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Research progress on the effect of type 2 diabetes and hypoglycemic drugs on the prognosis of patients with colorectal cancer

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Abstract: In recent years, the comorbidity of colorectal cancer (CRC) and diabetes mellitus has become more and more common, and has become one of the public health problems that seriously endanger human health. The pathological mechanisms of diabetes mellitus such as hyperglycemia, insulin resistance and chronic inflammation can promote the progression of CRC. In addition, the effects of hypoglycemic drugs such as insulin, metformin, glucagon-like peptide-1 (GLP-1) receptor agonist and sodium-glucose cotransporter-2 (SGLT2) inhibitor on the prognosis of patients with type 2 diabetes mellitus (T2DM) complicated with CRC are also controversial. This article will comprehensively analyze the molecular mechanism of T2DM affecting the prognosis of CRC and the effects of different hypoglycemic drugs on the prognosis of CRC patients with T2DM.

Keywords: Colorectal cancer; Type 2 diabetes; Insulin resistance; Glucagon-like peptide-1 receptor agonist; Sodium-glucose cotransporter-2 inhibitor; Prognosis

Currently, colorectal cancer (CRC) is the third most common malignant tumor globally and the second leading cause of cancer-related death. Although the overall cancer mortality rate in China has shown a downward trend since 2000, the CRC mortality rate remains in an upward stage due to the difficulty of diagnosis and treatment and insufficient early screening. In diabetic patients, long-term poor blood glucose control can lead to chronic damage to different tissues and organs such as the kidneys, ocular microvasculature, heart, and nerves [1]. Approximately 95% of diabetic patients have type 2 diabetes mellitus (T2DM). Because T2DM and CRC share similar pathogenic backgrounds, such as a high-calorie, high-fat, low-protein, low-fiber dietary structure, obesity, sedentary lifestyle, and other unhealthy lifestyles, T2DM and CRC often coexist clinically, affecting patients' survival rate and quality of life [2-3].

T2DM significantly increases the risk of developing CRC. According to the latest global data for 2025, the risk of developing CRC in diabetic patients is 20%-40% higher than in non-diabetic patients. Particularly, the incidence of CRC in East Asia accounts for 52.3% of the global total, which may be related to the rapid rise in the diabetes prevalence rate [4]. Furthermore, CRC patients with comorbid T2DM show a trend toward younger onset; their median age of onset is at least 5 years earlier than that of the non-diabetic group. Factors such as obesity and insulin resistance within metabolic syndrome are considered key factors. A pooled analysis of data from 31 prospective cohort studies showed that the combined hazard ratio (HR) for gastrointestinal malignancies in patients with metabolic syndrome (including obesity and hyperglycemia) was 1.28 (95%*CI*: 1.15-1.42), indicating that metabolic syndrome increases the risk of gastrointestinal malignancies by approximately 28% [1,4-5]. Among these, the risk elevation for pancreatic cancer (*HR*=1.35) and CRC (*HR*=1.30) was especially significant.

In terms of survival outcomes, CRC patients with diabetes have significantly poorer prognosis, and those with a diabetes duration ⩾ 10 years or glycated hemoglobin (HbA_{1c}) ⩾ 7.5% have an even higher risk of mortality [5-6]. This difference may be related to the chronic inflammatory state of diabetic patients and changes in the tumor microenvironment (TME). Moreover, hyperglycemia is also associated with chemotherapy resistance and metastasis in CRC cells, as elevated glucose levels can reduce the efficacy of 5-fluorouracil. For instance, in CRC patients treated with the FOLFOX regimen, the disease control rate (DCR) in the diabetic group was significantly lower than in the non-diabetic group, which may be related to hyperinsulinemia inhibiting chemotherapy-induced apoptosis of tumor cells [7-8]. Therefore, T2DM impacts the prognosis of CRC patients in multiple ways.

1 Molecular Mechanisms by which T2DM Affects CRC Prognosis

1.1 Insulin Resistance and Hyperinsulinemia

T2DM is a metabolic disorder characterized by dysfunction of pancreatic β-cells, presenting as insulin resistance, hyperinsulinemia, and hyperglycemia, all of which are critical in cancer progression, especially in CRC [8-9]. In T2DM patients, insulin resistance leads to compensatory hyperinsulinemia. Insulin and its analogs activate the phosphatidylinositol 3-kinase (PI3K) / protein kinase B (AKT) pathway to inhibit apoptosis in CRC cells [9]. Studies have shown that elevated insulin levels can directly stimulate the phosphorylation of the insulin-like growth factor-1 receptor (IGF-1R), further activating the downstream RAS/ mitogen-activated protein kinase (MAPK) pathway, leading to enhanced tumor cell invasiveness [10-11].

1.2 Chronic Inflammation and Immune Micro-environment Imbalance

Patients with T2DM are in a state of chronic low-grade inflammation, with significantly elevated serum levels of inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6). These cytokines activate the nuclear factor (NF)-κB pathway, inducing tumor cells to produce pro-metastatic factors such as matrix metalloproteinase-9 (MMP-9), which degrade extracellular matrix and basement membrane fibers, facilitating tumor cell infiltration and metastasis [12-14]. Additionally, diabetes-associated inflammation can lead to the accumulation of regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs) in the TME. These cells interact to promote immune evasion, ultimately enhancing the inhibitory response to programmed death-1 (PD-1) and its ligand PD-L1 immune checkpoints [14-15]. Studies have shown that CRC patients with diabetes have 1.5 times higher Treg cell levels in tumor tissues compared to non-diabetic patients, leading to poorer prognosis in these patients [15]. More importantly, in CRC tissues, a new B cell subpopulation expressing high levels of transforming growth factor-β1 (TGF-β1) and leucyl tRNA synthetase 2 secretes cytokines such as IL-10 and TGF-β to inhibit T cell activity. This subpopulation forms a positive feedback loop with Tregs, further promoting tumor immune evasion.

