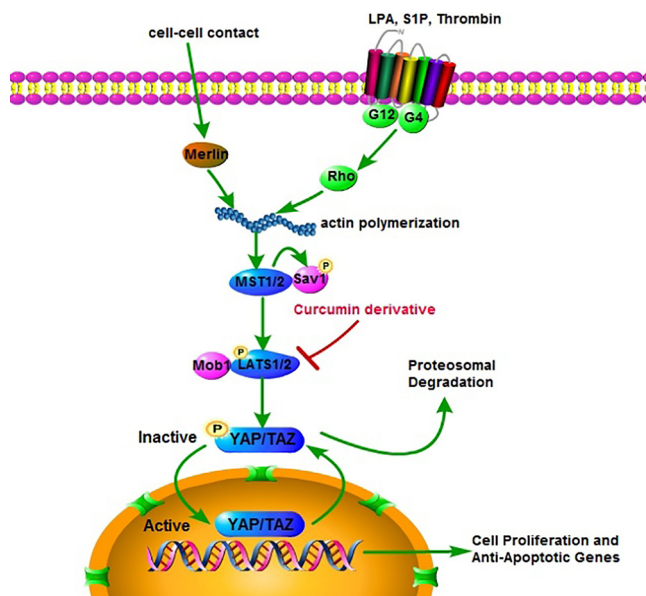


Fig. 7. Interaction of key factors upstream and downstream in Hippo signaling pathway.

blocking of this pathway (Yang et al., 2018). Lycopene belongs to the carotenoid family and contributes to red–orange color of fruits and vegetables including tomato, watermelon, guava, and pink grapefruit. Reactive oxygen species (ROS) are known to activate the epidermal growth factor receptor (EGFR), which causes the activation of the Ras/MAPK pathway. Lycopene could induce apoptosis and suppress proliferation via inhibition of ROS-activated EGFR/Ras/ERK and p38 MAPK pathways and NF-κB-mediated COX-2 gene expression in gastric cancer cells (Han, Lim, & Kim, 2019). Jianpi Jiedu Decoction (*Astragali Radix, Akebiae Caulis, Atractylodis Macrocephalae Rhizoma, Agrimoniae Herba, Vitis quinquangularis Rehd., Salviae Chinensis Herba, Coicis Semen*) can down-regulate the expression of COX-2 mRNA and protein in gastric cancer cells induced by *H. pylori* infection, inhibit the phosphorylation of p38MAPK induced by *H. pylori*, and significantly restrain the activity of its downstream transcription factor ATF-2, indicating Jianpi Jiedu Decoction inhibited *Hp*-induced the expression of COX-2 through regulating p38MAPK/ATF-2 signaling pathway. In

addition, the high expression of EGFR, ERK1/2, p-ERK1/2 and abnormal activation of EGFR/MAPK cell signal transduction pathway were significantly inhibited by Yiqi Huayu Jiedu Granule (*Codonopsis Radix, Lillii Bulbus, Linderae Radix, Citri Fructus, Salviae Miltiorrhizae Radix et Rhizoma, Notoginseng Radix et Rhizoma, Curcumae Rhizoma, Taraxaci Herba, Hedyotis Diffusae Herba*), which may be one of the effective mechanisms for the treatment of CAG with dysplasia, the reversal of PLGC, and the prevention and treatment of gastric cancer (Liu et al., 2011; Wei, Yang, Wang, Peng, & An, 2015).

### 2.8. TGF-β/Smad signaling pathway

TGF-β signaling is a crucial regulator of intestinal homeostasis and inflammation, therefore, dysregulation of this pathway could be associated with inflammation-related carcinogenesis of the GI tract. Altered signaling pathways can disturb the regulatory mechanism of TGF-β to block chronic inflammation followed by carcinogenesis (Gu, Ling, Cong, & Li, 2020). As a tumor suppressor gene, TGF-β can inhibit initiation of cell transformation, through growth inhibition and apoptosis in normal epithelium. During changes in the genetic and epigenetic context of transforming cells, the responsiveness of cells to TGF-β is decreased, but the expression and activation of TGF-β are markedly increased. Deletion of Smad proteins also leads to loss of the regulatory role of immune suppression and induces malignant cell proliferation. Deficiency of Smad4 in mutant mice causes gastric polyps and progression to gastric tumor in old age (Luo, Chen, & Li, 2019). In humans, deletion of Smad4 is found in juvenile polyposis syndrome and is a strong risk factor for GI cancer. High levels of TGF-β expression are correlated with tumor progression, metastasis and angiogenesis, which results in poor prognostic outcome. In addition to its oncogenic nature related to TGF-β mutation, TGF-β, which is secreted from tumor cells, can control tumor progression by suppressing cytotoxic immune reactions, stimulating expression of cell survival factors, or regulating autonomous signaling of tumor cells, depending on cell type and context (Stolfi, Troncone, Marafini, & Monteleone, 2020). At the late stage of tumor development, invasive and metastatic potentials are important properties, and TGF-β signaling is a crucial pathway for tumor cell invasion and metastasis by inducing epithelial to mesenchymal transition (EMT). EMT progresses by decreasing the expression of E-cadherin to inhibit cell–cell adhesion and by increasing the expres-

