REVIEW

Preventative and Therapeutic Effects of Metformin in Gastric Cancer: A New Contribution of an Old Friend

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Abstract: Gastric cancer (GC) is a cancer with high prevalence, and is one of the leading causes of cancer death worldwide. Metformin is a widely used hypoglycemic agent for type-2 diabetes mellitus (T2DM). Recently, metformin has drawn increasing attention in the field of cancer research for its emerging anti-cancer roles. However, the efficacy and underlying molecular mechanisms of metformin in the prevention and treatment for GC remain controversial. This review summarized the present clinical and mechanistic studies that investigated the efficacy of metformin in GC. It was found that the majority of clinical studies affirmed protective roles of metformin in both gastric cancer risk and survival rate. In addition, metformin's effects in the prevention and treatment for GC involve multiple pathways mainly via AMPK and IGF-1R. It was concluded that metformin presents a unique opportunity for application against GC, but further clinical and mechanistic investigations are required to solidify the roles of metformin in GC.

Keywords: gastric cancer, metformin, AMPK, anti-tumor

Introduction

Gastric cancer (GC) remains as a global issue and is responsible for over 1,000,000 new cases and an estimated of 783,000 deaths in 2018.[1] It is the fifth most commonly diagnosed cancer and the third leading cause of cancer-associated death worldwide.[1] Even after complete surgical resection and conventional chemotherapy, approximately 50% of GC patients experience recurrence and metastasis,[2] and the 5-year relative survival rate among locally advanced GC patients is 36%, according to the MAGIC trial.[3] Therefore, the discovery and investigation of new therapeutic options are urgently needed. Repurposing approved drugs for cancer prevention and treatment has been an important strategy of cancer drug discovery. The present study focused on the potential of repurposing metformin for GC prevention and treatment.

Metformin is derived from galegine or isoamylene guanidine, which is the active substance of *Galega officinalis*, also known as Goat's Rue, the French lilac or Italian Fitch.[4] Metformin has been the most widely used oral hypoglycemic agent in the biguanide class for the treatment of T2DM since its approval in the 1950s in the United Kingdom and in 1995 in the United States.[4] Mechanistic studies revealed that metformin activates adenosine monophosphate-activated protein kinase (AMPK) signaling. Thus, this sensitizes the response of liver and

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peripheral tissues to insulin signals, and enhances the glucose uptake into muscles and/or increasing fatty acid oxidation in adipose tissues.[5,6]

Since the early 2000s, several studies have linked the use of metformin with decreased risk of different cancers,[7] neurodegeneration[8] and cardiac hypertrophy.[9] Therefore, it was proposed that the use of metformin could be repurposed as an anti-cancer agent, a neuroprotective agent, and a cardiovascular protective agent.[7–9] According to a retrospective study in 2005, metformin decreased the overall cancer incidence by 44% when administered for more than five years.[10] Numerous studies have investigated the antineoplastic effect of metformin on liver cancer,[11] pancreatic cancer,[12,13] colorectal cancer[14] and prostate cancer.[15] In contrast, limited studies concerning the antitumor effect of metformin on GC has been conducted. However, some meaningful results have been attained in recent years. Therefore, the present study provides an overview of the potential role of metformin in GC prevention and treatment from previous clinical studies. These studies enlightened the mechanism research of metformin. We summarize the latest advances of metformin in perturbing cancer cell metabolism, inhibiting the proliferation, metastasis and stemness, and inducing apoptosis.

The Efficacy of Metformin for Gastric Cancer in Clinical Practice

The effects of metformin on GC risk and survival rate have attracted the attention of clinicians and researchers. Metformin is a widely prescribed first-line drug for T2DM. The large population of metformin users with T2DM provides great opportunity for researchers to investigate metformin's impact on GC incidence and survival rate. In addition, most clinical studies have investigated the roles of metformin in GC among T2DM patients.