1.3 Epigenetic Regulation

Hyperglycemia and insulin resistance can induce hypermethylation in the promoter regions of tumor suppressor genes such as APC and p16, leading to their silencing. Studies have shown that in CRC patients, methylation of APC in the Wnt/β-catenin pathway increases, promoting β-catenin nuclear translocation, which drives tumor cell proliferation and invasion. Moreover, the low expression of diabetes-related gene CD36 in CRC is likely associated with hypermethylation in its promoter region, and the low expression of CD36 is significantly linked to poor prognosis [16]. Additionally, hyperinsulinemia can inhibit histone deacetylase activity, increasing histone acetylation levels of oncogenes like c-Myc, enhancing their transcriptional activity and promoting tumorigenesis [17]. Long non-coding RNAs participate in CRC proliferation, invasion, migration, apoptosis, and drug resistance through competitive endogenous RNA mechanisms. Among these, metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) can enhance the activity of the β-catenin signaling pathway through histone methylation modification, promoting CRC proliferation, invasion, and metastasis. Studies have shown that Jumonji C domain-containing 2C (JMJD2C), a protein overexpressed in CRC tumor tissues, can bind directly to the MALAT1 promoter region, reducing histone methylation levels and promoting CRC proliferation, invasion, and metastasis. Therefore, MALAT1 could be a potential target for preventing and treating CRC metastasis [18].

1.4 Dysbiosis of Gut Microbiota

The gut microbiota is vast and diverse, playing an essential role in metabolic and immune regulation to maintain health and ecological balance within the body. *Fusobacterium nucleatum* can activate the extracellular signal-regulated kinase (ERK) signaling pathway by binding to DEAH-box helicase 15 (DHX15) protein, promoting tumorigenesis in KRAS-mutated CRC. The abundance of this bacteria significantly increases in the gut microbiota of T2DM patients. In contrast, *Bacteroides distasonis* can compete with *Fusobacterium nucleatum* to suppress its carcinogenic effects, regulate the gut barrier, and contribute to immune responses and metabolic regulation. However, the abundance of this bacterium is decreased in T2DM patients, resulting in a weakened protective effect [19]. Moreover, when the balance of the gut microbiota is disrupted, it leads to reduced production of short-chain fatty acids (e.g., butyrate) and increased production of secondary bile acids (e.g., deoxycholic acid), weakening the gut's anti-inflammatory capacity and promoting tumor cell proliferation [19-20]. Furthermore, due to impaired intestinal barriers and increased permeability in T2DM patients, endotoxins such as lipopolysaccharide (LPS) quickly enter the bloodstream, triggering a systemic chronic inflammatory response. LPS can also activate the Toll-like receptor 4 (TLR4) signaling pathway, promoting the release of inflammatory cytokines and further inducing angiogenesis and immune suppression in the TME [20].

2 Impact of T2DM Treatment on Colorectal Cancer Patients

2.1 Insulin and Insulin Analogs

Insulin, besides being a metabolic hormone regulating blood glucose, also acts as a growth factor by binding to the insulin receptor and activating downstream MAPK and PI3K/AKT signaling pathways. This interferes with the cell cycle and inhibits apoptosis, thereby promoting cancer cell proliferation and tumor progression [21]. Clinical studies indicate that advanced CRC patients with concomitant diabetes, who use insulin, have a significantly lower median overall survival compared to those in the non-insulin treatment group (9.6 months *vs* 11.8 months), with insulin dose being positively correlated with tumor recurrence rate [22]. However, some studies suggest that this result may be related to the longer duration of diabetes and poorer blood glucose control in the insulin-treated population [23]. Additionally, due to the structural homology between insulin and IGF-1R, there is cross-activation between the two. Thus, insulin-like growth factor 1 (IGF-1) and insulin-induced downstream cellular signaling pathways are identical. Studies have shown that overexpression of IGF-1R significantly impacts the depth of CRC tumor invasion and lymph node metastasis [24-25].

Insulin provides energy and a favorable growth microenvironment for cancer cells by regulating glucose metabolism. Research indicates that insulin activates the PI3K/AKT signaling pathway, promoting the expression of glucose transporters (GLUT1/3) and providing energy for cancer cell proliferation. At the same time, insulin enhances the activity of key enzymes in glycolysis, such as 6-phosphofructo-2-kinase (PFKFB3) and phosphofructo-kinase-1 (PFK-1), through the activation of hypoxia-inducible factor-1α (HIF-1α), accelerating glucose breakdown and lactate accumulation. As lactate accumulates, the acidic microenvironment promotes angiogenesis [25]. Furthermore, the large amount of lactate can drive immune escape by promoting tumor-associated macrophage polarization and weakening T-cell immunity [26].

