REVIEW

School of Pharmaceutical Sciences[1], Shandong University; Ji'nan Central Hospital[2] Affiliated to Shandong University, Ji'nan, China

# Contribution of drugs acting on the TLRs/MyD88 signaling pathway on colitis-associated cancer

Mingliang Zhu[1], Kewei Yu[2], Lu Wang[2,*], Shuwen Yu[1,2,*]

*Received February 28, 2018, accepted March 23, 2018*

**Corresponding authors: Shuwen Yu, Lu Wang, Ji'nan Central Hospital, Ji'nan, China, 250013*
*yaoxuebu2012@163.com, lulucc@163.com*

*Pharmazie 73: 363-368 (2018)* *doi: 10.1691/ph.2018.8388*

Toll-like receptors play a particularly significant role in colitis-associated cancer (CAC). MyD88 is the mediator in TLRs signal transduction process and it is indispensable for TLRs signaling except for TLR3. The conclusion of studies about the role of TLRs/MyD88 signaling in colon cancer remains contradictory: on one hand, TLRs/MyD88 signaling contributes to colon tumor cell proliferation, invasion and metastasis and inhibition of the expression of TLRs or MyD88 could prevent the growth of colon cancer cells; on the other hand, activation of the TLRs/MyD88 signaling pathway could inhibit the proliferation of colon cancer cells. This article is based on the expression levels of TLRs or MyD88 and the activation degrees of TLRs/MyD88 signaling pathway in different periods of colon cancer and, reviews the roles of TLRs/MyD88 signaling in the tumorigenesis and procession of CAC and the clinical application of agonists and inhibitor of TLRs or MyD88. This article is intended to explore the diverse roles of TLRs/MyD88 signaling pathway in CAC and to reveal the related molecular mechanism.

## 1. Introduction

Chronic inflammation can accelerate the process of disease and even cause malignancy (Balkwill et al. 2005; Lowe and Storkus 2011). The relationship between inflammation and cancer has widespreadly been paid attention to. Evidence shows that chronic inflammation plays an important role in the pathogenesis and progression of cancer (Mantovani et al. 2008;Pollard 2015). For instance, *Helicobacter pylori* infection may cause gastric cancer and HBV infection could lead to liver cancer (Lee et al. 2016; Wang et al. 2017). In America, despite the fact that there is a decline in cancer mortality, there are still 97,200 patients with colorectal cancer who have been diagnosed in 2018 and this cancer has been viewed as the third most common malignancy (Siegel et al. 2018). The ratio of colorectal cancer in young people has also increased (Siegel et al. 2017).

Inflammation as a response to invasion reduce the extent of infection when the invasion happens. However, long-term inflammation causes the intestinal epithelium canceration which is mediated by TLRs (mainly through the TLRs/MyD88 signaling pathway) rather than having a beneficial immune effect (Sardi et al. 2017; Siddique and Khan 2011; Stanislawowski et al. 2009; Szebeni et al. 2008; Torok et al. 2017). There are several pattern recognition receptors (PRRs) in the human intestinal epithelium which serve as essential elements of the response system, such as TLRs (Gordon 2002). Furthermore, there are lots of microorganisms in human intestine, known as the intestinal flora, which are beneficial to the human body when they are in balance. Studies show that the intestinal flora can accelerate cancer development by enhancing the exposure of intestinal epithelial cells to carcinogens (Klimesova et al. 2013). These microbes also act as pathogen-associated molecular patterns (PAMPs) for TLRs and activate the TLRs/MyD88 signaling pathway. TLR agonists and TLR or MyD88 inhibitors have been used to treat cancer, graft rejection and many other diseases. These regimens inhibiting CAC with TLR or MyD88 inhibitors have not been applied clinically yet, but achieved the expected results in pharmacological experiments (Braza et al. 2016; He et al. 2016; Qi et al. 2015; Shiratori et al. 2017; Zhang et al. 2016). Through these reports we can confidently believe that the study of TLRs/MyD88 signal pathway will help to find new treatments for CAC. Therefore, in this review, we will discuss the TLRs/MyD88 signaling pathway and the contribution of inhibiting the development of CAC when this pathway is activated or inhibited.

## 2. TLRs/MyD88 and CAC

### *2.1. TLRs and TLRs/MyD88*

Toll-like receptors are a group of cell surface receptors recognizing specific structures on the surface of pathogens or the specific elements of their own proteins or tissues (Tchorzewski et al. 2014). They belong to the interleukin-1 receptor superfamily. Until now there are not less than thirteen mammalian TLRs (Akira et al. 2006), and ten of them are found among human beings. The first TLR which can activate genes associated with adaptive immunity has been discovered in 1997 (Medzhitov et al. 1997) and was identified as a receptor for LPS. This receptor was named TLR4 shortly after its discovery. TLRs are the first barriers against infectious diseases inside humans' body, and different TLRs can identify different pathogen-associated molecular patterns (PAMPs).

MyD88 is the connector during the TLR signal transduction process and it is indispensable for TLR signaling except for TLR3. MyD88 consists of three functional areas: N-terminal death domain (DD), intermediate region and C-terminal Toll region (Hardiman et al. 1997). The DD region includes about 90 amino acids that mediate the interaction between proteins containing DD sequences. The TIR region, with about 130 amino acids that deliver the signal by recruiting the connexin, is similar to the cytoplasmic region of the IL-1 receptor. Activation of TLRs (other than TLR3) triggers the MyD88 pathway. Upon activation, MyD88 recruits and activates IRAK-4, IRAK-1, and then generated TRAF-6. TRAF6 interacts with TAK1 (a MAP kinase which is activated with TAB1, -2, -3, and -4) and undergoes a series of pathways to ultimately activate MAP kinase and NF-κB. (Fig. 1) (Imajo et al. 2006; Gohda 2004; Muzio et al. 1997; Zou and Shankar 2015). Because all of the above steps, some genes which encode prion-inflammatory

cytokines and chemokines was activated, such as TNF-α and IL-1 (Ghosh et al. 1998). In recent years, scholars pay much attention to this signaling pathway.