Metformin Use and Gastric Cancer Risk

For the last 10 years, epidemiological studies have shown controversial results for the association between metformin therapy and incidence of GC (Table 1). Six of 11 studies revealed that metformin use in DM patients significantly reduced the risk of developing GC.[15,16,19,20,22,24] Kim et al reported that in T2DM patients, metformin significantly reduced GC risk in non-insulin users, but not in insulin users.[16] However, further investigations are needed to determine whether exogenous insulin treatment interferes with the protective effect of metformin.[16]

Several studies have compared metformin with other antidiabetic agents and revealed that lowering GC risk could be a unique feature of metformin. Tseng et al reported that the use of metformin significantly reduced GC risk, especially when the cumulative duration was more than approximately two years.[20] Ruiter et al reported that exposure to metformin was generally associated with lower incidence of cancer, specifically gastric cancer, when compared to exposure to sulfonylurea derivatives.[15] Similarly, Dulskas et al reported that metformin decreased the risk of GC, while sulfonylureas behaved quite the opposite.[24] However, Valent et al concluded that sulfonylurea could also reduce the risk of GC with a similar effect to metformin.[19] These studies indicate that the protective roles of metformin against cancer risk might be independent of its hypoglycemic roles. Cheung et al reported that metformin use was associated with lower GC risk among *H. pylori*-eradicated diabetic patients in a duration- and dose-dependent manner.[22]

On the contrary, a study conducted in the United Kingdom revealed that the use of metformin had a similar incidence for total cancer and gastric cancer, when compared to the use of sulfonylurea.[18] Murff et al reported the strong inverse association between metformin and liver cancer, but not gastric cancer.[17] Population-based studies in the Netherlands, Sweden and Taiwan also indicated that metformin did not reduce GC risk.[14,21,23]

Recently, Shuai et al reported a meta-analysis that the use of metformin reduced 21% of GC incidence (HR: 0.790, 95% CI 0.624–1.001). The subgroup analysis revealed that compared to Western populations, Asian patients with T2DM are more likely to benefit from metformin against the development of GC.[25] Randomized controlled trials of metformin for the prevention of GC would be useful to verify these observations.

Metformin Use and Gastric Cancer Survival

Accumulating studies have determined whether metformin could improve survival in tumor patients.[26,27] Studies on GC are presently limited, and there is only one ongoing prospective clinical trial registered at clinicaltrials.gov.

To date, only four retrospective studies have investigated the association between metformin use and gastric cancer survival (Table 2). Among these studies, three of four reported that use of metformin improved GC patient survival. The study led by Baglia et al did not present the

Table 1 Characteristics of Studies on Metformin and Gastric Cancer Risk

Author (Year)	Population	District	Groups	No. of Patients	Results for Metformin Users
Lee (2011)[14]	DM	Taiwan	Metformin; non-metformin	15,717 (4,327/11,390)	No impact on GC risk
Ruiter (2012)[15]	DM using metformin or sulfonylurea	Netherland	Metformin; sulfonylurea	85,289 52,698/32,591	Reduced GC risk
Kim (2014)[16]	T2DM, insulin non-users	Republic of Korea	Metformin; non-metformin	32,978 (26,690/6,288)	Reduced GC risk
Murff (2014)[17]	DM using metformin or sulfonylurea	U. S.	Metformin; sulfonylurea	84,434 (42,217/42,217)	No impact on GC risk
Tsilidis (2014)[18]	DM using metformin or sulfonylurea	U. K.	Metformin; sulfonylurea	69,748 (51,484/18,264)	No impact on GC risk
Valent (2015)[19]	T2DM	Italy	Metformin; non-metformin	138,521 (63,119/75,402)	Reduced GC risk
Tseng (2016)[20]	T2DM	China	Metformin; non-metformin	304,188 (287,971/16,217)	Reduced GC risk
De Jong (2017)[21]	DM using ≥1 non-insulin antidiabetic drug (NIAD)	Netherland	Metformin; other NIADs	57,114 (37,215/19,899)	No impact on GC risk
Cheung (2019)[22]	DM with HP eradication	China	Metformin; non-metformin	7,266 (5,368/1,898)	Reduced GC risk
Zheng (2019)[23]	DM	Sweden	Metformin; non-metformin	544,130 (334,506/ 209,624)	No impact on GC risk
Dulskas (2020)[24]	Gastric cancer with T2DM, compared to the expected number	Lithuania	Metformin and other medication; insulin and other medication; metformin and insulin; sulfonylurea	337 (230/18/15/74)	Reduced GC risk

