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GLP-1 RECEPTOR AGONISTS AND COLORECTAL CANCER: BIOLOGICAL PLAUSIBILITY AND CURRENT EVIDENCE

Bartosz Nowak *(Corresponding Author, Email: bartosz.nowak.bo@gmail.com)*
Alma Mater Studiorum - Università di Bologna, Medical and Surgical Sciences - DIMEC, Bologna, Italy
ORCID ID: 0009-0002-4452-0000

Miszela Kałachurska
Pomeranian Medical University Hospital No.2, Szczecin, Poland
ORCID ID: 0009-0006-0687-638X

Martyna Rożek
Pomeranian Medical University Hospital No.1, Szczecin, Poland
ORCID ID: 0009-0000-9141-8493

Maria Nowakowska
Pomeranian Medical University Hospital No.1, Szczecin, Poland
ORCID ID: 0009-0007-2321-0464

Aleksandra Kowalewska-Kurek
Pomeranian Medical University Hospital No.2, Szczecin, Poland
ORCID ID: 0009-0004-7686-0872

Aleksandra Lisowska
Municipal Hospital in Siemianowice Śląskie, Siemianowice Śląskie, Poland
ORCID ID: 0009-0008-4917-821X

Oliwia Jerzyńska
Pomeranian Medical University Hospital No.2, Szczecin, Poland
ORCID ID: 0009-0001-5427-3069

Maria Sierant
Nicolaus Copernicus Voivodeship Hospital, Koszalin, Poland

Mateusz Gural
Pomeranian Medical University Hospital No.1, Szczecin, Poland
ORCID ID: 0009-0000-2601-4126

Constancia Esther Guy
Alma Mater Studiorum - Università di Bologna, Medical and Surgical Sciences - DIMEC, Bologna, Italy
ORCID ID: 0009-0008-2344-6650

ABSTRACT

Background: Colorectal cancer (CRC) remains one of the leading causes of cancer-related morbidity and mortality worldwide. Besides tumor-intrinsic factors, CRC risk and progression are strongly influenced by metabolic dysfunction - including obesity, insulin resistance, and T2DM. These implications emphasize the need for therapeutic strategies that address both tumor biology and the metabolic context.
Objectives: This review examines the emerging role of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in colorectal cancer biology, synthesizing mechanistic, preclinical, and human evidence to evaluate their potential relevance beyond well-known glycemic control.
Methods: We integrate experimental studies, animal models, and epidemiologic and clinical data to evaluate the effects of GLP-1RAs on colorectal cancer–related pathways, tumor growth and progression, and resulting clinical outcomes, with special attention given to metabolic and signaling mechanisms.
Key Findings: Preclinical evidence suggests that GLP-1RAs may modulate pathways involved in cancer cell proliferation, survival, metabolism, angiogenesis, and invasion, including PI3K/Akt/mTOR, ERK, and hypoxia-associated signaling. In vivo models showcase inhibitory effects on tumor growth and metastatic potential, heightened in metabolically dysregulated settings. Human observational studies report heterogeneous but generally neutral to protective associations between GLP-1RA exposure and CRC risk, while randomized trials have primarily addressed cardiometabolic outcomes rather than being tumor-focused.
Conclusions: Collectively, current evidence supports a biologically plausible role for GLP-1 receptor signaling in colorectal cancer growth and progression. Definitive clinical data are lacking, but evidence regarding GLP-1RAs justifies further investigation into their potential relevance.

KEYWORDS

GLP-1 Receptor Agonists, Colorectal Cancer, Tumor Metabolism, PI3K/Akt/mTOR Signaling, Type 2 Diabetes, Cancer Epidemiology

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I. Introduction

Colorectal cancer (CRC) remains one of the most commonly diagnosed malignancies worldwide and one of the leading causes of cancer-related mortality, accounting for approximately 1.93 million new cases and 904,000 deaths worldwide according to the 2022 GLOBOCAN estimates (Bray et al., 2024). Multiple modifiable factors, including obesity, type 2 diabetes mellitus, smoking, physical inactivity, and dietary patterns, have been consistently associated with an increase in colorectal cancer risk, pointing to a significant contribution of metabolic dysregulation to colorectal carcinogenesis (Seo et al., 2023; Aleksandrova et al., 2014). Despite major improvements in early detection and multimodal therapy, colorectal cancer outcomes remain constrained by suboptimal screening uptake, limited effectiveness of current treatments in advanced disease, and persistent gaps in addressing metabolic risk (Toth et al., 2024).