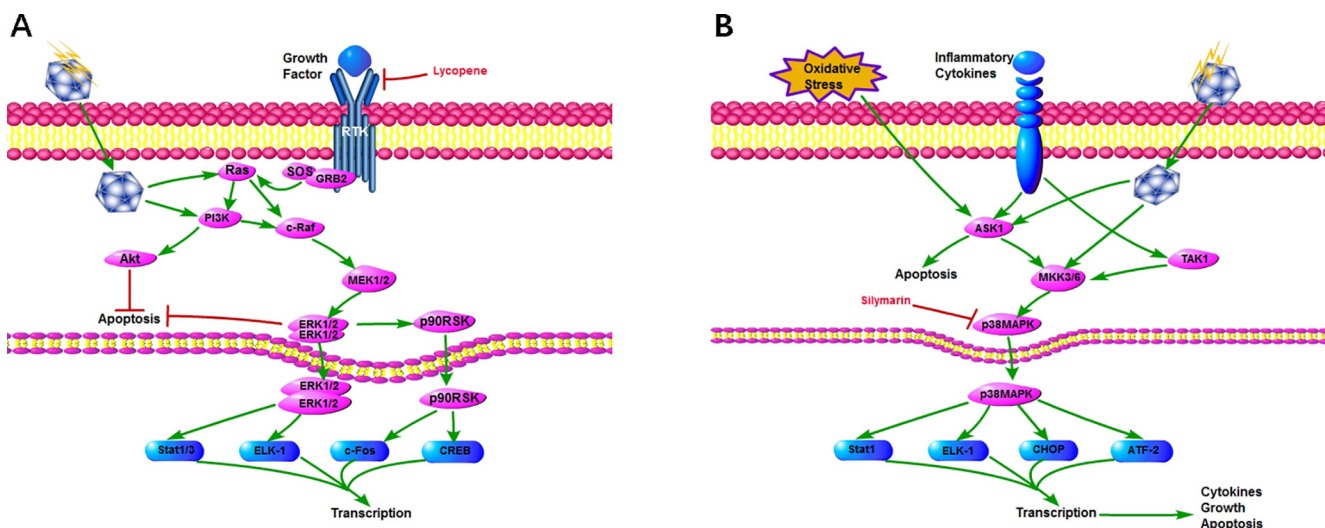


Fig. 8. Interaction of key factors upstream (A) and downstream (B) in MAPK signaling pathway.

sion of laminin-5, vimentin, integrins, and fibulin-5 that are involved in cell-extracellular matrix associations (Soudeh et al., 2021). Key targets as well as upstream and downstream relationships in TGF- $\beta$ /Smad3 signaling pathway are shown in Fig. 9.

In the study of CAG, Shuangpu Powder (*Typhae Pollen*, *Taraxaci Herba*, *Pseudostellariae Radix*, *Corium Erinacei*, *Hedyotidis Diffusae Herba*, *Faeces trogopterori*, *Salviae Chinensis Herba*, *Galli Gigerii Endothelium Corneum*, *Membrana Follicularis Ovi*) can effectively down-regulate the expression of Bcl-2, P53, PCNA, Ag-NORs, EGF, TGF- $\beta$ 1 in gastric mucosal cells of CAG rats and up-regulate the expression of Smad3, indicating that Shuangpu Powder inhibited the proliferation of dysplastic cells and promoted the repair of gastric mucosal injury by modulating the TGF- $\beta$ 1/Smad3 signaling pathway (Yang et al., 2016). Piwei Peiyuan Decoction (*Astragali Radix*, *Dendrobii Caulis*, *Cinnamomi Ramulus*, *Atractylodis Macrocephalae Rhizoma*, *Cyperii Rhizoma*, *Curcumae Rhizoma*) also significantly lessened the level of TGF- $\beta$ 1 protein and increased the level of Smad3 protein in gastric tissue, which suggested that Piwei Peiyuan Decoction exerts its therapeutic effect on TGF- $\beta$ 1/Smad3 signaling pathway and the downstream correlative cytokines (Li, Chen, & Li, 2019).