Table 2 Characteristics of Studies on Metformin and Gastric Cancer Survival

Author (Year)	Population	District	Groups	No. of Patients	Results for Metformin Users
Lee (2016)[28]	Gastric cancer after gastrectomy	Republic of Korea	Metformin; non-metformin	326 (132/194)	Improved survival, decreased recurrence
Lacroix (2018)[29]	Gastric cancer with DM	Belgium	Metformin; non-metformin	298 (228/70)	Improved overall survival
Seo (2019)[30]	Gastric cancer after gastrectomy	Republic of Korea	Metformin; non-metformin; non-DM	2,187 (103/139/ 1,945)	Improved survival, decreased recurrence
Baglia (2019)[31]	Gastric cancer with DM	China	Metformin; non-metformin	130	No impact on survival

significant impact of metformin, and this might be deviated by the relatively smaller cohort (130 patients only) in the study.[31] Lee et al and Seo et al both reported that increasing the cumulative duration of metformin use could significantly improve the survival and reduce the recurrence rate in GC patients with diabetes who underwent gastrectomy.[28,30] It has been shown that in general, DM patients have a poorer prognosis, when compared to non-DM patients with cancers. Interestingly, gastrectomy per se has been shown to relieve T2DM, which made the problem more complicated.[32,33] Furthermore, Seo et al reported that the DM+metformin group even had significantly a better overall survival, when compared to the non-DM group.[30] The study based on a Belgian population indicated that metformin improved the overall survival, but not cancer-specific survival.[29] It remains unclear

whether metformin would have similar beneficial effects in patients with gastric cancer without DM. Hence, further prospective studies to evaluate metformin's role as adjuvant therapy in non-DM GC patients are needed.[34]

In summary, these present limited studies suggest that the use of metformin might significantly improve the survival of GC patients. However, these studies are not able to address whether metformin has a direct anti-cancer effect. Therefore, the direct impact of metformin on GC cells and its potential molecular mechanisms need to be further explored, which will be the focus of the following sections of the present study.

Metformin Perturbs Cancer Cell Metabolism

Altered metabolism is one of the 10 emerging hallmarks of cancer.[35] Back in 1924, Otto Warburg proposed a connection between cellular metabolism and malignancy, where tumor tissue or cells preferentially utilize glycolysis, rather than oxidative phosphorylation (OXPHOS), even when oxygen is sufficient.[36] Mitochondrial Complex I is a crucial enzyme in the electron transfer chain (ECT) in the mitochondrial in OXPHOS. Metformin has a very polar guanidine structure and a highly hydrophilic base, which exists in a positive charged form under physiological conditions. The uptake of metformin involves transmembrane transporters, such as organic cation transporters (OCTs), multidrug and toxic extrusion transporters (MATE), and plasma membrane monoamine transporter (PMAT).[37] Following its uptake, metformin accumulates within the mitochondria inner membrane driven by the mitochondria transmembrane electrochemical potential, and directly targets complex I. The inhibition of complex I by metformin decreases the proton gradient and mitochondrial oxygen consumption rate (OCR), which slows down tricarboxylic acid (TCA) cycle and decreases cellular ATP level.[38,39] As a compensatory response, cells can increase the glucose uptake and upregulate glycolysis[39] to partially refuel the TCA cycle and provide intermediates for biosynthesis. If the compensatory upregulation of glycolysis fails to meet the cellular ATP demand, the cellular AMP/ATP ratio would increase, and AMP would bind to the AMPK complex, and promote its phosphorylation and activation.[40] The activation of AMPK would result in the potentiation of catabolic metabolism and downregulation of anabolic reactions.[39] If the AMPK cascade continues to be active,

and cell proliferation would be ultimately inhibited.[41] Overall, the end result of cells exposed to metformin would be cellular energetic stress. In addition, metformin can act as a cytotoxic agent when cancer cells fail to compensate for this energetic stress, or a cytostatic agent when the cells are able to compensate.[42]

The protein complex AMPK belongs to a family of serine-threonine protein kinase complexes, and this serves as a major cellular energy sensor that maintains cellular energy homeostasis via a variety of pathways. AMPK is a heterotrimer that comprises a catalytic subunit (AMPKα) and two regulatory subunits (AMPKβ and AMPKγ).[40] The complex can be activated via the phosphorylation of Thr172 in the α-subunit mainly by three kinases, liver kinase B1 (LKB1),[43,44] calmodulin-mediated kinase kinase b (CaMKKb),[45,46] and transforming growth factor-b activated kinase 1 (TAK1).[47,48] Metformin can activate the catalytic AMPKα, inducing cell cycle arrest, autophagy, apoptosis and migration.[41]