There are two types of TLR signaling pathway, Myd88-dependent pathway and Non-Myd88-dependent pathway (Bagchi et al. 2007). TLR1, TLR2, TLR5, TLR6, TLR7, TLR8 and TLR9-mediated signaling pathways belong to MyD88-dependent signaling pathways. TLR3-mediated signaling pathway is MyD88-independent, and TLR4 is the only receptor that activates the both pathways simultaneously (Kawai and Akira 2010).

Fig. 1: A common diagram of TLR signaling pathway. As shown in the figure, different TLRs are activated by different PAMPs, including LBP, LPS, dsRNA, ssRNA, Triacylated lipopeptide and so on. There are two types of TLR signaling pathway, Myd88-dependent pathway and Non-Myd88-dependent pathway. MyD88 is the connector during the TLR signal transduction process and it is indispensable for TLR signaling except TLR3.MyD88 recruits and activates IRAK-4, IRAK-1, and then generated TRAF-6. The involvement of TRAF6 eventually leads to the activation of MAP kinases (p38, JNK) and NF-κB leading to the secretion of proinflammatory cytokines. The TLR7, -8, and -9 signals are also dependent on MyD88 and also cause IRF7 activation, ultimately promoting IFN secretion. TLR3-dependent TRIF activates TRAF6 or TRAF3. The former mediates the inflammatory response, and the latter causes TBK1 and IKK to activate IRF3 to produce IFN. TLR4 is the only receptor that activates the both pathways simultaneously.

### 2.2. *Colitis-associated cancer*

Colitis is a common intestinal disease which may develop into ulcerative colitis (UC). Ulcerative colitis, as a chronic inflammation, that is confined mainly to the colorectal mucosa and submucosa, to the distal end of the distal colon, and to retrograde proximal development, even involving the entire colon. The common symptoms of ulcerative colitis are diarrhea, abdominal pain and mucus bloody stools. A large number of clinical and epidemiological studies have confirmed that: chronic inflammation is a high-risk factor of colorectal cancer (Hussain 2007) and also increases the risk of systemic cancer (such as cholangiocarcinoma and breast cancer; Gulamhusein et al. 2016; Ming-Shian Tsai et al. 2015). The cancer caused by ulcerative colitis was named as colitis-associated cancer (CAC). How does inflammation promote the progress of cancer and what are the signaling nodes for the networks of cancer development? A step-by-step analysis of colitis-related cancers may help explain the problem. From the beginning of chronic inflammation, through the process of inflammatory hyperplasia, atypical hyperplasia, adenocarcinoma, it finally progresses to colon cancer with invasive metastasis of the abdominal cavity. This evolution may involve complex networks of multi-level