## 2.9. TLRs signaling pathway

Both innate immunity and adaptive immunity are important in cancer. In the innate immune system, pattern recognition receptors (PRRs) activate immune responses by recognizing pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) (Hu, Liu, Zhu, & Lu, 2016). Toll-like receptors (TLRs) are a class of pattern recognition receptors (PRRs). TLRs are type I transmembrane glycoproteins, whose structure includes a leucine-rich repetitive sequence in the extracellular domain, a transmembrane domain, and a conserved Toll/IL-1R homologous domain (TIR) in the cytosolic region, as they are homologous with the signaling domain of IL-1R family members (Echizen, Hirose, Maeda, & Oshima, 2016). Extracellular domain induces homo-dimerization of intracellular TIR by recognition of ligands (except for TLR1/2 and TLR2/6). Then TLRs recruit TIR domain-containing adaptor proteins including myeloid differentiation primary response protein 88 (MyD88) and TIR-domain containing adaptor-inducing interferon- $\beta$  (TRIF) that initiate signaling pathways to activate the transcription factors nuclear factor-kappa B (NF- $\kappa$ B), interferon regulatory factor (IRFs), or mitogen-activated protein kinase (MAPK) to regulate the expression of cytokine and chemokine genes including interleukin-2 (IL-2), IL-6, IL-12, monocyte chemoattractant protein-1 (MCP-1), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (Barton and Kagan, 2009), ultimately involved in establishing a regulatory innate and adaptive immune response (Cui, Wang, & Zhang, 2021). Key targets as well as upstream and downstream relationships in TLRs signaling pathway are shown in Fig. 10.

Astragaloside is able to block the activation of MyD88 and TLR4 receptors and improve SOD activity, which has a therapeutic effect on CAG (Zhang, Zhou, & Liu, 2013). The largest insect of *Blattidae* *Handlirsch* is *Periplaneta americana*, whose extractive can significantly meliorate the gastric mucosal tissue morphology in CAG rats and reduce the serum inflammatory factors. The mechanism of action is achieved by inhibiting the expression of TLR4, MyD88 and NF- $\kappa$ B p65 proteins in the TLR4/NF- $\kappa$ B signaling pathway (Zhou & Yuan, 2017). *Polygonum capitatum* lowered the expression of TLR2, TLR4, TLR5, TLR9 and MyD88, TRAF6 mRNA and protein in gastritis cells, indicating that *P. capitatum* regulated the expression of innate immune receptors on cell membrane surface and thus improve the related inflammation induced by *H. pylori* through intervening in TLRs signaling pathway (Jiang et al., 2019). *H. pylori* activates the downstream MAPK/NF- $\kappa$ B signaling pathway by up-

regulating TLR2 and TLR4, thereby increasing the production of NO catalysed by iNOS and finally causing the changes of CAG in gastric mucosa. Nevertheless, Xiangsha Liujunzi Decoction can block the activation of *H. pylori* on MAPK/NF- $\kappa$ B signaling pathway, which is to eradicate *H. pylori* and treat CAG from the etiology (Lin, Wang, Hong, & Fu, 2016). In contrast with CAG model rats, Jianpi Qinghua Decoction (*Lablab Semen Album*, *Poria*, *Coicis Semen*, *Artemisia Scopariae Herba*, *Eupatorii Herba*, *Amomi Fructus Rotundus*, *Coptidis Rhizoma*, *Magnoliae Officinalis Cortex*, *Paeoniae Radix Rubra*) significantly reduced the protein expression levels of TLR4, MyD88, NF- $\kappa$ B, COX-2 in tissue and the concentration of TNF- $\alpha$  in serum. Hence, the therapeutic mechanism of JQCC in CAG rats is related to the expressions of the relevant proteins of TLR4-MyD88-dependent pathways and the expressions of anti-inflammatory cytokines (Huang et al., 2016).