Apart from its direct effect on cancer cells, metformin can also exert an indirect effect on cancer cells by reducing serum glucose, and thereby, the insulin levels.[49] Metformin inhibited hepatic gluconeogenesis by opposing glucagon-mediated signaling in the liver, resulting in the decrease of glucose.[50,51] On the other hand, metformin improved the affinity of insulin receptor for glucose uptake in skeletal muscle, leading to the reduction in insulin resistance[52] and the decline in hyperinsulinemia.[49] Hyperinsulinemia is responsible for the increased level of insulin-like growth factors (IGFs), leading to the increase in free or bioactive IGF-1 levels and the activation of insulin-like growth factor receptor (IGF-1R).[53] The activation of IGF-1R resulted in cell growth survival through the MAPK and PI3K signaling pathways.[54] However, metformin blocks the GC cell cycle in G0-G1 in vitro and in vivo through the reduction of IGF-1R activity.[55]

Metformin's Anti-Tumor Effects on Gastric Cancer

As mentioned in the last section, metformin can act as either a cytostatic or cytotoxic agent in cancer cells via the activation of AMPK and the inhibition of IGF-1R. This section reviews the roles of a variety of gene products that are responsible for metformin's anti-cancer effects downstream of the AMPK activation. These genes can be categorized based on their involvement in different biological processes, namely, the proliferation, apoptosis, metastasis and maintenance of stemness, which are summarized in Figure 1.
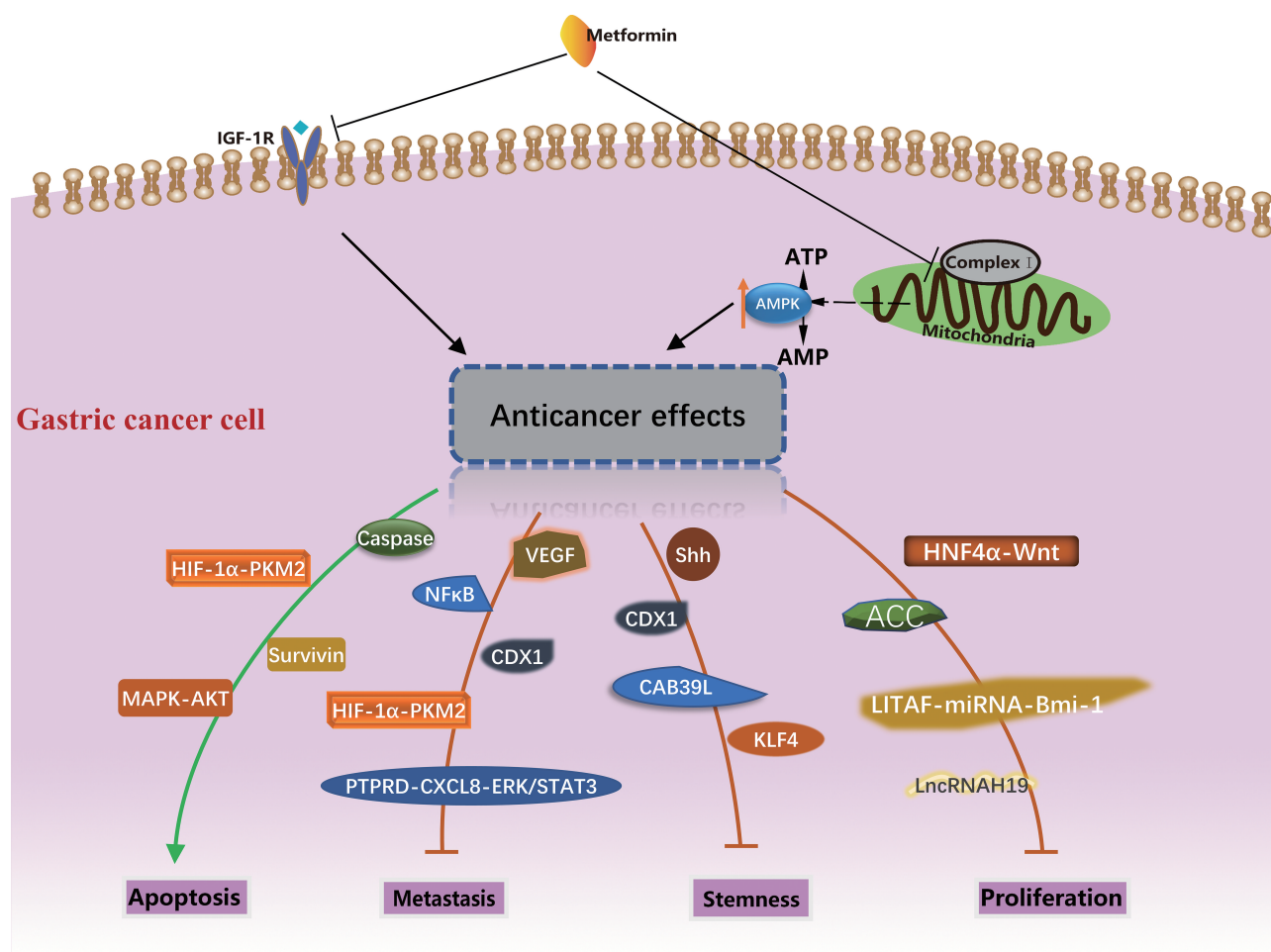
Figure 1 Potential molecular mechanism of anti-cancer activity of metformin in gastric cancer. The different biological processes and molecules involved were summarized.