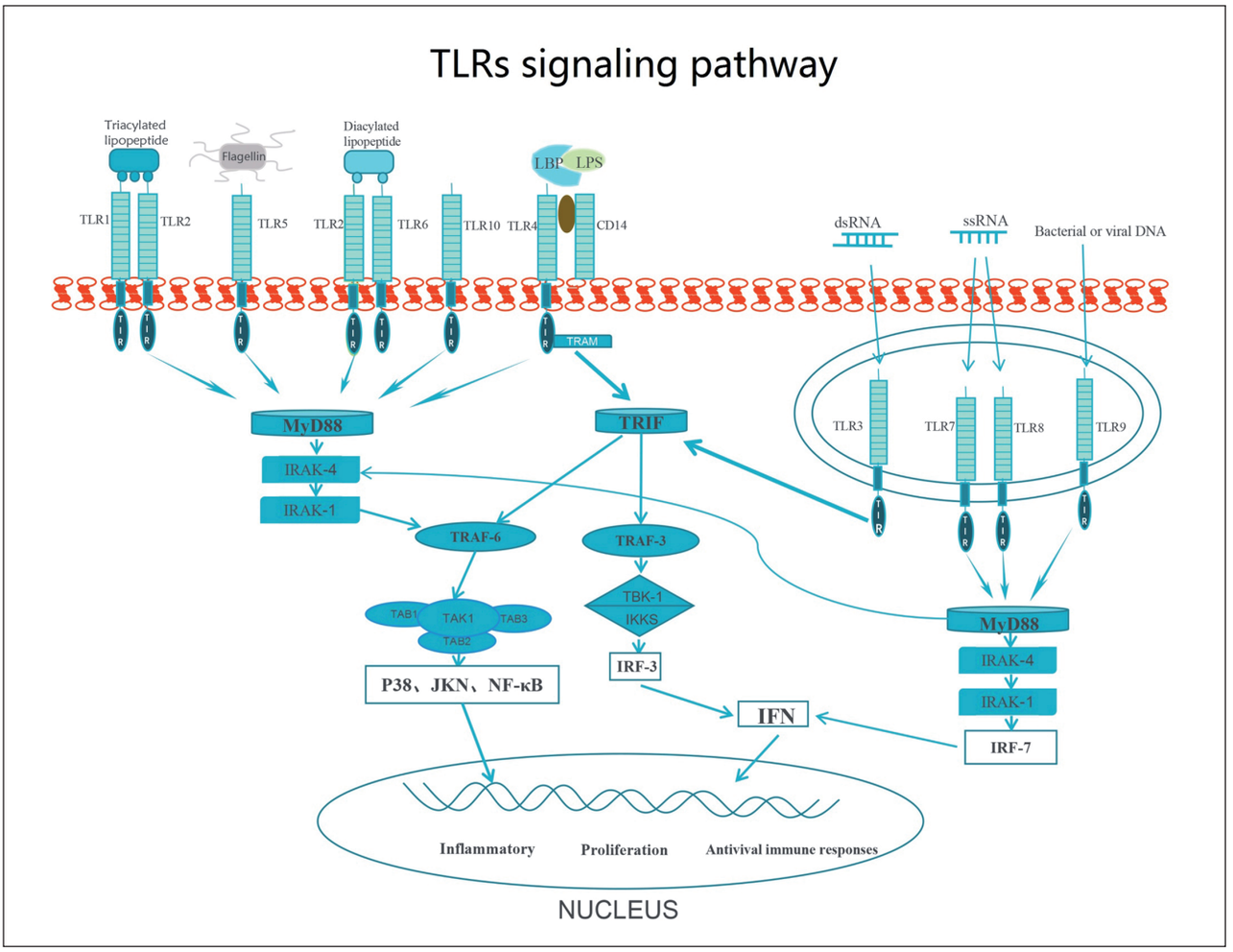


Fig. 1: A common diagram of TLR signaling pathway. As shown in the figure, different TLRs are activated by different PAMPs, including LBP, LPS, dsRNA, ssRNA, Triacylated lipopeptide and so on. There are two types of TLR signaling pathway, Myd88-dependent pathway and Non-Myd88-dependent pathway. MyD88 is the connector during the TLR signal transduction process and it is indispensable for TLR signaling except TLR3.MyD88 recruits and activates IRAK-4, IRAK-1, and then generated TRAF-6. The involvement of TRAF6 eventually leads to the activation of MAP kinases (p38, JNK) and NF-κB leading to the secretion of proinflammatory cytokines. The TLR7, -8, and -9 signals are also dependent on MyD88 and also cause IRF7 activation, ultimately promoting IFN secretion. TLR3-dependent TRIF activates TRAF6 or TRAF3. The former mediates the inflammatory response, and the latter causes TBK1 and IKK to activate IRF3 to produce IFN. TLR4 is the only receptor that activates the both pathways simultaneously.

systems, multiple stages, multiple signal transduction pathways, and multiple gene molecular regulatory mechanisms. If any node changes in this complex network, which may be abnormal cytokine expression or a group of abnormal cell activity, may affect the development and extent of colon cancer, and may even affect the prognosis of the disease. Wnt/β-catenin pathway is one of these nodes. The renewal of intestinal epithelial cells requires the participation of Wnt/β-catenin pathway. And this signaling pathway, as a regulator, plays an important role in normal cells and cancer cells proliferation. The mutations which can active the Wnt/β-catenin signaling pathway happen in nearly 90% of sporadic colitis-associated cancers (Schneikert and Behrens 2007). The activation of Wnt/β-catenin plays an important role in colitis/carcinogenesis. From the inflammatory bowel disease, mild atypical hyperplasia, severe atypical hyperplasia to colon cancer, the expression of β-catenin gradually increases in intestinal mucosal cytoplasmic (Grivennikov 2013). However, inflammation can also increase the β-catenin signaling without mutations (Imai et al. 2007; Loilome et al. 2016; Ma and Hottiger 2016; Zeng et al. 2016). This may be the reason that inflammation can accelerate the development of colon cancer. Inflammation increases β-catenin signaling through the following inflammatory pathways, such as NF-κB, PI-3K and Akt pathways (Bansal et al. 2011; Lee et al. 2010; Liu et al. 2016; Trucco et al. 2017). In addition, the role of chromosomal instability (CIN), immunomodulatory cells and vascular endothelial growth factor (VEGF) in promoting colorectal carcinogenesis has also been continuously observed (Barresi et al. 2017; Mehdawi et al. 2016; Su et al. 2016).

### *2.3. The expression level of TLRs and MyD88 in CAC*

In colon tumors, TLRs including TLR1-4 have been found (Furrie et al. 2005; Yoshioka et al. 2001). In earlier reports, TLR4, which mediates the inflammatory response, was found to be upregulated in many tumor cells and tissues (Crespo-Lessmann et al. 2016; Deng et al. 2017). The expression of TLR and myd88 were detected in colorectal cancer tissues, adjacent tissues and normal tissues by immunohistochemistry. Wang et al. (2010) found that the expression of TLR and myd88 in normal colorectal tissues was very low, whereas it was significantly higher in colorectal cancer tissues than in paracancerous tissues. But recent experiments come to different conclusions. Researchers analyzed the expression of TLR2 and TLR4 in 118 CRC patients by immunohistochemistry and then they found that TLR4 expression was lower than that of normal epithelial cells while TLR2 was highly expressed (Paarnio et al. 2017). They also hold the opposite view of the effect of TLR4 overexpression on the five-year survival of colitis-associated cancer patients. The main reason for such contradictory results may be due to the different detection methods they used. In a later study, researchers analyzed the TLR content of the tumor volume and the invasive front, respectively, which is not the same as in the previous study. This may mean that TLR4 plays different roles in different parts of the tumor. In addition, TLR5 is mainly expressed in intestinal endothelial cells and TLR5-gene polymorphism associated with human colorectal cancer have been reported (Klimosch et al. 2013). In an experiment designed to elucidate the relationship between TLR9 diversity and colon cancer susceptibility to colon cancer, a reduction of TLR-9 mRNA expression in colon cancer tissues was reported (Semlali et al. 2017). All of these results suggest that TLR plays an important role in colitis-associated cancers.

### *2.4. The two-way effect of TLRs/MyD88 on cancer*

The TLRs/MyD88 signaling pathway can accelerate the development of cancer. First of all, we are interested in TLRs/MyD88 as an upstream signaling pathway that regulates the inflammatory pathways. With long-term chronic inflammation, the high risk of cancer is on the rise. On the other hand, NF-kB activated by the TLRs/MyD88 signaling pathway controls the expression of anti-apoptotic genes and has potent anti-apoptotic effects (Sahu et al. 2017). High expression of TLR and myd88 contributes to the proliferation, invasion and transfer (Wang et al. 2010). In early experiments, it was seen that the TLR4/MyD88 signaling pathway is beneficial to proliferation and anti-apoptotic, which may increase the possibility of colitis-related canceration (Fukata et al. 2006). Another evidence showed that mice were genetically engineered to overexpress TLR4, increasing their susceptibility to inflammation-induced neoplasia (Fukata et al. 2011).

Although it has been reported that the TLRs/MyD88 signaling pathway has a tumor-inhibiting action and it actually shows a tumor-suppressive effect. One of those experiments shows the patients with high TLR4 expression had a 5-year cancer-specific survival rate 36.9% higher than patients with low expression (Paarnio et al. 2017). Studies have demonstrated that the promotion of TLRs and downstream mediators can translate the immunomodulatory effects of TLRs/MyD88 into antitumor effects (Mikulandra et al. 2017).

The role of TLR as an anti-tumor or a pro-tumor agent depends on the type of TLR, different tumor subtypes and the environment in which the tumor cells are located. In some experiments, the experimenter used different tumor models and thus came to controversial conclusions.