GLP-1 receptor agonists have attracted interest in colorectal cancer research because of their well-established effects on glucose regulation, insulin resistance, and adiposity, but also emerging evidence suggesting the possibility of direct modulation of metabolic and signaling pathways involved in cancer cell growth and progression (Tong et al., 2022).

Glucagon-like peptide-1 (GLP-1) is an incretin hormone secreted by intestinal L cells in response to nutrient intake, exerting its effects through the GLP-1 receptor, a G-protein–coupled receptor that activates cAMP/PKA signaling to regulate insulin secretion, glucagon suppression, gastric emptying, and energy balance (Lymperopoulos et al., 2025).

Pharmacologic GLP-1 receptor agonists have evolved from short-acting agents such as exenatide, associated with gastrointestinal side effects, to longer-acting analogues with higher homology to human GLP-1, like liraglutide and semaglutide, followed by dual incretin agonists such as tirzepatide that engage both GLP-1 and glucose-dependent insulinotropic polypeptide receptors (Gong et al., 2025). Although GLP-1 receptor agonists were originally developed for glucose lowering in type 2 diabetes, evidence from cardiovascular outcome trials and large observational cohorts indicates additional renal and cardiovascular benefits that appear to extend beyond glycemic control and weight loss (Chen et al., 2024; Chen et al., 2025; Sposito et al., 2018).

This review synthesizes mechanistic, preclinical, and human evidence to examine the role of GLP-1 receptor agonists in colorectal cancer biology, with a focus on pathways relevant to tumor growth and progression and their potential implications for future research and clinical understanding.

II. Methodology

The aim of this narrative review was to summarize both preclinical and translational findings related to the impact of GLP-1RAs on CRC biology. For its preparation a literature search was carried out utilizing PubMed, in order to identify relevant studies published before December 2025. A combination of "GLP-1 RAs," "liraglutide," "semaglutide," "exenatide," "tirzepatide," "CRC," "colon tumor," and "tumor metabolism" was used as search terms. Reference list of key articles was created by manual screening of relevant studies.

Eligible papers chosen by us included in-vitro studies, in-vivo animal models, as well as human observational or interventional studies evaluating mechanistic, biological, or oncologic findings related to GLP-1RA exposure in CRC models. Data from review articles was used solely for background information and was not considered primary evidence.

Review's data extraction was performed qualitatively, focusing on alterations in signalling pathways, metabolic background, tumor-related outcomes (proliferation, apoptosis, metastasis), as well as translational relevance. Due to variable results among different studies, results were synthesized narratively.

III. Results:

How GLP-1 Receptor Agonists Influence Key Hallmarks of Colorectal Carcinogenesis

Cell Proliferation & Cell Cycle Control

A growing number of studies indicate that GLP-1 agonists can play a role in cell cycle control. Zheng demonstrated that GLP-1 agonists suppress colorectal cancer cell proliferation through activation of the cAMP–PKA pathway and subsequent inhibition of mitogenic signaling. After a successful link between ligand and GLP-1 receptor, an increase in intracellular cAMP leads to PKA activation. Subsequently, the proliferative cascade ERK/MAPK is downregulated (Zheng et al., 2024). A study by Koehler conducted on the mouse CT26 colon cancer cells indicated that GLP-1R stimulation reduced ERK1/2 phosphorylation and promoted apoptotic signaling (Koehler et al., 2011). These observations have been broadly supported by the recent in vitro studies on human colorectal cancer models.

For instance, in vitro studies showed that GLP-1RA liraglutide reduced CRC cell proliferation by blocking the cell cycle. The mechanism was inhibition of the PI3K/AKT/mTOR signaling pathway and reduced concentration of cyclin D, a main protein responsible for the transition from G1 to S phase in the cell cycle (Tong et al., 2022; Cuttica et al., 2023).