Endogenous hyperinsulinemia is common in insulin-resistant T2DM patients. Sustained high insulin levels activate insulin receptor subtype A and IGF-1R, promoting CRC cell proliferation and invasion. Exogenous insulins like insulin glargine and insulin degludec, due to the lack of liver first-pass effect, result in prolonged exposure of peripheral tissues to high insulin concentrations, thereby accelerating tumor progression [27]. A retrospective study involving 145 T2DM patients with CRC found that the lymph node metastasis rate (53% *vs* 32%), advanced pathological staging (III+IV stage, 57% *vs* 32%), and Ki-67 positive rate (76% *vs* 53%) were significantly higher in the insulin treatment group compared to the non-insulin group (P<0.05), suggesting that exogenous insulin may exacerbate CRC invasion and metastasis, leading to poor prognosis [23, 28-29].

Therefore, clinical evaluation should compre-hensively assess the patient's current metabolic status and tumor-related risks, prioritizing non-insulin drugs. Moreover, future research should focus on exploring novel therapeutic approaches that can precisely target the insulin signaling pathway, developing treatments that address both glucose control and cancer therapy.

2.2 Metformin

Metformin not only lowers blood glucose but also exhibits anti-cancer properties. Studies have found that metformin downregulates inhibin βA, weakening the activity of the TGF-β/PI3K/AKT signaling pathway, leading to a decrease in G1/S-specific cyclin D1 and cell cycle arrest, thereby inhibiting cancer cell proliferation [30]. A cohort study involving 108 patients showed that the disease control rate (DCR) in the metformin group increased to 62%, significantly higher than the insulin group (48%) [31]. Additionally, metformin regulates the expression of small RNAs, including microRNAs, to further inhibit tumor-associated genes and delay cancer cell growth. Moreover, metformin combined with cisplatin can inhibit cancer cell activity, enhance the sensitivity of SW480 and SW620 cell lines to cisplatin, and suppress tumor growth and invasion [32].

Metformin demonstrates significant anti-cancer effects in specific populations. For example, in CRC patients with *KRAS* mutations, metformin accumulates intracellularly due to decreased expression of the membrane channel protein METE1. When reaching high concentrations, it significantly inhibits cancer cell proliferation, extending overall survival to 37.8 months in *KRAS*-mutant patients, with no significant benefit in wild-type patients. Therefore, based on this mechanism, metformin may be particularly effective in *KRAS*-mutant patients. Selecting suitable individuals for metformin treatment can further achieve personalized, precise treatment [33]. Different doses of metformin may exert varying effects. High concentrations of metformin (e.g., 2.5 mmol/L) exert anti-cancer effects by inhibiting the activity of mitochondrial respiratory chain complex I, while low concentrations of metformin may promote fatty acid oxidation by activating the AMP-activated protein kinase (AMPK)/acetyl-CoA carboxylase (ACC) /fatty acid β-oxidation (FAO) pathway, accelerating the proliferation of some cancer cells. The differences in efficacy produced by these different doses may be a key reason for the inconsistency in clinical research results [34]. However, current CRC-related studies have not accurately demonstrated that low-dose metformin has a carcinogenic effect. Further experiments are needed to investigate the dose threshold at which metformin inhibits CRC cells, effectively avoiding potential risks associated with low-dose metformin.

Metformin has shown various potentials in CRC treatment, but current research mainly consists of in vitro experiments or retrospective analyses, lacking evidence from large-scale randomized controlled trials. Moreover, trial groupings often overlook molecular heterogeneity and drug dosage differences, which may affect the accuracy of the conclusions. Future research should therefore rigorously design trial protocols, conduct stratified studies, and promote precision medicine to advance individualized diagnosis and treatment.

2.3 Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs)

Obesity is a major factor contributing to the occurrence and development of CRC. Research has shown that for every 5 kg/m² increase in body mass index (BMI), the risk of CRC increases by 10% to 20%. Furthermore, visceral fat can secrete pro-inflammatory cytokines such as IL-6 and TNF-α, as well as adipokines like leptin and adiponectin, which can directly promote intestinal inflammation and TME formation. Therefore, with every 10 cm² increase in visceral fat area, the risk of CRC increases by 15% [35-36]. However, the emergence of GLP-1RAs has significantly reduced the risk of CRC. A retrospective study based on the U.S. TriNetX platform found that compared to insulin, the *HR* for developing CRC in the GLP-1RA group was 0.56 (95%*CI*: 0.44–0.72), and compared to metformin, the HR was 0.75 (95%*CI*: 0.58–0.97). Therefore, the use of GLP-1RAs in overweight or obese patients can significantly reduce the risk of CRC [37].

GLP-1RAs can regulate metabolic pathways related to glucose and lipid metabolism, such as AMPK and mammalian target of rapamycin (mTOR), thereby cutting off the energy supply to the TME. Additionally, by modulating the NF-κB signaling pathway, they reduce the levels of pro-inflammatory cytokines like IL-6 and TNF-α, decreasing intestinal mucosal inflammation and inhibiting tumor cell proliferation. GLP-1RAs not only coordinate metabolic and immune processes but also activate satiety signals in the central nervous system, significantly reducing visceral fat, thus improving CRC prognosis [38]. Weight loss can also improve insulin sensitivity and lipid metabolism disorders, indirectly inhibiting the TME. Similarly, GLP-1RAs have direct anti-tumor effects. By activating the AMPK pathway, GLP-1RAs inhibit CRC cell proliferation, induce cell cycle arrest, and downregulate vascular endothelial growth factor (VEGF) and MMP-9 expression, thereby inhibiting tumor angiogenesis and invasion [39]. Studies show that tirzepatide can significantly delay the tumor progression in CRC patient-derived xenograft models by promoting the ubiquitination and degradation of HIF-1α and inhibiting the glycolysis mediated by PFKFB3-PFK-1 [40].