## 3. TLRs/MyD88s in CAC therapy

### *3.1. TLR agonists in CAC therapy*

With the new advances in TLR in the treatment of other diseases (Carvalho et al. 2017; Zhang et al. 2016), there has been an increasing number of studies on the role of TLR in cancer therapy. In fact, almost all of studies about the anticancer function of TLRs/MyD88 have been focused on TLR agonists. Because the activation of TLRs/MyD88 signaling pathway promote the secretion of IFN, proinflammatory cytokines and enhance the antigen presenting ability of Dendritic Cells (DC) with anticancer effect(Fig. 2; Kubo et al. 2004; Muzio et al. 2000; Wu et al. 2016). Xu et al. (2017) reported that TLR-dependent DC can inhibit tumor cell growth when activated by *Rehmannia glutinosa* polysaccharide (RGP).

Fig. 2: Activation of TLR activates NF-κB pathway and promotes the release of inflammatory cytokines. Eventually make DC cells mature, strengthen DC cell antigen presenting ability, produce antitumor effect.

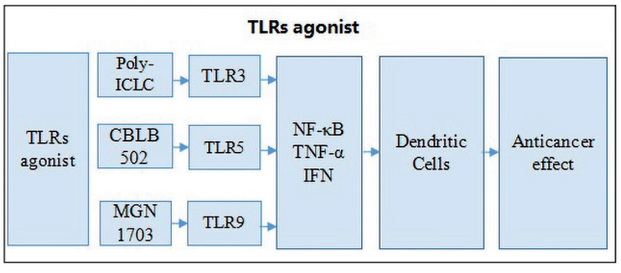


Fig. 2: Activation of TLR activates NF-κB pathway and promotes the release of inflammatory cytokines. Eventually make DC cells mature, strengthen DC cell antigen presenting ability, produce antitumor effect.

There has been a large number of basic experiments on the activation of TLRs/MyD88 signaling pathways for immunotherapy of colorectal tumors. Some TLR agonists have also been used in clinical experiments, although most of them are only used as adjunctive treatments. For example, GLA-SE, a TLR4 agonist, can reduce 40-75% of the metastatic development of colon cancer in mice and reduce cancer metastatic in perioperative treatment without on adverse effects (Matzner et al. 2016). In another study, they used a combination of vasculature disrupting agent and TLR7/8 agonist-gardiquimod to treat tumor growth and made a remarkable effect (Seth et al. 2017).

Up to now, there are not many TLR agonist drugs for CAC treatment, which are mainly showed in the following

**Table 1: The progress in clinical research of TLRs agonist.**

| Phase | Experimental design | Aim | TLR agonist | Conditions | Interventions | Status |
|---|---|---|---|---|---|---|
| **I/II** | Phase 1: i. Pembrolizumab 200 mg(IV) every 3 weeks ii. Poly-ICLC(IM) twice weekly: 1 mg or 2 mg. Each dose level will enroll 3-6 participants,12 participants total. For 1 year (~17 cycles). Phase 2: all participants will receive the standard pembrolizumab dose (200 mg IV q3w) in addition to the maximum tolerated dose of poly-ICLC (either 1 mg or 2 mg), as determined by the Phase 1 arm. Up to 30 participants will be treated in Phase 2. For 1 year (~17 cycles). | 1. Determine the dose of poly-ICLC that is safe and tolerable when it is combined with pembrolizumab in patients with colon cancer. 2. Evaluate how the combination of pembrolizumab and poly-ICLC activates the immune system in the patient's blood and inside the tumor; how it affects the size and number of tumor(s) in each patient; and how effective the combination is in patients with colon cancer that is unlikely to respond to pembrolizumab alone. | Poly-ICLC (TLR3 agonist) | Colon cancer | Pembrolizumab Poly-ICLC | Not yet recruiting |
| **II** | 4 arms:1-2 injections of CBLB502 0.35 or 0.45 μg/kg or Placebo at Day 1 (and 4) before tumor removal. | Randomized single-blind placebo-controlled clinical study of safety and tolerability of CBLB502 as a neoadjuvant treatment in patients with colorectal cancer, with different doses and regimens. | CBLB502 (TLR5 agonist) | Colorectal cancer | Placebo CBLB502 | Recruiting |
| **III** | MGN1703 treatment as maintenance therapy | Prove the efficacy and safety of MGN1703 as a maintenance therapy after first-line chemotherapeutic treatment of metastatic colorectal cancer. | MGN1703 (TLR9 agonist) | Advanced Colorectal Carcinoma | Usual Maintenance MGN1703 | Active, not recruiting |
| **II** | MGN1703 solution, 60 mg, twice a week, until progression | Evaluate efficacy and safety of a maintenance therapy with the immunomodulator MGN1703 compared to placebo control. The study will be conducted in patients with advanced colorectal carcinoma (AJCC Stage IV) with disease control after first-line standard chemotherapy regimens. | MGN1703 (TLR9 agonist) | Metastatic Colorectal Cancer | Placebo MGN1703 | Completed |

categories (Table; Jiang et al. 2008; Schmoll et al. 2014; Takemura et al. 2015; Xu et al. 2016). Poly-ICLC is a TLR3 agonist which can be used as the treatment of many types of cancer, mostly in combination with other drugs. Poly-ICLC and pembrolizumab are combined to treat metastatic colon cancer in a clinical trial designed by the University of Augusta which is mainly used to determine the safe and tolerable dose of them. CBLB502, a TLR5 agonist named Entolimod, is used to treat colorectal cancer. The result of this clinical trial shows that Entolimod was well tolerated. MGN1703 is a TLR9 agonist which can be used as a maintenance therapy after first-line chemotherapeutic treatment of metastatic colorectal cancer. It is noteworthy that MGN1703 achieved the expected result in its Phase I/II clinical trials (Weihrauch et al. 2015) and entered Phase III clinical trials.