One of the most commonly seen alterations in colorectal cancer cells is the KRAS mutation. It results in constitutive activation of the MAPK and PI3K pathways (Zhu et al., 2021; Chida et al., 2021). Although there is an indisputable importance of KRAS mutation in the development of colorectal cancer, no studies have evaluated the impact of GLP-1RA on KRAS-mutant CRC models.

Resisting Cell Death

Preclinical in vitro evidence indicates that liraglutide can promote apoptosis and inhibit CRC cell survival. GLP-1RAs inhibit the PI3K/Akt/mTOR survival pathway, lowering the threshold for apoptosis (Tong et al., 2022).

There is some limited evidence showing that GLP-1 receptor agonists can modulate mitochondrial apoptotic pathways by increasing permeability of the mitochondrial membrane, followed by cytochrome c release and activation of the apoptotic cascade. However, to date, this mechanism has only been demonstrated in LNCaP prostate cancer cells (Li et al., 2017). No study on colorectal cancer cells has yet confirmed that this mitochondrial apoptotic pathway is promoted by GLP-1RA.

Migration, Invasion, and Metastatic Potential

The PI3K/Akt/mTOR signaling pathway is one of several regulators of migration, invasion, and metastatic potential of the CRC cells. The crucial enzyme responsible for the degradation of basement membrane and extracellular matrix, therefore responsible for metastatic potential, is matrix metalloproteinase 11 (MMP-11). An experiment conducted by Tong showed weakening of the invasion and migration ability of CRC cells and decreased expression of MMP-11 after intervention with GLP-1RA, liraglutide (Tong et al., 2022; Cuttica et al., 2023).

GLP-1RA Effects on Tumor Metabolism and Hypoxic Adaptation

Zhang and colleagues have extensively investigated the role of tirzepatide (TZP) in colorectal cancer metabolism. Their findings showed that tirzepatide, as a dual GIP/GLP-1 receptor agonist, takes part in decreasing glucose uptake by reducing the number of glucose transporters, such as GLUT1, GLUT3, GLUT4, and GLUT12.

According to Zhang, TZP has an additional trait of disrupting the stability of hypoxia-inducible factor 1-alpha (HIF-1α). Zhang's latest research showed that a falling level of HIF-1α comes with a notable decline in expression and activity of enzymes, like 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) and phosphofructokinase-1 (PFK-1). Their suppression leads to numerous effects - a noticeable impairment of glycolysis, the effective suppression of tricarboxylic acid cycle, and a critical shortage of energy derived from glucose metabolism in colorectal cancer cells (Zhang et al., 2025).

Angiogenesis

GLP-1RAs have many metabolic effects, for instance an influence on tumor angiogenesis. Tirzepatide restrains glucose uptake and destabilizes HIF-1α in CRC cells (Zhang et al., 2025). In a low oxygen environment, HIF-1α promotes angiogenesis. Therefore, this destabilization of HIF-1α mediated by GLP-1RAs may reduce the formation of new blood vessels within the tumor.

Another study showed that liraglutide inhibits PI3K/Akt/mTOR signaling in CRC cells (Tong et al., 2022). Growth of new vessels can be induced by hypoxic response, as mentioned before, or mediated by PI3K/Akt/mTOR signaling pathway, which leads to the production of VEGF (Nicolini & Ferrari, 2024; Fang et al., 2025).

Correlation between high glucose levels, insulin resistance and colorectal cancer

One study conducted by Ma investigated the mechanism through which high glucose-induced insulin resistance in type 2 diabetes (T2DM) promotes the progression of CRC. The common factor in T2DM and CRC was elevated bone morphogenetic protein 4 (BMP4). The highest BMP4 concentration was observed in patients who presented with both T2DM and CRC.

Ma argues that exposure to high glucose is responsible for increase in BMP4 expression in CRC cells, further activating the BMP4/Smad1/5/8 signaling pathway. This results in promotion of proliferation, migration, and epithelial–mesenchymal transition.