Metformin Inhibits Gastric Cancer Cell Proliferation

The phosphorylation and activation of AMPK lead to the phosphorylation and inactivation of Acetyl-CoA carboxylase (ACC), the rate-limiting enzymes in de novo fatty acid synthesis, thereby causing a reduction in lipogenesis.[56] Fang et al reported that in GC patients, lower expression of pACC was significantly correlated with poorer differentiation, higher lymph node and overall TNM stage, and worse overall survival.[57] A further mechanistic study conducted by the same group revealed that metformin inhibits GC cell proliferation and colony formation by upregulating pACC through the activation of AMPK.[57]

Hepatocyte nuclear factor-4α (HNF4α), a transcription factor, is overexpressed in many types of cancer, and is involved in cell proliferation.[58] Chang et al reported that the upregulation of HNF4α is a key event in the development of GC in both Asian and Caucasian populations.[59] Furthermore, they found that HNF4α can be downregulated by AMPKα

signaling and AMPK agonist metformin in vivo and in vitro.[59] In addition, they reported WNT5A as a direct target gene of HNF in GC.[60] Further animal models confirmed the AMPK-HNF4α-WNT signaling cascade involved in cyclin down-regulation, cell cycle arrest, and tumor growth inhibition.[59]

A previous study identified lipopolysaccharide-induced TNFα factor (LITAF) as a downstream effector of AMPK in the regulation of tumor cell growth in prostate cancer.[61] Huang et al first depicted the regulatory axis sequentially tethering AMPK-LITAF-miRNAs-Bmi-1 in GC cells and other cancer cells.[62] B-lymphoma Moloney murine leukemia virus insertion region-1 (Bmi-1) is a transcriptional regulator that promotes tumor cell self-renewal, and epithelial to mesenchymal transition and its upregulation is associated with tumor progression.[63] AMPK activation increased the abundance of LITAFs and concurrently reduced the expression of Bmi-1, while the knockdown of LITAF upregulated Bmi-1 and promoted the aggressive behaviors of GC cells.[62] Metformin upregulated expression of miR-15a, miR-128,

miR-192 and miR-194, which can be abolished by the knock-down of LITAF.[62] Similarly, Kato et al reported that metformin inhibits human GC cell proliferation and tumor growth, possibly by suppressing the cell-cycle-related molecules via the alteration of miRNAs.[55] They found that the expression of has-mir-638 in metformin-treated cells was 3.3 times higher than that in untreated cells, suggesting that has-mir-638 might be a new therapeutic target in GC.[55]

Apart from miRNAs, long noncoding RNA (lncRNA) H19 was found to be overexpressed in GC tissues, when compared to normal tissue. In addition, the increased expression of H19 was correlated with more advanced pathological tumor stage.[64] Metformin could not further activate AMPK in H19 knocked down GC cells, indicating that H19 is a key component in the AMPK signaling pathway of metformin for suppressing GC cell proliferation and invasion.[64]