### *3.2. Contribution of inhibiting TLRs/MyD88 to prevent CAC*

However, Toll-like receptors show a dual function in tumor development: on one hand, they could activate the death signal of the tumor; on the other hand, they are also beneficial to the proliferation, invasion and transfer. (Fukata et al. 2011; Garaude et al. 2012). When TLRs present as a factor promoting inflammation, and act anti-apoptotic, they will show a tumor-promoting action. TLR promotes inflammation, mainly through the TLRs/MyD88 signaling pathway we mentioned before. TLR2 and TLR4-mediated signaling pathways both belong to MyD88-dependent signaling pathways, but we cannot find a theory to explain why there exists a difference in the development between the TLR2-deficient and TLR4-deficient mice. The experimental results show that Myd88 may make different effects on cancer development if we use the different models: TLR4-deficient mice are resistant to CAC but TLR2-deficient has same susceptibility to colitis or CAC (Salcedo et al. 2010). Although the effect of TLRs/MyD88 on colitis-associated cancer is not completely clear so far, there are still many experiments demonstrating that antagonism of Myd88 can play a role in inhibiting the development of colitis-associated cancers. Zhang et al (2017) showed that using andrographolide can obviously promote apoptosis of SW620 cells by inhibiting the expression of TLR4 and MyD88 protein in SW620 cells. In another study (Zhang et al. 2015), apple polysaccharide was used to reduce the incidence of cancer. It was found that the TLRs/MyD88 signaling pathway was activated in LPS-induced CRC cells, but apple polysaccharide could reduce the level of this signaling pathway which may be the reason why it is protective. Xie et al. (2016) attempted to block the homodimerization of MyD88 and TLRs/MyD88 signaling pathway with a MyD88 inhibitor and this inhibitor (TJ-M2010-5) was eventually confirmed to achieve the desired effect. The final mortality rate in the experimental group was 0%, and the mortality rate in the control group was much higher than that in the experimental group (53 %). Inhibition of MyD88 homodimerization and TLRs/MyD88 signaling pathway can completely prevent CAC development. The drug ST2825 has the similar effects on inhibiting MyD88 homodimerization and function (Loiarro et al. 2013). In addition, MyD88 can also promote cancer through Ras/Erk, not only the TLRs/MyD88-NF-κB pathway and colon tumor cells become more sensitive to genotoxic agents by knocking down MyD88 (Kfoury et al. 2013). Inhibiting MyD88 may also have an effect on this Ras/Erk pathway. These facts show that TLRs/MyD88 inhibitors can produce good anti-cancer effects. In fact, some inhibitors have been used clinically, especially in autoimmune disorders, inflammatory diseases and pain. In some experiments, TLR inhibitors were used as new therapies for the treatment or prevention of cancer although there are currently no completed experimental projects. It is noteworthy that the application of TLR inhibitors in the treatment of inflammatory bowel disease, to a certain extent, may play a positive role in the treatment of colitis-associated cancer. We can believe that

with the continuous research on TLR inhibitors, more and more TLR inhibitors will exhibit unique functions in the field of cancer therapy.

## 4. Concluding remarks

TLRs/MyD88 can trigger an inflammatory response and is an important pathway for autoimmunity. Inflammation acts on many aspects of colitis-associated cancers and drives cancer progression. TLRs/MyD88 signaling pathway has been identified as a pivotal signaling pathway for the pathogenesis and progression of CAC. Although our CAC have seen new clinical breakthroughs in the treatment of tumors using TLR agonist immunomodulation, TLR inhibitors still show promising results in tumor suppression. Increased study of TLR inhibitors may be able to open up new avenues of CAC therapy. In addition, we should be aware of the possible contradictory results of TLRs/MyD88 signaling-related experimental data. When we apply TLR agonist immunomodulatory therapy to clinical treatment, we cannot ignore the possible contribution of TLR receptors activation to tumor progression.

Acknowledgements: Authors would like to thank the Shandong Provincial Natural Science Foundation, China (ZR2017BH093) for supporting this study.

Conflict of interest: Authors declare that there is no conflict of interest.

### References


Akira S, Uematsu S,Takeuchi O (2006) Pathogen recognition and innate immunity. Cell 124: 783-801.

Bagchi A, Herrup E, Warren H, Trigilio J, Shin H, Valentine C, Hellman J (2007) MyD88-dependent and MyD88-independent pathways in synergy, priming, and tolerance between TLR agonists. J Immunol 178: 1164-1171.

Balkwill F, Charles KA, Mantovani A (2005) Smoldering and polarized inflammation in the initiation and promotion of malignant disease. Cancer Cell 7: 211-217.

Bansal K, Trinath J, Chakravortty D, Patil SA, Balaji KN (2011) Pathogen-specific TLR2 protein activation programs macrophages to induce Wnt-beta-catenin signaling J Biol Chem 286: 37032-37044.

Barresi V, Castorina S, Musso N, Capizzi C, Luca T, Privitera G, Condorelli DF (2017) Chromosomal instability analysis and regional tumor heterogeneity in colon cancer. Cancer Genet 210: 9-21.

Braza F, Brouard S, Chadban S, Goldstein D (2016) Role of TLRs and DAMPs in allograft inflammation and transplant outcomes. Nat Rev Nephrol 12: 281-290.

Carvalho JL, Britto A, de Oliveira AP, Castro-Faria-Neto H, Albertini R, Anatriello E, Aimbire F (2017) Beneficial effect of low-level laser therapy in acute lung injury after i-I/R is dependent on the secretion of IL-10 and independent of the TLR/MyD88 signaling. Lasers Med Sci 32: 305-315.

Crespo-Lessmann A, Mateus E, Vidal S, Ramos-Barbón D, Torrejón M, Giner J, Soto L, Juárez Cn, Plaza V (2016) Expression of toll-like receptors 2 and 4 in subjects with asthma by total serum IgE level. Respir Res 17: 41.

Deng S, Yu K, Jiang W, Li Y, Wang S, Deng Z, Yao Y, Zhang B, Liu G, Liu Y, Lian Z (2017) Over-expression of Toll-like receptor 2 up-regulates heme oxygenase-1 expression and decreases oxidative injury in dairy goats. J Animal Sci Biotechnol 8: 3.

Fukata M, Chen A, Klepper A, Krishnareddy S, Vamadevan AS, Thomas LS, Xu R, Inoue H, Arditi M, Dannenberg AJ, Abreu MT (2006) Cox-2 is regulated by Toll-like receptor-4 (TLR4) rignaling: role in proliferation and apoptosis in the intestine gastroenterology 131: 862-877.