Therefore, treatment with a GLP-1 receptor agonist lowers glucose levels, which subsequently significantly downregulates BMP4 expression and inhibits tumor cell proliferation and migration. Moreover, the apoptosis was enhanced in CRC cells (Ma et al., 2023).

Selectivity of GLP-1 Receptor Agonists and the Role of GLP-1R Expression in Colorectal Carcinogenesis

Zhang's work presents results that GLP-1 receptor agonists act selectively in colorectal cancer cells that express GLP-1 receptors. Additionally, Zhang claims that TZP blocks proliferation in colorectal cell lines and shows minimal activity in non-colorectal malignancy cell lines, including gastric and pancreatic cancer (Zhang et al., 2025).

Another study, conducted by Tong, indicates that only colorectal cancer cells which express GLP-1R are able to inhibit PI3K/Akt/mTOR signaling and arrest the cell cycle as a response to GLP-1RA treatment. Subsequently, no cytotoxic effect was observed in normal colonic epithelial cells (Tong et al., 2022).

Evidence From Pre-Clinical Studies

In-Vitro Studies

There is a growing number of preclinical research investigating the effects of GLP-1RAs on colorectal cancer (CRC) cell biology. In vitro studies utilizing a variety of established human CRC cell lines, such as HT29, HCT116, and SW480, have demonstrated that GLP-1RAs can modulate key signaling pathways involved in proliferation, apoptosis, migration, and cell invasion (Xie et al., 2021). More precisely, it has been demonstrated that liraglutide, exendin-4, and TZP suppress PI3K/Akt/mTOR pathway, leading to cell cycle arrest, reduced proliferative capabilities, and enhanced apoptosis (Tong et al., 2022; Li et al., 2025). These

outcomes have been associated with shifts in apoptosis associated signaling mediators, including increased activation of caspase-3, increased expression of BAX, and reduced BCL-2 expression, which is consistent with a cell survival defect (Li et al., 2025).

Other studies have indicated modulation of signaling in inflammatory and stress-related responses. TZP, a dual GIP/GLP-1RA, has demonstrated inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. It was also found to activate p53-dependent pathways and upregulate caspase-8 expression. As such, it facilitated apoptosis and provided a mechanistic link between metabolic regulation and inflammatory control in CRC cells (Fadhil et al., 2025). Moreover, a high glucose environment simulating insulin resistance appears to enhance signaling in bone morphogenetic protein 4 (BMP4) and Smad1/5/8 pathways, facilitating epithelial-mesenchymal transition (EMT) and metastasis, which can be reduced by GLP-1RAs via BMP4 downregulation (Ma et al., 2023; Wang & Kim, 2022). Although the expression of functional GLP-1Rs varies across cell lines, with some studies reporting limited or non-existent receptor levels in certain human CRC cells, the overall consensus is that GLP-1RA treatment can positively affect survival and proliferative signaling in responsive cell lines (Wenjing et al., 2017).

Some limitations related to in vitro studies include the frequent use of supraphysiologic drug concentrations, variable GLP-1R expression levels, and a focus on reductionism of cell culture systems, which cannot fully showcase tumor microenvironmental interactions. Despite this, similar effects have been consistently observed across multiple varied CRC cell lines, reflecting involvement of common oncogenic signaling pathways (Fadhil et al., 2025).

In-Vivo Animal Models

Animal model data generally supports the described in vitro findings. In murine studies, treating CT26 tumor-bearing mice with the GLP-1RAs has been shown to reduce proliferation and enhance irinotecan-induced apoptosis (Koehler et al., 2011; Fujita et al., 2015). Notably, GLP-1R stimulation in these models increased caspase-dependent apoptosis and altered activity of kinases such as glycogen synthase kinase 3 (GSK-3) and extracellular signal-regulated kinase 1/ 2 (ERK1/2), effects which occurred at least partially via protein kinase A (PKA) activation of GLP-1R signaling pathway (Koehler et al., 2011). Parallel studies conducted using high glucose CRC mice modeling insulin resistance showed that GLP-1RAs could suppress hyperglycemia induced EMT, BMP4 upregulation, and metastasis, suggesting a potential application to diabetic CRC patients (Ma et al., 2023).