However, due to the individual differences in GLP-1 receptor expression in CRC tissues and the interference of various confounding factors, the potential role of GLP-1RA drugs in obesity-related cancers still requires long-term exploration. Future research should focus on newer, more potent GLP-1RAs, and combine them with different molecular subtyping for targeted studies to determine the optimal treatment drugs and strategies.

2.4 Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i)

Although there is currently a lack of direct trial evidence on the impact of SGLT2i on the prognosis of CRC patients with T2DM, based on SGLT2i's metabolic pathways, anti-inflammatory mechanisms, and regulation of gut microbiota, it can be speculated that it has potential positive effects on CRC patients. Chronic inflammation can lead to the occurrence and development of CRC. Research shows that dapagliflozin can reduce the release of pro-inflammatory cytokines like IL-1β by inhibiting nucleotide-binding, oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activity in the kidneys, thereby suppressing the inflammatory response. Therefore, based on renal disease models, SGLT2i may suppress intestinal inflammation and delay the progression of colorectal cancer precursors, thereby reducing the risk of CRC [41].

SGLT2i can inhibit renal glucose reabsorption and promote urinary glucose excretion, improving the metabolic disorder status in T2DM patients. Since tumor cells rely on glycolysis for energy, SGLT2i may indirectly cut off the energy supply to tumor cells by lowering circulating glucose levels and inhibiting tumor proliferation. Additionally, SGLT2i promotes increased urinary glucose excretion, and a high-glucose environment may promote the proliferation of specific intestinal microbiota. The short-chain fatty acids they produce have anti-tumor activity, potentially inhibiting CRC cell proliferation and further affecting CRC patient prognosis [42].

Future research should continue to explore the potential value of SGLT2i in CRC patients with T2DM. For example, studies could investigate whether SGLT2i inhibits cancer cell growth through suppression of the HIF-1α pathway or the AMPK/mTOR signaling axis. Furthermore, since insulin treatment can lead to CRC progression and is associated with increased lymph node metastasis and shorter survival, SGLT2i, as a non-insulin-dependent glucose-lowering therapy, may avoid insulin-related risks and become a better option for lowering blood sugar in cancer patients in the future. Therefore, head-to-head studies are needed to compare the differences in prognosis for CRC patients with T2DM between SGLT2i and insulin, providing ample evidence support for clinical medication decisions. Metabolic syndrome is an independent risk factor for CRC, but

SGLT2i can not only control blood sugar but also improve metabolic disorders such as obesity and hypertension. Hence, in combination with the cardiovascular-renal-metabolic syndrome management concept, further evaluation is needed on whether SGLT2i's regulation of weight, blood lipids, and other metabolic parameters can synergistically improve CRC patient prognosis.

3 Summary and Outlook

T2DM and CRC share common metabolic disturbances, such as abnormal glycolysis and insulin signaling dysfunction. Therefore, the long-term management of CRC patients with T2DM should establish a "Cancer Treatment - Metabolic Control - Complication Prevention" tri-dimensional system. The metabolic disorders associated with T2DM not only accelerate tumor progression but also increase the difficulty of cancer treatment, making blood glucose control a central step in metabolic management. Insulin resistance and hyperinsulinemia can promote CRC cell proliferation, so metformin and other drugs that improve insulin sensitivity should be prioritized when controlling blood glucose, and long-term use of insulin analogs should be avoided. Regulating gut microbiota and improving gut barrier function are also emerging metabolic intervention strategies. Additionally, short-term lifestyle interventions such as low glycemic index diets and regular exercise can significantly regulate the microbiome-metabolite axis and improve blood glucose fluctuations. While controlling blood glucose, it is also crucial to monitor for early prevention and control of tumor recurrence, metastasis, and cardiovascular and renal complications, continuously improving cancer patients' survival rate and quality of life.

The association between T2DM and CRC results from a multi-factorial, multi-layered interaction. To further improve the survival rate and quality of life for CRC patients with T2DM, future research should explore the anti-tumor potential of metabolic pathway-targeted drugs. For the key nodes in the shared pathogenesis of T2DM and CRC, dual-function drugs that regulate both inflammatory factors and metabolic enzymes should be developed, such as combining TNF-α antagonists with AMPK agonists. This approach could alleviate the chronic inflammatory response in T2DM patients while inhibiting the Warburg effect in CRC cells. GNE-149, developed by Genentech, both fully antagonizes estrogen receptors and induces their degradation, providing a new endocrine therapy option for breast cancer patients. Similar strategies could also be applied to the design of dual-function drugs targeting T2DM and CRC comorbidities. Moreover, future research needs to break through the single-mechanism perspective by adopting a multidisciplinary joint diagnosis and treatment model, constructing an interdisciplinary collaborative treatment approach, and transitioning from "Disease Comorbidity Management" to "Mechanism-Driven Therapy".