Fukata M, Shang L, Santaolalla R, Sotolongo J, Pastorini C, España C, Ungaro R, Harpaz N, Cooper HS, Elson G, Kosco-Vilbois M, Zaias J, Perez MT, Mayer L, Vamadevan AS, Lira SA, Abreu MT (2011) Constitutive activation of epithelial TLR4 augments inflammatory responses to mucosal injury and drives colitis-associated tumorigenesis. Inflamm Bowel Dis 17: 1464–1473.

Fukata M, Shang L, Santaolalla R, Sotolongo J, Pastorini C, España C, Ungaro R, Harpaz N, Cooper HS, Elson G, Kosco-Vilbois M, Zaias J, Perez MT, Mayer L, Vamadevan AS, Lira SA, Abreu MT (2011) Constitutive activation of epithelial TLR4 augments inflammatory responses to mucosal injury and drives colitis- associated tumorigenesis. Inflamm Bowel Dis 17: 1464-1473.

Furrie E, Macfarlane S, Thomson G, Macfarlane GT (2005) Toll-like receptors-2, -3 and -4 expression patterns on human colon and their regulation by mucosal-associated bacteria Immunology 115: 565-574.

Garaude J, Kent A, van Rooijen N, Blander JM (2012) Simultaneous targeting of toll- and nod-like receptors induces effective tumor-specific immune responses Sci Transl Med 4: 120ra116.

Ghosh S, May MJ, Kopp EB (1998) NF-kappa B and Rel proteins: evolutionarily conserved mediators of immune responses. Annu Rev Immunol 16: 225–260.

Gohda J, Matsumura T, Inoue J. (2004) Cutting edge: TNFR- associated factor (TRAF) 6 is essential for MyD88-dependent pathway but not Toll/IL-1 receptor domain-containing adaptor- inducing IFN. J Immunol 173: 2913–2917.

Gordon S (2002) Pattern recognition receptors: doubling up for the innate immune response. Cell 111: 927-930.

Grivennikov SI (2013) Inflammation and colorectal cancer: colitis-associated neoplasia. Semin Immunopathol 35: 229-244.

Gulamhusein AF, Eaton JE, Tabibian JH, Atkinson EJ, Juran BD, Lazaridis KN (2016) Duration of inflammatory bowel disease is associated with increased risk of cholangiocarcinoma in patients with primary sclerosing cholangitis and IBD. Am J Gastroenterol 111: 705-711.

Hardiman G, Jenkins N, Copeland N, Gilbert D, Garcia D, Naylor S, Kastelein R, Bazan J (1997) Genetic structure and chromosomal mapping of MyD88 Genomics 45: 332-339.

He W, Zhang L, Li C (2016) Short-term MyD88 inhibition ameliorates cardiac graft rejection and promotes donor-specific hyporesponsiveness of skin grafts in mice. Transpl Int 29: 941-952.

Hussain S (2007) Inflammation and cancer: an ancient link with novel potentials Int J Cancer 121: 2373–2380.

Imai T, Fukuta K, Hasumura M, Cho YM, Ota Y, Takami S, Nakagama H, Hirose M (2007) Significance of inflammation-associated regenerative mucosa characterized by Paneth cell metaplasia and beta-catenin accumulation for the onset of colorectal carcinogenesis in rats initiated with 1,2-dimethylhydrazine. Carcinogenesis 28: 2199-2206.

Imajo M, Tsuchiya Y, Nishida E (2006) Regulatory mechanisms and functions of MAP kinase signaling pathways. IUBMB Life 58: 312–317.

Jiang Q, Wei H, Tian Z (2008) Poly I:C enhances cycloheximide-induced apoptosis of tumor cells through TLR3 pathway. BMC Cancer 8: 12.

Kawai T, Akira S (2010) The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors. Nat Immunol 11: 373-384.

Kfoury A, Corf KL, Sabeh RE, Journeaux A, Badran B, Hussein N, Lebecque S, Manié S, Renno T, Coste I (2013) MyD88 in DNA repair and cancer cell resistance to genotoxic drugs. J Natl Cancer Inst 105: 937-946.

Klimesova K, Kverka M, Zakostelska Z, Hudcovic T, Hrncir T, Stepankova R, Rossmann P, Ridl J, Kostovcik M, Mrazek J, Kopecny J, Kobayashi KS, Tlaskalova-Hogenova H (2013) Altered gut microbiota promotes colitis-associated cancer in IL-1 receptor-associated kinase M-deficient mice. Inflamm Bowel Dis 19: 1266-1277.

Klimosch SN, Forsti A, Eckert J, Knezevic J, Bevier M, von Schonfels W, Heits N, Walter J, Hinz S, Lascorz J, Hampe J, Hartl D, Frick JS, Hemminki K, Schafmayer C, Weber AN (2013) Functional TLR5 genetic variants affect human colorectal cancer survival. Cancer Res 73: 7232-7242.

Kubo T, Hatton RD, Oliver J, Liu X, Elson CO,Weaver CT (2004) Regulatory T cell suppression and anergy are differentially regulated by proinflammatory cytokines produced by TLR-activated dendritic cells. J Immunol 173: 7249-7258.

Lee G, Goretsky T, Managlia E, Dirisina R, Singh AP, Brown JB, May R, Yang GY, Ragheb JW, Evers BM, Weber CR, Turner JR, He XC, Katzman RB, Li L, Barrett TA (2010) Phosphoinositide 3-kinase signaling mediates beta-catenin activation in intestinal epithelial stem and progenitor cells in colitis. Gastroenterology 139: 869-881.

Lee YC, Chiang TH, Chou CK, Tu YK, Liao WC, Wu MS,Graham DY (2016) Association Between Helicobacter pylori Eradication and Gastric Cancer Incidence: A Systematic Review and Meta-analysis Gastroenterology 150: 1113-1124.

Liu W, Crott JW, Lyu L, Pfalzer AC, Li J, Choi SW, Yang Y, Mason JB,Liu Z (2016) Diet-and Genetically-induced Obesity Produces Alterations in the Microbiome, Inflammation and Wnt Pathway in the Intestine of Apc+/1638N Mice: Comparisons and Contrasts J Cancer 7: 1780-1790.