## 2.10. Notch signaling pathway

Notch signaling activation promotes tumor cell proliferation or survival and *in vivo* tumorigenesis through: a. HES1-mediated CDKN1B (p27) repression and subsequent cellular proliferation; b. HES1-mediated dual specificity phosphatase 1 repression and subsequent ERK activation; c. HES1-mediated phosphatase and tensin homolog repression and subsequent AKT signaling activation; d. HES1-mediated STAT3 activation and cSL-independent, NF- $\kappa$ B-dependent interleukin 6 (IL-6) upregulation, and subsequent JAK-STAT signaling activation. By contrast, Notch signaling activation blocks tumor cell proliferation or survival and *in vivo* tumorigenesis through: a. direct upregulation of CDKN1A; b. HES1-mediated GLI family zinc finger 1 repression; c. HEY1 mediated snail family transcriptional repressor 2 and twist family bHLH transcription factor 1 repression, and subsequent mesenchymal-to-epithelial transition; d. HEY1-mediated IL-6 downregulation and subsequent depletion of cancer stem cells (Katoh & Katoh, 2020). Because Notch signals drive lateral induction as well as lateral inhibition to finetune organ development and homeostasis, bifunctional cellular responses are a common feature of Notch signaling during embryogenesis, adult tissue homeostasis and tumorigenesis (Pancewicz, 2020). Key targets as well as upstream and downstream relationships in Notch signaling pathway are shown in Fig. 11.

Triptonide, extracted from *Tripterygium wilfordii* Hook. f., potentially inhibited gastric cancer cell tumorigenicity and metastasis through suppression of Notch1 and NF- $\kappa$ B signaling pathways via reducing oncogenic Notch1 protein levels by ubiquitination-proteasome system, decreasing the levels of Notch1 downstream RBPJ, IKK $\alpha$ , IKK $\beta$ , and phosphorylated-NF- $\kappa$ B proteins (Xiang et al., 2019). Banxia Xiexin Decoction (*Pinelliae Rhizoma*, *Scutellariae Radix*, *Zingiberis Rhizoma*, *Salviae Miltiorrhizae Radix et Rhizoma*, *Coptidis Rhizoma*, *Jujubae Fructus*, *Glycyrrhizae Radix et Rhizoma*) can significantly reverse the up-regulation of the mRNA and protein expressions of Notch1, Notch2, Notch1/2 target gene Hes1, and Notch1/2 ligand Jagged1, suggesting that Banxia Xiexin Decoction has a therapeutic effect in a rat model of CAG by targeting the Notch signaling pathway, which blocked CAG from progressing to early gastric cancer (Bai et al., 2019).

## 3. Conclusion and future perspectives

Cell signaling is a communication process of cell activities mediated by downstream genes and proteins. Distraction of signaling process induce disturbance in cellular mechanisms and may cause diseases, such as cancer, autoimmunity, and diabetes (Park, Pyun, & Park, 2020). In the major category, the signaling pathways are divided into intracellular activating signaling pathways, such as