Conflict of Interest None

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·研究进展·

2型糖尿病及降糖药物对结直肠癌患者预后影响的研究进展

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摘要： 近年来结直肠癌与糖尿病共病现象愈发普遍，已成为严重危害人类健康的公共卫生问题之一。高血糖状态、胰岛素抵抗及慢性炎症等糖尿病病理机制可促进结直肠癌进展。此外，胰岛素、二甲双胍、胰高血糖素样肽-1受体激动剂（GLP-1RA）和钠-葡萄糖共转运蛋白2抑制剂（SGLT2i）等降糖药物对2型糖尿病（T2DM）合并结直肠癌患者的预后影响也存在争议。本文将从T2DM影响结直肠癌预后的分子机制及不同降糖药物对结直肠癌合并T2DM患者预后的影响进行综合分析。

关键词： 结直肠癌；2型糖尿病；胰岛素抵抗；胰高血糖素样肽-1受体激动剂；钠-葡萄糖共转运蛋白2抑制剂；预后
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Research progress on the effect of type 2 diabetes and hypoglycemic drugs on the prognosis of patients with colorectal cancer

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Abstract: In recent years, the comorbidity of CRC and DM has become more and more common, and has become one of the public health problems that seriously endanger human health. The pathological mechanisms of DM such as hyperglycemia, insulin resistance and chronic inflammation can promote the progression of CRC. In addition, the effects of hypoglycemic drugs such as insulin, metformin, glucagon-like peptide-1 receptor agonist and SGLT2i on the prognosis of patients with T2DM complicated with CRC are also controversial. This article will comprehensively analyze the molecular mechanism of T2DM affecting the prognosis of CRC and the effects of different hypoglycemic drugs on the prognosis of CRC patients with T2DM.

Keywords: Colorectal cancer; Type 2 diabetes; Insulin resistance; Glucagon-like peptide-1 receptor agonist; SGLT2 inhibitor; Prognosis

目前结直肠癌（colorectal cancer，CRC）是全球发病率第三、死亡率第二的恶性肿瘤。虽然中国癌症总死亡率自2000年起呈下降趋势，但CRC死亡率因诊疗难度大、早期筛查不足，仍处于上升阶段。糖尿病患者若血糖长期控制不良可导致肾脏、眼部微血管、心脏、神经等不同组织器官的慢性损伤[1]。糖尿病患者中约有95%为2型糖尿病（type 2 diabetes mellitus，T2DM）。由于T2DM与CRC具有相似的发生背景，如高热量、高脂肪、少蛋白、少纤维饮食结构，肥胖和久坐等不良生活方式，因此临床上T2DM与CRC常合并存在，影响患者的生存率及生存质量[2-3]。

T2DM极大增加了CRC患病风险。根据2025年全球最新数据显示，糖尿病患者罹患CRC的风险较非糖尿病患者增加20%~40%，尤其是东亚地区的CRC发病率占全球52.3%，这可能与糖尿病患病率快速上升相关[4]。此外，合并T2DM的CRC患者有年轻化趋势，中位发病年龄较非糖尿病组提前至少5年，肥胖、胰岛素抵抗等代谢综合征因素被认为是关键因素。综合31项前瞻性队列的数据显示，具有肥胖、高血糖等代谢综合征患者发生胃肠道恶性肿瘤的合并风险比（hazard ratio，*HR*）为1.28（95%*CI*：1.15~1.42），提示代谢综合征使患者发生胃肠道恶性肿瘤的风险增加约28%[1,4-5]。其中，胰腺癌和CRC的风险升高尤为明显（*HR*分别为1.35和1.30）。

在生存结局方面，合并糖尿病的CRC患者预后显著较差，

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且糖尿病病程≥10年、糖化血红蛋白≥7.5%的患者死亡风险更高[5-6]。这一差异可能与糖尿病患者的慢性炎症状态及肿瘤微环境改变相关。并且高血糖还与CRC细胞的化疗耐药性和转移有关，葡萄糖水平升高会降低5-氟脲嘧啶的疗效。例如，接受FOLFOX方案治疗的CRC患者中，糖尿病组的疾病控制率(disease control rate，DCR)较非糖尿病组明显降低，这可能与高胰岛素血症抑制化疗药物诱导的肿瘤细胞凋亡有关[7-8]。所以T2DM在不同方面影响着CRC患者的预后。

1　T2DM影响CRC预后的分子机制

1.1　*胰岛素抵抗和高胰岛素血症*　T2DM是一种以胰岛β细胞功能障碍为特征的代谢类疾病，可表现为胰岛素抵抗、高胰岛素血症和高血糖，这些在癌症进展中至关重要，尤其是CRC[8-9]。T2DM患者由于体内胰岛素抵抗导致代偿性高胰岛素血症，胰岛素及其类似物通过激活PI3K/AKT通路，抑制CRC细胞凋亡[9]。研究发现，患者体内胰岛素水平升高可直接刺激胰岛素样生长因子-1受体(insulin-like growth factor 1 recepter，IGF-1R)磷酸化，进一步激活下游RAS/MAPK通路，导致肿瘤细胞侵袭性增强[10-11]。

1.2　*慢性炎症与免疫微环境失衡*　T2DM患者长期处于慢性低度炎症状态，其血清中肿瘤坏死因子α(tumor necrosis factor-α，TNF-α)、白细胞介素(interleukin，IL)-6等炎症细胞因子水平明显升高，通过激活NF-κB通路，诱导肿瘤细胞产生基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)等促转移因子，降解细胞外基质和基底膜中的纤维网架分子，为肿瘤细胞的浸润和转移提供便利[12-14]。并且糖尿病相关炎症反应可导致肿瘤微环境中调节性T细胞(regulatory T cells，Treg)和髓源性抑制细胞的富集，两者相互串扰促进免疫逃逸，最终增强对程序性死亡受体-1/程序性死亡受体-配体1(programmed death-1/programmed cell death-ligand 1，PD-1/PD-L1)免疫检查点的抑制反应[14-15]。研究显示，合并糖尿病的CRC患者肿瘤组织中Treg比例较非糖尿病患者高1.5倍，所以该类患者晚期预后相对较差[15]。更重要的是，CRC组织中富集一类高表达转化生长因子(transforming growth factor，TGF)-β1的亮氨酸tRNA合成酶2的B细胞新亚群，通过分泌IL-10、TGF-β等细胞因子抑制T细胞活性，并与Treg细胞形成正反馈，从而极大程度地促进肿瘤免疫逃逸。