Metformin treatment inhibited GC cell growth in vitro and in vivo by blocking the cell cycle with the decreased expression of Cyclin D1.[55] Yu et al further demonstrated that cell growth and colony formation were inhibited with metformin treatment in a dose-dependent manner, and that this is correlated with the decreased expression of Cyclin D1 and CDK4.[65]

Metformin Induces Gastric Cancer Cell Apoptosis

Han et al reported that metformin selectively induces apoptosis in GC, but not noncancerous gastric cells, and they suggested that the apoptotic effect of metformin appears to be associated with poorer differentiation of GC.[66] The study conducted by Lu demonstrated that metformin-induced apoptosis was accompanied by the upregulation of AMPK Thr172 phosphorylation, and downregulation of AKT (Ser473), mTOR (Ser2448) and p70S6K (Ser424) phosphorylation.[67] The data also demonstrated that the attenuation of AMPK signaling using an AMPK inhibitor (Compound C) abrogated the effects of metformin on the viability of gastric adenocarcinoma cells (AGS).[67] AMPK/mTOR-mediated inhibition of survivin expression contributes, at least in part, to the metformin-induced apoptosis of GC cells.[66] In addition, metformin promotes the caspase-dependent mitochondria-derived apoptosis in AGS cells.[67]

The increase in hypoxia-induced factor 1α (HIF-1α) level is associated with increased risk of mortality in multiple human cancers, including gastric cancer.[68] Chen et al reported that the expression of HIF1α and pyruvate kinase M2 (PKM2) were higher in GC tissues than in gastritis tissues, and found that metformin significantly induced apoptosis, inhibited cell invasion and migration of GC cells.[69] In addition, their data support a model where metformin exhibits its anti-tumor effect for GC by inducing intrinsic apoptosis via the inhibition of HIF1α/PKM2 signaling pathway.[69] In addition, HIF1α plays a critical role in the regulation of tumor angiogenesis in response to hypoxia.[68]

Limited studies have provided little available information on the effect of metformin combined with chemotherapy. The combination of rapamycin and metformin appears to be more favorable in anti-gastric cancer.[65] However, the effect of metformin combined with cisplatin remains controversial. Yu et al reported that on MKN45 xenografts and BGC823 cells, the combined administration with metformin enhanced the chemo-induced reduction of tumor growth in GC.[65] On the contrary, Lesan et al reported that on the human gastric MKN-45 cell line, metformin diminishes the anti-proliferative effects of cisplatin when used in combination with metformin.[70] The antagonistic effect of metformin on cisplatin could be through the survivin and mTOR/AKT signaling pathways in the MKN-45 cell line.[70] The discrepancy may lie in the difference in cancer type and cell type.

Metformin Inhibits Cancer Metastasis

One of the key features of malignancy in cancer cells is their ability to reduce cell-cell adhesion and invade surrounding tissues.[71] Metformin could inhibit the metastasis of GC, but its specific mechanism remains on debate. Cadherins are a group of cell membrane proteins critical in the formation of cell-cell adherence junctions and can be classified by their distinct immunological and tissue specificities, such as E- for epithelial and N- for neural. Loss of E-cadherin can lead to initiation of epithelial–mesenchymal transition (EMT), which is characterized by reduced cell polarity, and increased migratory and invasive growth properties.[72] Different from the general metastatic phenotype alternation, Valaee et al indicated that EMT inhibition by metformin in the GC cell line was in concordant with E-cadherin enhancement.[73] On the other hand, Jun et al reported that brain metastasis in advanced GC was significantly correlated with the expression of vascular endothelial growth factor (VEGF), but not E- or N-cadherin.[74] Metformin treatment affects the metastatic capacity of GC by reducing VEGF expression and blocking EMT.[74]

E-cadherin can be regulated by Protein tyrosine phosphatase receptor delta (PTPRD) to influence cell migration.[75] PTPRD is frequently inactivated in GC. The loss of PTPRD induces CXCL8, via both ERK and STAT3 signaling, promoting angiogenesis, and consequently, metastasis.[76] Researchers have further proposed that metformin could exert its anti-cancer effect by reversing the downregulated PTPRD expression.[76]