Other studies have further validated these findings in dual GIP/GLP-1RAs. In a patient-derived xenograft (PDX) tumor model TZP lowered glucose uptake, inhibited HIF-1α stabilization, and downregulated glycolytic enzymes PFK-1 and PFKFB3, resulting in suppression of both glycolysis and citric acid cycle in tumor regions. These effects were associated with delayed tumor progression, suggesting an involvement of tumor metabolism modulation in the anti-tumor effect of GLP-1RAs in vivo (Zhang et al., 2025; Htoo et al., 2016).

Importantly, this observed impact did not alter the efficacy of standard antineoplastic agents in these preclinical models. Exenatide co-administered with oxaliplatin, for instance, facilitated recovery from chemotherapy-induced peripheral neuropathy (CIPN) without affecting tumor growth suppression, indicating potential safety in combination therapy (Koehler et al., 2011). Similarly, in a DMH-induced model of CRC diabetic mice, exenatide reduced angiogenesis and proliferation (CD34 and Ki-67) markers, providing evidence of a chemopreventive effect in inflammatory models of colon carcinogenesis (Tawfik & Mohamed, 2016).

Synthesis of Preclinical Data

Overall, the preclinical data indicates that GLP-1RAs have multi-modal effects on CRC, including inhibition of proliferative pathways (PI3K/Akt/mTOR, NF-κB, GSK-3, ERK1/2), as well as modulation of metabolic and anti-inflammatory regulators (BMP4, HIF-1α) (Tong et al., 2022; Li et al., 2025; Wenjing et al., 2017). Consistent findings observed in vitro across multiple CRC cell lines demonstrate reduced proliferation, while in vivo murine models support the conclusion that GLP-1RAs enhance tumor cell apoptosis and decrease metastasis (Fadhil et al., 2025; Koehler et al., 2011). The mechanisms of these drugs appear to involve both receptor-dependent and metabolic pathways. If the theory of mechanistic convergence is shown to function as described above, GLP-1RAs could have the potential to be applicable for CRC chemoprevention, particularly for hyperglycemic and diabetic individuals (Ma et al., 2023; Zhang et al., 2025). There exists limitations associated with the existing preclinical studies, including variability in GLP-1R expression across various models, the use of supraphysiologic GLP-1RA dosage, and species-specific differences, all of which may cast translational concerns (Tong et al., 2022; Wenjing et al., 2017; Koehler et al., 2011; Tawfik & Mohamed,

2016). Nevertheless, the evidence supports the need for further clinical studies to confirm the findings of preclinical studies using the GLP-1RAs.

Evidence From Human Studies – Clinical Trials & Observational Data

Epidemiology & Real-World Cohorts

Human studies have largely consisted of dataset analyses, and several meta-analyses. The CRC-related randomized control trials (RCTs) assessed primarily cardiovascular outcomes, rarely having CRC as an end point, thus having insufficient power to assess the oncological use of the GLP-1RAs (Zhong et al., 2025; Wu et al., 2025). Observational studies have produced mixed results, with several high-quality cohort analyses showing a reduced CRC incidence with exposure to GLP-1RAs, especially when compared with insulin therapy in obese patients (Wang, Xu, et al., 2024; Wang, Wang, et al., 2024)

A large scale nation-wide target trial emulation from Taiwan, which included 11,726 propensity-score matched new user pairs of GLP-1RA vs long-acting insulin, demonstrated a significantly reduced CRC risk in patients taking GLP-1RAs, primarily driven by a lower risk of rectal cancer (Wu et al., 2025). A separate multicenter United States Electronic Health Record analysis of over 1.6 million patients with type-2 diabetes reported a lower incidence of ten obesity-associated cancers, including CRC, in GLP-1RA users, following propensity-score matching baseline covariates (Wang, Xu, et al., 2024). Similar directional associations were obtained in TriNetX-based analyses and Explorys database studies, showing lower odds of CRC among GLP-1RA users compared with metformin or other controls (Kuo et al., 2025; Wang & Kim, 2022).