1.3　*表观遗传调控*　高血糖和胰岛素抵抗可诱导APC、p16等抑癌基因的启动子区超甲基化，导致其表达沉默。研究发现CRC患者Wnt/β-catenin通路的APC甲基化水平升高，促进β-catenin核转位，驱动肿瘤细胞增殖和侵袭。此外，糖尿病相关基因CD36在CRC中低表达，可能与其启动子区高甲基化相关，而CD36的低表达与不良预后显著相关[16]。并且高胰岛素血症可通过抑制组蛋白去乙酰化酶活性，增加c-Myc等促癌基因的组蛋白乙酰化水平，提高其转录活性，促使肿瘤的发生发展[17]。长链非编码RNA通过竞争性内源RNA参与CRC的增殖、侵袭、迁移、凋亡以及耐药。其中转移相关肺腺癌转录物1(metastasis associated lung adenocarcinoma transcript 1，MALAT1)可通过组蛋白甲基化修饰，增强β-catenin信号传导途径的活性，促进CRC增殖、侵袭和转移。研究发现，十字形结构域蛋白2C(JMJD2C)在CRC肿瘤组织中过表达，JMJD2C可通过与MALAT1启动子区域直接结合，降低组蛋白甲基化水平，促进CRC增殖、侵袭和转移。因此，MALAT1可能是预防和治疗CRC转移的潜在靶点[18]。

1.4　*肠道菌群失调*　肠道菌群数目庞大且种类繁多，参与机体代谢和免疫调节，对维持机体健康和保持体内生态平衡尤为重要。其中具核梭杆菌可通过结合DEAH盒解旋酶15(DHX15)蛋白激活ERK信号通路，促进KRAS突变型CRC的肿瘤发生。该菌群在T2DM患者肠道菌群中丰度显著增加。而狄氏副拟杆菌可通过与具核梭杆菌竞争抑制其致癌作用，调节肠道屏障、发挥免疫应答和代谢调节的功能。但T2DM患者肠道中该菌丰度降低，保护效应明显减弱[19]。并且当肠道菌群比例发生失衡时，会导致短链脂肪酸(如丁酸)合成减少、次级胆汁酸(如脱氧胆酸)生成增加，导致肠道自身抗炎能力削弱，促使肿瘤细胞增殖[19-20]。并且由于T2DM患者肠道屏障被破坏、通透性增加，脂多糖等内毒素迅速进入血液，激发全身慢性炎症反应。脂多糖还可通过激活Toll样受体4信号通路，促进炎症细胞因子释放，进一步诱导肿瘤微环境中血管生成和免疫抑制[20]。

2　T2DM治疗对结直肠癌患者的影响

2.1　*胰岛素与胰岛素类似物*　胰岛素不仅是调节血糖的代谢激素，还可作为生长因子与胰岛素受体结合，激活下游MAPK和PI3K/AKT信号通路，通过干扰细胞周期和抑制细胞凋亡，促进癌细胞增殖、肿瘤进展[21]。临床研究表明，合并糖尿病的晚期CRC患者使用胰岛素后，中位总生存期显著低于非胰岛素治疗组(9.6个月 *vs* 11.8个月)，且胰岛素剂量与肿瘤复发率呈正相关[22]。但部分研究认为，这一结果可能与胰岛素使用人群的糖尿病病程更长、血糖控制更差相关[23]。此外，由于胰岛素与IGF-1R具有结构同源性，两者存在交叉激活现象。遂胰岛素样生长因子1(insulin-like growth factor 1，IGF-1)和胰岛素诱导的下游细胞信号转导通路是相同的。并且研究显示，IGF-1R过表达显著影响结直肠癌肿瘤侵袭深度和淋巴结转移程度[24-25]。

胰岛素通过调节糖代谢为癌细胞提供能量和生长适宜微环境。研究表明，胰岛素通过激活PI3K/AKT信号通路促进葡萄糖转运蛋白1/3阳性表达，为癌细胞增殖提供能量；同时胰岛素通过激活低氧诱导因子-1α(hypoxia inducible factor-1α，HIF-1α)增强糖酵解关键酶，如6-磷酸果糖-2-激酶(6-phospho-fructo-2-kinase/fructose-2，6-biphosphatase 3，PFKFB3)、磷酸果糖激酶1(phosphofructokinase-1，PFK-1)的活性，加速葡萄糖分解和乳酸积累。随着乳酸不断堆积，酸性微环境可促进血管生成[25]。并且大量乳酸还可通过促进肿瘤相关巨噬细胞极化和削弱T细胞免疫能力，最终驱动免疫逃逸[26]。

内源性高胰岛素血症常见于胰岛素抵抗的T2DM患者，其持续高胰岛素水平通过激活胰岛素受体亚型A和IGF-1R

促进CRC细胞增殖与侵袭；甘精胰岛素、德谷胰岛素等外源性胰岛素因缺乏肝脏首过效应，导致外周组织长期暴露于高浓度胰岛素环境中，从而加速肿瘤进展[27]。一项针对145例T2DM合并CRC患者的回顾性研究发现，胰岛素治疗组淋巴结转移率（53% *vs* 32%）、晚期病理分期（Ⅲ+Ⅳ期比例57% *vs* 32%）及Ki-67阳性率（76% *vs* 53%）均显著高于非胰岛素组（P<0.05），结果提示外源性胰岛素可能加剧CRC侵袭和转移，导致预后不良[23,28-29]。