In addition, loss of E-cadherin could enhance the inflammatory signals, particularly NF-κB induced EMT.[77,78] More specifically, Sekino et al reported that metformin inhibited the GC peritoneal metastasis on a NF-κB-, but not AMPK-, dependent manner.[79]

Metformin Inhibits Cancer Cell Stemness

Cancer stem cells (CSC), or tumor-initiating cells, are a subset of cancer cells that are considered to have indefinite potential of self-renewal, and could lead to tumorigenesis.[80,81] Courtois et al reported that metformin can target GC stem cells, and decrease their self-renewal ability both in vitro and in vivo.[82] Previous evidence has demonstrated that in GC cells, the Sonic hedgehog (Shh) pathway are abnormally activated, and the overexpression of Shh protein could contribute to tumorogenesis.[83] Glioma associated oncogene (Gli), a downstream target gene of the hedgehog signal pathway, is represented by Gli-1, Gli-2 and Gli-3 in mammalians.[84] In the study conducted by Song, the Shh pathway maintained the GC stem-like cells (CSLCs) have characteristics, including chemoresistance and tumorigenic capacity.[85] A follow-up study led by the same group showed that both protein and mRNA levels of Shh and Gli 1, Gli2, Gli3 were decreased by metformin in two GC cell lines in a dose- and time-dependent manner.[86]

Caudal type homeobox 1 (CDX1), as a transcription factor, act a pivotal part in human intestinal development and maintenance.[87] The aberrant expression of CDX1 can be triggered by *H. pylori* virulence factor CagA.[88] Patients with *H. pylori* tended to have more CDX1 expression than non-infected and enhanced GC tumorigenesis and progression.[88] Human tissue samples with higher CDX1 levels revealed the prominent stem cell markers CD44/SOX2 expression.[88] Likewise, in a murine xenograft model, combining metformin or shCDX1 with cisplatin-reduced tumor growth, increased caspase-3 cleavage, and reduced the expression of the stem cell markers CD44 and MMP-9 to a greater degree, when compared to cisplatin alone.[88]

In addition, Li et al identified the aberrant silencing of Calcium Binding Protein 39-Like (CAB39L) in GC by promoter hypermethylation, and represented an epigenetic mechanism that contributes to metabolic dysregulation and GC development.[89] CAB39L elicited an anti-Warburg effect via a LKB1-AMPK-PGC1α axis to inhibit gastric tumorigenesis, and CAB39L-silenced GC cells exhibited an increased sensitivity to metformin.[89]

Recently, Miao et al demonstrated that AMPK activates Krüppel-like factor 4 (KLF4) in progenitors to govern gastric epithelial progenitor differentiation, reduce self-renewal, and promote parietal cell (PC) fate, while the PC-specific activation of AMPK-PGC1α promotes maturation.[90] This may provide a potential suggestion for why metformin increases acid-secretion and reduces GC risk.[90]

Conclusion and Future Perspective

Clinical studies have suggested that the regular use of metformin may decrease the risk and mortality of multiple cancers in T2DM patients. In terms of GC, several clinical studies have revealed that metformin can reduce GC risk and improve overall survival. Furthermore, studies have shown that metformin is an anti-cancer agent, and can inhibit proliferation, metastasis and stemness, promote tumor apoptosis, and increase the chemosensitivity of GC cells. Mechanistic studies have revealed a wide range of gene products and signaling pathways involved in metformin's anti-cancer effect.

Compared with liver cancer, pancreatic cancer and colon cancer, both clinical studies and mechanism researches in GC are still relatively rare. In clinical practice, more prospective clinical trials are needed to confirm its effect, and the synergistic action between metformin use and chemotherapy or immunotherapy is also an attractive aspect for GC. For the mechanism research, uptake is an important process for metformin to exert its activity. It was found that promoter variants in transporter MATE and the heterogeneity of transporter OCT1 expression might affect the pharmacokinetics and pharmacodynamics of metformin.[91,92] Further investigations are needed to elucidate the uptake of metformin in different types of GC cells and the results it caused. On the other hand, accumulating evidence has indicated the potential roles of microbiome on the anti-cancer activity of metformin in pancreatic and colorectal cancer,[93,94] the interaction between metformin and gut microbiota is worth studying in gastric cancer prevention and treatment.

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Disclosure

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