However, not all pooled studies have shown a similar positive result. A recent meta-analysis of seven retrospective cohort studies, which pooled data from over 5 million patients, reported a significantly increased risk of CRC among GLP-1RA users, thus illustrating the presence of contradictory findings in literature and the influence of study selection, comparative therapy, and residual bias (Zhong et al., 2025). Other cohort studies conducted using active controls (GLP-1RA when compared with long-acting insulin or metformin) have often demonstrated non-significant or protective associations, but are sensitive to latency assumptions, exposure definitions, and adjustment variables (Htoo et al., 2016; Abrahami et al., 2018).

Clinical Trials

Large RCTs targeting the cardiometabolic and weight-loss indications of drugs such as liraglutide, semaglutide, and TZP, have reported safety data, however, are not prospectively assessing CRC incidence (Silverii et al., 2025).

Meta-analyses conducted on RCT studies have generally reported non-significant excess risk for overall cancer incidence among subjects taking GLP-1RAs. Signals which appeared concerning specific types of GI malignancies, have been inconsistent and based on a small number of events (Zhong et al., 2025). Thus, while these studies do not indicate any substantial safety concern, neither have they allowed a definitive assessment concerning such efficacy in human patients.

Then, some concerning signals arise from real-world evidence studies utilizing medical registry data, which support collective study findings observing neutral to protective associations when adequate confounder controls are in place, strengthening the plausibility of a protective effective, but still coming short of showcasing causal proof (Abrahami et al., 2018; Wu et al., 2025; Wang, Xu, et al., 2024; Kuo et al., 2025).

Safety Signals

Historically, safety concerns with GLP-1RA therapies have been focused on pancreatic and thyroid findings observed in animal toxicity studies and signal detection in postmarketing surveillance programs (Marso et al., 2016; Lomeli et al., 2024; Capuccio et al., 2024). Regarding colorectal outcomes, preclinical observations of mucosal hyperplasia, including crypt and villus hypertrophy, have raised theoretical safety concerns, despite challenge studies with carcinogens failed to demonstrate increased adenoma formation with either liraglutide and exendin, and have not shown definite carcinogenic activity of GLP-1RAs in human studies (Tawfik & Mohamed, 2016; Kissow et al., 2012; Ungvari et al., 2025). Human biomarker data however does indicate that GLP-1 system is impaired in patients with colorectal adenoma, with one case-control study demonstrating that patients with CRC adenoma had lower GLP-1 secretion after oral glucose tolerance test when compared to controls. Additionally, an inverse correlation of GLP-1 area under the curve with the size and number of adenomas was observed, supporting the idea that endogenous GLP-1 has rather a protective than pathogenic role in colorectal neoplasia (Sasaki et al., 2018).

Genetic studies provide limited additional insight, with a Mendelian randomization analysis using GLP1R genetic proxies showing no evidence of a causal relationship with CRC or overall cancer risk following disruption of GLP1R (Yarmolinsky et al., 2023).

Taken together, human mechanistic and biomarker data suggest a protective role for GLP-1 signaling in colorectal neoplasia, however postmarketing and database safety surveillance have produced mixed epidemiological signals, primarily driven by the heterogeneity in methodology (Zhong et al., 2025; Wang, Xu, et al., 2024; Sasaki et al., 2018; Yarmolinsky et al., 2023).

IV. Discussion

Integrative interpretation of mechanistic, preclinical, and human evidence

Evidence reviewed above suggests the presence of biologically relevant effects exerted by GLP-1 receptor agonists on colorectal cancer (CRC) cells. Mechanistic, preclinical and human data underwent comparison in parallel, allowing for identification of shared patterns. Across in vitro and in vivo models, exposure to GLP-1 receptor agonists has been associated with changes in signaling pathways involved in tumor growth and progression - including those related to cell proliferation, metabolism, survival and invasive abilities. Several of the observed effects were more apparent in settings of metabolic dysfunction, such as hyperglycemia or insulin resistance, pointing to an effect of systemic metabolic environment on tumor behavior.