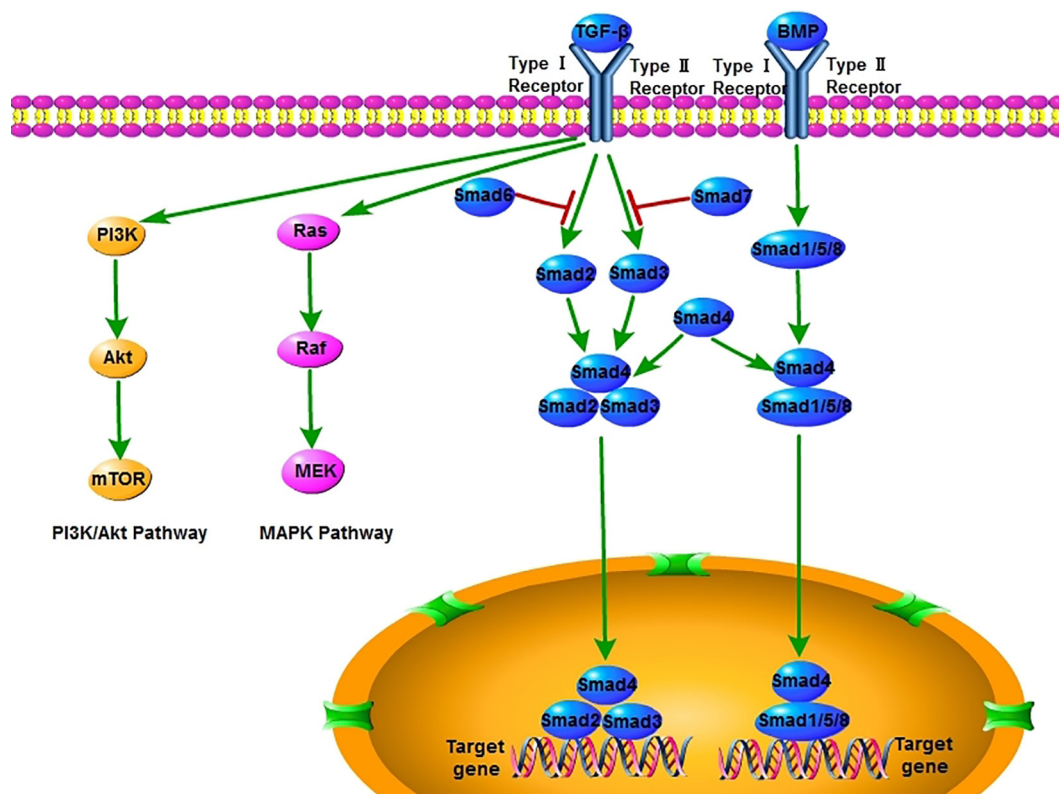


Fig. 9. Interaction of key factors upstream and downstream in TGF-β1/Smad3 signaling pathway.

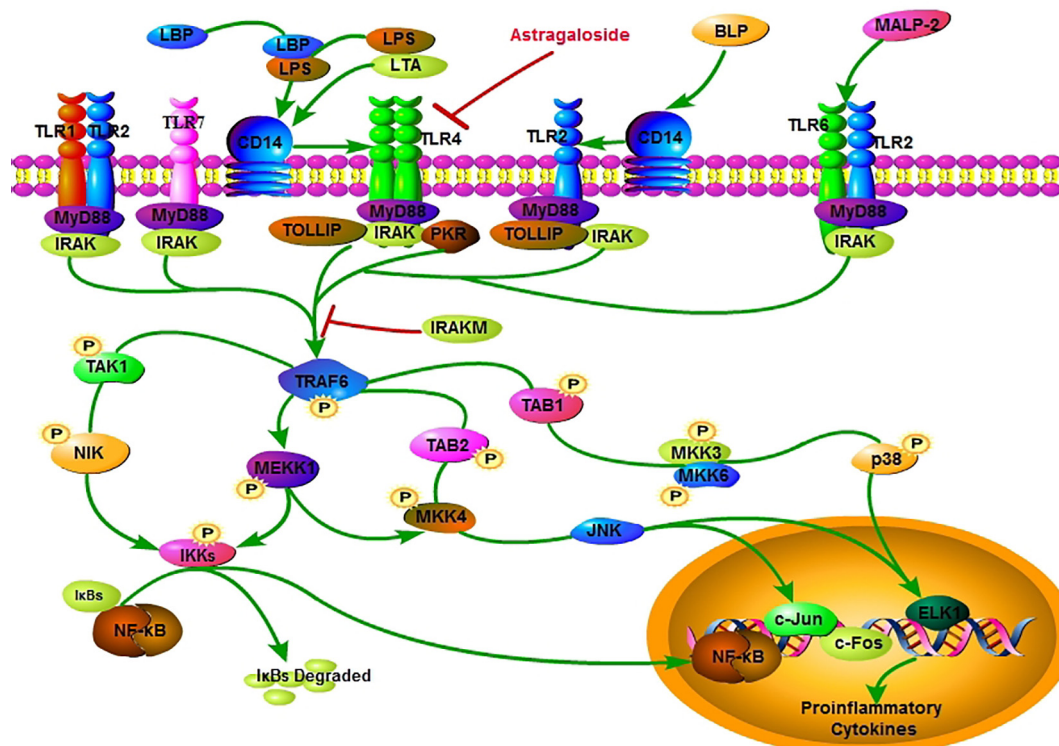


Fig. 10. Interaction of key factors upstream and downstream in TLRs signaling pathway.

Hippo signaling and Notch signaling pathways or the extracellular activating pathways, for instance, MAPK signaling, NF-κB, JAK/STAT signaling pathway, Wnt signaling pathways, Hedgehog,

TGF-β/Smad signaling pathway, and PI3K signaling pathways. The Smad signaling is critical in TGF-β signaling, which controls the transcription. MAPK signaling pathway makes use of three differ-