Loiarro M, Ruggiero V,Sette C (2013) Targeting the Toll-like receptor/interleukin 1 receptor pathway in human diseases: rational design of MyD88 inhibitors Clin Lymphoma Myeloma Leuk 13: 222-226.

Loilome W, Bungkanjana P, Techasen A, Namwat N, Yongvanit P, Puapairoj A, Khuntikeo N,Riggins G (2016) Activated macrophages promote Wnt/β-catenin signaling in cholangiocarcinoma cells Tumour Biol 35: 5357–5367.

Lowe DB,Storkus WJ (2011) Chronic inflammation and immunologic-based constraints in malignant disease Immunotherapy 3: 1265-1274.

M. Muzio, J. Ni, P. Feng,Dixit VM (1997) IRAK (Pelle) family member IRAK-2 and MyD88 as proximal mediators of IL-1 signaling Science 278: 1612-1615.

Ma B,Hottiger MO (2016) Crosstalk between wnt/β-Catenin and NF-κB Signaling Pathway during inflammation Front Immunol 7: 378.

Mantovani A, Allavena P, Sica A,Balkwill F (2008) Cancer-related inflammation Nature 454: 436-444.

Matzner P, Sorski L, Shaashua L, Elbaz E, Lavon H, Melamed R, Rosenne E, Gotlieb N, Benbenishty A, Reed SG,BenEliyahu S (2016) Perioperative treatment with the new synthetic TLR-4 agonist GLA-SE reduces cancer metastasis without adverse effects International journal of cancer 138: 1754–1764.

Medzhitov R, Preston-Hurlburt P,Janeway CJ (1997) A human homologue of the Drosophila Toll protein signals activation of adaptive immunity Nature 388: 394-397.

Mehdawi L, Osman J, Topi G,Sjölander A (2016) High tumor mast cell density is associated with longer survival of colon cancer patients Acta oncologica 55: 1343-1442.

Mikulandra M, Pavelic J,Glavan TM (2017) Recent Findings on the Application of Toll-like Receptors Agonists in Cancer Therapy Current Medicinal Chemistry 24: 1-22.

Ming-Shian Tsai, Chen H-P, Chao-Ming Hung, Lee P-H, Lin C-L,Kao C-H (2015) Hospitalization for Inflammatory Bowel Disease is Associated with Increased Risk of Breast Cancer: A Nationwide Cohort Study of an Asian Population. Annals of Surgicai Oncology 22: 1996–2002.

Muzio M, Bosisio D, Polentarutti N, D'amico G, Stoppacciaro A, Mancinelli R, Veer Cvt, Penton-Rol G, Ruco LP, Allavena P,Mantovani A (2000) Differential Expression and Regulation of Toll-Like Receptors (TLR) in Human Leukocytes: Selective Expression of TLR3 in Dendritic Cells The Journal of Immunology 164: 5998-6004.

Paarnio K, Väyrynen S, Klintrup K, Ohtonen P, Mäkinen MJ, Mäkelä J,Karttunen TJ (2017) Divergent expression of bacterial wall sensing toll-like receptors 2 and 4 in colorectal cancer. World J Gastroenterol 23: 4831-4838.