The evidence reviewed in the Results section points to GLP-1 receptor agonists influencing CRC biology through both direct and indirect mechanisms. In the cited studies, direct effects are observed in CRC cell lines expressing GLP-1 receptors and include cell cycle arrest and apoptosis, while indirect effects seen under hyperglycemic conditions led to improved systemic glucose control and suppression of BMP4 signaling. Several studies point to them interfering with key oncogenic signaling cascades often dysregulated in CRC, including PI3K/Akt/mTOR and ERK/MAPK pathways. Mentioned pathways are influenced by growth signals, metabolism and inflammation and their modulation offers a plausible explanation for reduced proliferation, enhanced apoptotic susceptibility and reduced invasive capacity observed across experimental models. The reported effects of GLP-1 receptor agonists appear to depend on GLP-1 receptor expression, which varies across both tissue type and models.

Emerging literature points towards tumor metabolism and hypoxic adaptation. Recent preclinical studies suggest that GLP-1 receptor agonists can disrupt glucose uptake and destabilize hypoxia-inducible factor 1-alpha (HIF-1α), therefore limiting the metabolic capabilities of tumor cells. Considering the reliance of CRC cells on glycolysis and hypoxia-driven angiogenesis for survival and further growth, research findings may present a crucial antitumor mechanism, although it is unknown whether described effects are driven by direct receptor signaling or reflect metabolic changes.

Conditions of metabolic dysregulation provide further context for interpretation of presented findings. Hyperglycemia and insulin resistance promote CRC growth and metastasis through pathways such as BMP4/Smad signaling, the effects of which may be attenuated by improving glycemic control through GLP-1 receptor agonist exposure, therefore may be particularly relevant in patients with T2DM or obesity. Different metabolic statuses may help explain the heterogeneity observed in human studies regarding oncologic impact of GLP-1 receptor agonist therapy.

Selectivity remains a notable consideration, as several experimental studies show minimal cytotoxic effect of GLP-1RAs on normal colonic epithelial cells, as well as minimal activity in non-colorectal malignancies. While promising a future favorable therapeutic window, high variability in GLP-1 receptor expression across tumors brings uncertainty to patient-level applicability. Despite the reviewed premises, it remains unclear whether GLP-1 receptor expression could serve as a reliable biomarker for responsiveness to therapy.

Human data are largely indirect. Observational cohort studies and real-world analyses provided mixed but predominantly neutral or protective associations of GLP-1 receptor agonist exposure on CRC risk, compared to insulin-based therapies. Randomized trials were designed for heart and metabolic outcomes instead of cancer, therefore they cannot provide robust evidence for tumor prevention. Collected real-world safety data and trials do not show increased CRC risk, supporting the safety of the potential therapy, although it lacks solid proof regarding cancer benefit.

Several limitations need consideration while interpreting the available evidence. Preclinical studies tend to use supraphysiological drug doses and rely on simplified cell and animal models, not fully reflecting the real tumor microenvironment. Observational human studies may be subject to residual confounding or exposure misclassification. Collected data are mainly limited to established CRC settings, rather than cancer prevention and may also be sparse for molecular subtypes, such as KRAS-mutant CRC.

Taken together, the reviewed articles indicate that the observed effects of GLP-1 receptor agonists on CRC biology come from a combination of tumor-intrinsic signaling changes and broader metabolic influences. The relative contribution of these mechanisms varies due to tumor characteristics, receptor expression and metabolic settings, which may provide insight as to why preclinical findings appear much more consistent than the collected human data. The current body of evidence cannot support clinical efficacy, however shows biological plausibility and further emphasizes the need for targeted research in order to clarify causality and clinical relevance.

V. Conclusions

In summary, this narrative review synthesizes mechanistic, preclinical and human evidence on the potential effects that GLP-1 receptor agonists may exert on CRC cell growth, survival and incidence. Experimental data showcase biological plausibility and human data support safety, but the current body of evidence is insufficient to demonstrate protective or therapeutic effects. Our findings encourage cautious interpretation of current studies and the need for targeted future research.

Conflicts of interest: No conflicts of interest to declare.

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