所以临床需综合评估患者目前代谢状态与肿瘤相关风险，优先选择非胰岛素类药物，并且未来还需不断探索可精准靶向胰岛素信号通路的新型治疗方案，研究出能同时兼顾降糖和抗癌的治疗方案。

2.2 二甲双胍 二甲双胍不仅可降低血糖还可发挥抗癌作用。研究发现，二甲双胍通过下调抑制素βA，减弱TGF-β/PI3K-AKT信号传导通路的活性，导致G1/S-特异性周期蛋白-D1的减少和细胞周期停滞，从而抑制癌细胞增殖[30]。一项纳入108例患者的队列研究显示，二甲双胍组DCR提高至62%，显著高于胰岛素组（48%）[31]。此外，其通过调节微小RNA等小片段RNA的表达，进一步抑制肿瘤相关基因，延缓癌细胞生长。并且二甲双胍联合顺铂可抑制癌细胞活性、增强SW480和SW620细胞系对顺铂的敏感性，抑制癌肿生长、侵袭[32]。

二甲双胍在特定人群中可发挥出显著的抗癌作用。例如，在KRAS突变的CRC患者中，二甲双胍由于膜通道蛋白METE1表达下降导致在胞内蓄积，当达到较高浓度时可显著抑制癌细胞增殖，使KRAS基因突变的患者OS延长至37.8个月，而野生型患者无明显获益。所以基于该机制在KRAS基因突变的患者中表现突出，可通过筛选出适合二甲双胍治疗的特定群体，进一步达到个体化、精准化诊治[33]。并且不同剂量的二甲双胍可能发挥不同效应。高浓度二甲双胍（如2.5 mmol/L）可通过抑制线粒体呼吸链复合物Ⅰ的活性发挥抗癌作用，而低浓度二甲双胍可能通过激活AMPK-ACC-FAO通路，促进脂肪酸氧化，反而加速了部分癌细胞的增殖，所以上述不同剂量产生的疗效差异可能是临床研究结果不一致的重要原因[34]。但是目前CRC相关研究并未准确表明低剂量二甲双胍具有促癌效应，所以还需进一步设计试验探究二甲双胍抑制CRC细胞的剂量阈值，从而有效避免低剂量二甲双胍带来的潜在危险。

二甲双胍在CRC治疗中展现出多种潜能，但目前现有研究多为体外实验或回顾性分析，仍然缺乏大规模随机对照试验的证据支持。此外，试验分组往往会忽略分子的异质性和药物的剂量差异，可能会影响结论的准确性。所以未来还需严格设计试验方案、展开分层研究，促进精准化医疗、推动个体化诊疗。

2.3 胰高血糖素样肽-1受体激动剂（GLP-1RA） 肥胖是导致CRC发生、发展的重要因素。研究发现身体质量指数（body mass index，BMI）每增加5 kg/m^2，CRC风险升高10%~20%。并且内脏脂肪可分泌IL-6、TNF-α等促炎细胞因子和瘦素、脂联素等脂肪因子，可直接促使肠道炎症反应和肿瘤微环境形成。随着内脏脂肪面积增加10 cm^2，CRC发生风险随之提高15%[35-36]。但是GLP-1RA的出现使得CRC的发生风险明显降低。一项基于美国TriNetX平台的回顾性研究发现，与胰岛素相比，GLP-1RA使用组患CRC的*HR*为0.56（95%*CI*：0.44~0.72），与二甲双胍相比*HR*为0.75（95%*CI*：0.58~0.97），所以在超重或肥胖患者中使用GLP-1RA可显著降低CRC患病风险[37]。

GLP-1RA可调节AMP依赖的蛋白激酶（adenosine 5′-monophosphate-activated protein kinase，AMPK）、哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）等糖、脂代谢途径相关因子从而切断对肿瘤微环境的能量供应，同时通过调控NF-κB信号通路降低IL-6、TNF-α等促炎细胞因子的水平，减少肠道黏膜炎症反应，抑制肿瘤细胞增殖。GLP-1RA不仅可以协同调控代谢和免疫过程，还可以通过激活中枢神经系统的饱食信号，显著降低内脏脂肪，从而改善CRC预后[38]。减重还可改善胰岛素敏感性和脂代谢紊乱，间接抑制肿瘤微环境。同样，GLP-1RA也具有直接抗肿瘤效应。GLP-1RA通过激活AMPK通路抑制CRC细胞增殖、通过诱导细胞周期停滞并下调血管内皮生长因子和MMP-9表达，抑制肿瘤血管生成及侵袭转移[39]。研究显示，替尔泊肽（tirzepatide）通过促进HIF-1α泛素化降解，抑制PFKFB3-PFK-1介导的糖酵解，显著延缓结直肠癌病人来源肿瘤异种移植模型肿瘤进展[40]。

但是由于GLP-1R在CRC组织中的表达水平具有个体差异及各种混杂因素干扰，所以GLP-1RA类药物对肥胖相关癌症的潜在作用仍需坚持长期探索。未来还需关注更新型、更强效的GLP-1RA类药物，并且还可结合不同的分子分型开展靶向研究，探究出最佳的治疗药物与模式。