Pollard J (2015) Bacteria, inflammation and cancer. Nat Rev Immunol 15: 528.
Qi M, Zheng L, Qi Y, Han X, Xu Y, Xu L, Yin L, Wang C, Zhao Y, Sun H, Liu K ,Peng J (2015) Dioscin attenuates renal ischemia/reperfusion injury by inhibiting the TLR4/MyD88 signaling pathway via up-regulation of HSP70. Pharmacol Res 100: 341-352.
Sahu U, Choudhury A, Parvez S, Biswas S, Kar S (2017) Induction of intestinal stemness and tumorigenicity by aberrant internalization of commensal non-pathogenic E. coli. Cell Death Dis 8: e2667.
Salcedo R, Worschech A, Cardone M, Jones Y, Gyulai Z, Dai RM, Wang E, Ma W, Haines D, O'HUigin C, Marincola FM, Trinchieri G (2010) MyD88-mediated signaling prevents development of adenocarcinomas of the colon: role of interleukin 18. J Exp Med 207: 1625-1636.
Sardi C, Luchini P, Emanuelli A, Giannoni A, Martini E, Manara LM, Sfondrini L, Kallikourdis M, Sommariva M, Rumio C (2017) Three months of Western diet induces small intestinal mucosa alteration in TLR KO mice. Microsc Res Tech 80: 563-569.
Schmoll HJ, Wittig B, Arnold D, Knorrenschild JR, Nitsche D, Kroening H, Mayer F, Andel J, Ziebermayr R, Scheithauer W (2014) Maintenance treatment with the immunomodulator MGN1703, a Toll-like receptor 9 (TLR9) agonist, in patients with metastatic colorectal carcinoma and disease control after chemotherapy: a randomised, double-blind, placebo-controlled trial. J Cancer Res Clin Oncol 140: 1615–1624.
Schneikert J, Behrens J (2007) The canonical wnt signalling pathway and its apc partner in colon cancer development Gut 56: 417-425.
Semlali A, Parine NR, Amri AA, Azzi A, Arafah M, Kohailan M, Shaik JP, Abdulrahman M, Almadi, Aljebreen AM, Alharbi O, Azzam NA, Rouabhia M, Alanazi MS (2017) Association between TLR-9 polymorphisms and colon cancer susceptibility in Saudi Arabian female patients. OncoTargets Ther 10: 1-11.
Seth A, Lee H, Cho MY, Park C, Korm S, Lee J-Y, Choi I, Lim YT, Hong KS (2017) Combining vasculature disrupting agent and toll-like receptor 7/8 agonist for cancer therapy Oncotarget 8: 5371-5381.
Shiratori E, Itoh M, Tohda S (2017) MYD88 Inhibitor ST2825 suppresses the growth of lymphoma and leukaemia cells. Anticancer Res 37: 6203-6209.
Siddique I, Khan I (2011) Mechanism of regulation of Na-H exchanger in inflammatory bowel disease: role of TLR-4 signaling mechanism Dig Dis Sci 56: 1656-1662.
Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, Jemal A (2017) Colorectal cancer statistics, 2017. CA Cancer J Clin 67: 177-193.
Siegel RL, Miller KD,Jemal A (2018) Cancer Statistics, 2018. CA Cancer J Clin 67: 7-30.
Stanislawowski M, Wierzbicki P, Golab A, Adrych K, Kartanowicz D, Wypych J, Godlewski J, Smoczynski M, Kmiec Z (2009) Decreased Toll-like receptor-5 (TLR-5) expression in the mucosa of ulcerative colitis patients J Physiol Pharmacol 60: 71-75.
Su F, Li X, You K, Chen M, Xiao J, Zhang Y, Ma J, Liu B (2016) Expression of VEGF-D, SMAD4, and SMAD7 and their relationship with lymphangiogenesis and prognosis in colon cancer. J Gastrointest Surg 20: 2074–2082.
Szebeni B, Veres G, Dezsõfi A, Rusai K, Vannay A, Mraz M, Majorova E, Arató A (2008) Increased expression of Toll-like receptor (TLR) 2 and TLR4 in the colonic mucosa of children with inflammatory bowel disease Clin Exp Immunol 151: 34-41.
Takemura R, Takaki H, Okada S, Shime H, Akazawa T, Oshiumi H, Matsumoto M, Teshima T, Seya T (2015) PolyI: C-induced, TLR3/RIP3-dependent necroptosis backs up immune effector-mediated tumor elimination in vivo. Cancer Immunol Res 3: 902-914.
Tchorzewski M, Lewkowicz P, Dziki A, Tchorzewski H (2014) Expression of toll-like receptors on human rectal adenocarcinoma cells. Arch Immunol Ther Exp (Warsz) 62: 247-251.
Torok HP, Bellon V, Konrad A, Lacher M, Tonenchi L, Siebeck M, Brand S, De Toni EN (2017) Functional Toll-Like Receptor (TLR)2 polymorphisms in the susceptibility to inflammatory bowel disease PLoS One 12: e0175180.
Trucco LD, Roselli E, Araya P, Nunez NG, Mena HA, Bocco JL, Negrotto S, Maccioni M (2017) Downregulation of adaptor protein MyD88 compromises the angiogenic potential of B16 murine melanoma. PLoS One 12: e0179897.
Wang E, Qian Z, Nakasono M, Tanahashi T, Yoshimoto K, Bando Y, Kudo E, Shimada M, Sano T (2010) High expression of Toll-like receptor 4/myeloid differentiation factor 88 signals correlates with poor prognosis in colorectal cancer. Brit J Cancer 102: 908-915.
Wang M, Wang Y, Feng X, Wang R, Wang Y, Zeng H, Qi J, Zhao H, Li N, Cai J, Qu C (2017) Contribution of hepatitis B virus and hepatitis C virus to liver cancer in China north areas: Experience of the Chinese National Cancer Center. Int J Infect Dis 65: 15-21.
Weihrauch MR, Richly H, von Bergwelt-Baildon MS, Becker HJ, Schmidt M, Hacker UT, Shimabukuro-Vornhagen A, Holtick U, Nokay B, Schroff M, Wittig B, Scheulen ME (2015) Phase I clinical study of the toll-like receptor 9 agonist MGN1703 in patients with metastatic solid tumours Eur J Cancer 51: 146-156.
Wu J, Li S, Yang Y, Zhu S, Zhang M, Qiao Y, Liu Y-J,Chen J (2016) TLR-activated plasmacytoid dendritic cells inhibit breast cancer cell growth in vitro and in vivo. Oncotarget 8: 11708-11718.
Xie L, Jiang F-C, Zhang L-M, He W-T, Liu J-H, Li M-Q, Zhang X, Xing S, Guo H,Zhou P (2016) Targeting of MyD88 homodimerization by novel synthetic inhibitor tj-m2010-5 in preventing colitis-associated colorectal cancer JNCI J Natl Cancer Inst 108: djv364.
Xu L, Kwak M, Zhang W, Zeng L, Lee PC, Jin JO (2017) Rehmannia glutinosa polysaccharide induces toll-like receptor 4 dependent spleen dendritic cell maturation and anti-cancer immunity. Oncoimmunology 6: e1325981.
Xu Y, Dong H, Ge C, Gao Y, Liu H, Li W, Zhang C (2016) CBLB502 administration protects gut mucosal tissue in ulcerative colitis by inhibiting inflammation Ann Transl Med 4: 301.
Yoshioka T, Morimoto Y, Iwagaki H, Itoh H, Saito S, Kobayashi N, Yagi T, Tanaka N (2001) Bacterial lipopolysaccharide induces transforming growth factor beta and hepatocyte growth factor through toll-like receptor 2 in cultured human colon cancer cells J Int Med Res 29: 409-420.
Zeng H, Ishaq S, Zhao F,Wright A (2016) Colonic inflammation accompanies an increase of β-catenin signaling and Lachnospiraceae/Streptococcaceae bacteria in the hind gut of high-fat diet-fed mice. J Nutr Biochem 35: 30-36.
Zhang D, Mi M, Jiang F, Sun Y, Li Y, Yang L, Fan L, Li Q, Meng J, Yue Z, Liu L,Mei Q (2015) Apple polysaccharide reduces NF-Kb mediated colitis-associated colon carcinogenesis Nutr Cancer 67: 177-190.
Zhang LM, Liu JH, Xue CB, Li MQ, Xing S, Zhang X, He WT, Jiang FC, Lu X, Zhou P (2016) Pharmacological inhibition of MyD88 homodimerization counteracts renal ischemia reperfusion-induced progressive renal injury in vivo and in vitro. Sci Rep 6: 26954.
Zhang R, Zhao J, Xu J, Jiao DX, Wang J, Gong Z-Q,Jia JH (2017) Andrographolide suppresses proliferation of human colon cancer SW620 cells through the TLR4/NF-κB/MMP-9 signaling pathway. Oncol Lett 14: 4305-4310.
Zou J, Shankar N (2015) Roles of TLR/MyD88/MAPK/NF-kappaB signaling pathways in the regulation of phagocytosis and proinflammatory cytokine expression in response to E. faecalis infection. PLoS One 10: e0136947