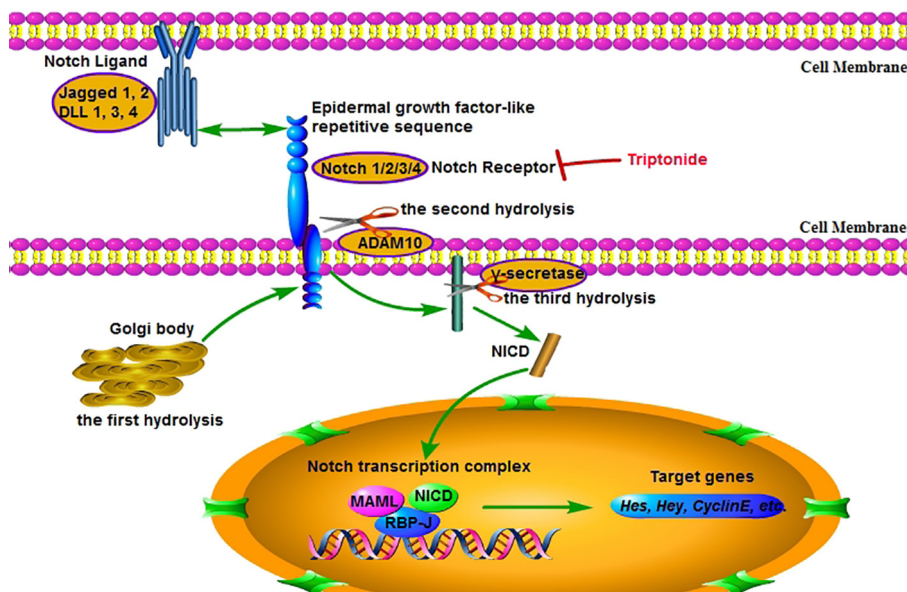


Fig. 11. Interaction of key factors upstream and downstream in Notch signaling pathway.

ent downstream effectors, including Extracellular-signal-regulated kinase pathway, c-Jun N-terminal kinase (JNK) pathway, and p38 pathway. Also, the Wnt signaling pathway is important in cell differentiation and proliferation. In Wnt signaling, the Wnt/ $\beta$ -catenin signaling pathway is the only canonical pathway. The p53 signaling is not a canonical signaling pathway but due to the p53 non-transcriptional functions, the role of this pathway in generating cancer and its interaction with other signaling pathways, p53 can be considered as an individual pathway (Tabibzadeh et al., 2020).

Mutations in signaling pathways, such as signal transduction systems, are the basic triggering mechanisms in different types of cancers. The role of MAPK signaling pathway, Wnt, TGF- $\beta$ , and JAK-STAT signaling pathways are more common in cancer induction. Mutation analysis of signaling pathway mediators could have prognostic impact on tumor development. Transformation of the epidermal growth factor receptor (EGFR) and its downstream pathway mediators could lead to development of human tumors. Two vital intracellular pathways affected by EGFR are the RAS/RAF/MAPK and the PIK3CA/PTEN/AKT signaling pathways. These pathways mediate activation of transcription factors like ERK (extracellular regulated MAP kinase) and p38 and lead to cell transformation reactions like the up-regulation of proliferation, relocation, mesenchymal separation induction, and apoptosis reduction. As EGFR has been a target for anti-tumor drugs, its mutations and related downstream signaling pathway mutations have become important (Adashek et al., 2020). Indeed, interaction of various signaling pathway mediator mutations and their behavior in cancer development has been a hot topic. These alterations could include susceptibility, resistant or nonsense for treatment management or tumorigenesis in different individuals geographically (Huang et al., 2020).

TCMs can regulate multiple signaling pathways of chronic atrophic gastritis and gastric carcinoma. On account of the complexity of the pharmacology of TCM, the characteristics of the multiple components determine the diversity of its functions, which manifests that the mechanism by TCMs playing the role in modulating the signaling pathways is often a combination of multiple factors, rather than be explained through a single pathway. It is precisely the complicity of tumor, inflammatory environment

and TCMs that the extensive intersection of multiple signal transduction pathways forms a large network in the process of inflammatory changes or tumor development. After activation, diversified signaling pathways also activated their respective positive or negative feedback regulation mechanisms to make the reaction tend to magnify or balance. Moreover, the same signaling pathway may exhibit opposite effects. This phenomenon may be related to different isoforms of kinases and suggests the possibility of new signaling pathways and even new regulatory molecules. The accurate interaction and regulation mechanism are still important research directions in the future. In short, the mechanism of monomers or compounds isolated from TCMs in the treatment of CAG and the reversal of PLGC is characterized by multifarious links and targets, mainly affecting the proliferation, differentiation, apoptosis, transformation and other processes of gastric tissue cells, which is of great significance for the prevention and treatment of gastric carcinoma.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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