2.4 钠-葡萄糖共转运蛋白2抑制剂（SGLT2i） 尽管目前关于SGLT2i对CRC合并T2DM患者的预后影响缺乏直接试验证据。但基于SGLT2i的代谢途径、抗炎和调节肠道菌群等机制，可推测其对CRC患者有潜在的积极影响。慢性炎症可导致CRC发生发展。研究表明，达格列净可通过抑制肾脏中核苷酸结合寡聚结构域样受体蛋白3（nucleotide-binding oligomerization domain-like receptor protein 3，NLRP3）炎症小体活性，减少IL-1β等促炎细胞因子释放，抑制炎症反应。所以根据肾脏病模型推测SGLT2i可能通过类似机制来抑制肠道炎症反应，延缓结直肠癌前病变的进展，从而降低发生CRC的风险[41]。

SGLT2i可抑制肾脏重吸收葡萄糖和促进尿糖排出，改善T2DM患者代谢紊乱的状态。由于肿瘤细胞依赖糖酵解获取能量，所以SGLT2i可通过降低循环葡萄糖水平，间接切断肿瘤细胞的能量供应，抑制肿瘤增殖。并且SGLT2i促进尿糖排泄增多，高尿糖环境下可能会促进肠道特定菌群增殖，其代谢的短链脂肪酸具有抗肿瘤活性，可能抑制CRC细胞增殖，进一步影响CRC患者预后[42]。

未来还需要继续探索SGLT2i在CRC合并T2DM患者中的潜在价值。例如，探究SGLT2i抑制癌细胞生长是否通过抑制HIF-1α通路或AMPK/mTOR等信号轴发挥作用。并且因为胰岛素治疗可导致CRC进展，且与淋巴结转移率升高和生存期缩短相关，所以SGLT2i作为非胰岛素依赖的降糖方案，可能规避胰岛素相关风险，成为未来降低癌症患者血糖的更优选

择。所以需要开展头对头研究，比较SGLT2i与胰岛素对CRC合并T2DM患者预后的差异，为临床用药提供充足的证据支持。代谢综合征是CRC的独立危险因素，然而SGLT2i不仅能控制血糖，还可改善肥胖、高血压等代谢紊乱。所以结合心血管-肾脏-代谢综合征管理理念，未来需进一步评估SGLT2i对体重、血脂等代谢参数的调控是否协同改善CRC患者预后。

3　小结和展望

T2DM与CRC共享代谢紊乱特征（如糖酵解异常、胰岛素信号失调），所以CRC合并T2DM患者的长期管理需构建“肿瘤治疗-代谢控制-并发症预防”三维体系[43]。T2DM的代谢紊乱不仅加速肿瘤进展，还增加癌症治疗难度，所以血糖控制是代谢管理的核心步骤。胰岛素抵抗和高胰岛素血症可促进CRC细胞增殖，因此在控制血糖时应该优先选择二甲双胍等改善胰岛素敏感性的药物，并且避免长期使用胰岛素类似物。调控肠道菌群、改善肠道屏障功能也是目前新兴的代谢干预方向[44]。此外，低升糖指数饮食、规律运动等短期生活方式干预可显著调节菌群-代谢物轴，改善血糖波动[45]。在调控血糖的同时还需注意检测肿瘤复发转移和心、肾并发症的早期防控，不断提升癌症患者的生存率和生存质量。

T2DM与CRC的关联是多因素、多层次共同作用的结果。为不断提升CRC合并T2DM患者的生存率及生存质量，未来需进一步挖掘代谢通路靶向药物的抗肿瘤潜力。针对T2DM与CRC共病机制中的核心节点，开发可同时调控炎症因子和代谢酶的双功能药物，例如整合TNF-α拮抗剂与AMPK激动剂的双功能药物，既能缓解T2DM患者的慢性炎症反应，又可抑制CRC细胞的瓦博格效应。基因泰克研发的GNE-149既能全拮抗雌激素受体又能诱导其降解，为乳腺癌患者提供了新型内分泌治疗选择，所以类似策略也可拓展用于CRC与T2DM共病靶点的双功能药物设计。并且未来研究还需突破单一机制视角，采用多学科联合诊疗模式，构建跨学科联合治疗模式，实现从“疾病共病管理”到“机制驱动治疗”的跨越。

利益冲突　无

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医学名词应使用全国科学技术名词审定委员会公布的名词。中医临床诊疗术语、经穴部位、耳穴名称与部位等应遵循相应的国家标准。对于没有通用译名的名词术语,在文内第一次出现时应注明原词。中西药名以最新版《中华人民共和国药典》和《中国药品通用名称》(均由中国药典委员会编写)为准。英文药物名称则采用国际非专利药名。在题名及正文中药名不得使用商品名,确需使用商品名时应先注明其通用名称。冠以外国人名的体征、病名、试验、综合征等,人名可以用中译文,但人名后不加“氏”(单字名除外,例如福氏杆菌);也可以用外文,但人名后不加“’s”。文中尽量少用缩略语。已被公知公认的缩略语可以不加注释直接使用,例如:DNA、RNA、HBsAg、PCR、CT、MRI等。不常用的、尚未被公知公认的缩略语以及原词过长在文中多次出现者,若为中文可于文中第一次出现时写出全称,在圆括号内缩略语境若为外文可于文中第一次出现时写出中文全称,在圆括号内写出外文全称及其缩略语。不超过4个汉字的名词不宜使用缩略语,以免影响论文的可读性。西文缩略语不得拆开移行。

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