

Review

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Review

Do SGLT2 Inhibitors Have a Place in the Oncology Toolbox?

Running Title: Repurposing SGLT2i for Cancer**Homayra Rahman Shoshi¹, Badar Uddin Umar^{1,2}, Tanbira Alam¹, Md Ziaul Haque¹ and S M Niazur Rahman^{1,3,*}**¹ Center for Biomedical Research and Training (CBRT), Dhaka, Bangladesh² Oxford College of Arts, Business and Technology, Ontario, Canada³ Department of Biomedical Sciences, Tilman J. Fertitta Family College of Medicine, University of Houston, Texas, United States

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Abstract

Sodium-glucose cotransporter 2 (SGLT2) inhibitors, widely used in the treatment of type 2 diabetes, have recently emerged as potential anticancer agents due to their effects on tumor metabolism and growth signaling pathways. This article presents a viewpoint on the growing body of preclinical evidence linking SGLT2 inhibition to antitumor activity, including reduced glucose uptake, AMPK activation, mTOR suppression, and cell cycle arrest. Agents such as canagliflozin, dapagliflozin, and empagliflozin have demonstrated efficacy across various cancer models, though clinical validation remains limited. We propose that SGLT2 inhibitors may offer a promising therapeutic strategy in metabolically active tumors, especially when guided by molecular profiling. While further research is needed, these findings support reconsidering the oncologic relevance of this drug class within a personalized medicine framework.

Keywords: SGLT2 inhibitors; cancer metabolism; metabolic oncology; drug repurposing; glucose transporters

1. Introduction

Cancer and type 2 diabetes (T2D) are two chronic conditions with rising global prevalence, together contributing to immense morbidity and mortality. In 2020, cancer caused about 10 million deaths worldwide [1], while diabetes affected more than 476 million people, 90% of whom had T2D [2,3]. Epidemiological studies over the past century have established an association between diabetes and increased cancer incidence [4]. Both diseases share common risk factors such as obesity, inactivity, and aging, and they involve metabolic dysregulation that favors cellular proliferation and survival.

Within this context, sodium–glucose cotransporter 2 (SGLT2) inhibitors, originally developed for glycemic control, have attracted attention for their unexpected anticancer effects. Preclinical studies suggest that these agents can reduce tumor growth through metabolic reprogramming, induction of apoptosis, and inhibition of oncogenic signaling pathways such as AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and Extracellular Signal-regulated kinase (ERK) 1/2 [5–8]. However, their clinical potential remains largely unexplored. This article examines the emerging evidence and mechanistic insights underlying the anticancer actions of SGLT2 inhibitors and offers a forward-looking perspective on their translational prospects in oncology.

2. SGLT2 Inhibitors: Mechanistic Basis and Evidence in Cancer Therapy

2.1. SGLT2 and Tumor Metabolism

Cancer cells exhibit increased glucose uptake to fuel rapid growth, a phenomenon known as the Warburg effect. While this is traditionally attributed to glucose transporters (GLUT), recent studies have demonstrated that SGLT proteins, particularly SGLT2, also facilitate glucose entry in certain tumor types [5]. The expression of SGLT2 has been confirmed in pancreatic, prostate, colon, and breast cancer cells, where it supports cellular energy demands and survival [7]. Blocking this pathway with SGLT2 inhibitors can limit glucose availability to tumor cells and trigger metabolic stress leading to growth arrest and apoptosis.

In addition to glucose restriction, SGLT2 inhibition alters downstream energy-sensing pathways. By reducing ATP levels, these drugs activate AMPK and consequently suppress mTOR signaling, a key axis that promotes cell growth and protein synthesis [8]. Furthermore, inhibition of ERK1/2 phosphorylation attenuates tumor cell proliferation and survival [9], indicating that SGLT2 inhibitors may act as metabolic checkpoint modulators in cancer therapy.

2.2. Canagliflozin: A Multifaceted Anticancer Agent

Canagliflozin (CANA) has been most extensively studied for its anticancer activity. In murine models of nonalcoholic steatohepatitis (NASH)-related hepatocellular carcinoma (HCC), CANA reduced tumor growth, liver fibrosis, and macrophage infiltration, while lowering ALT levels and oxidative stress [10]. Mechanistically, CANA induces cell-cycle arrest at the G0/G1 phase and enhances cleaved caspase-3 activity, promoting apoptosis [11].

By targeting the mTOR pathway, CANA decreases ATP production and lactate generation in tumor cells [8], disrupting their bioenergetic adaptation. Moreover, CANA demonstrates anti-angiogenic activity by downregulating vascular endothelial growth factor A (VEGFA) expression [12], reducing neovascularization. Together, these findings position CANA as a multi-target therapeutic agent that interferes with tumor metabolism, cell cycle progression, and angiogenesis.

2.3. Dapagliflozin: Insulin-Dependent and Cell-Specific Effects

Dapagliflozin (DAPA) has shown antitumor efficacy in obesity-associated mouse models of breast (E0771) and colon (MC38) cancers, primarily through an insulin-dependent mechanism [13]. Beyond its systemic effects, DAPA modulates tumor cell signaling by enhancing ERK1/2 phosphorylation, which disrupts cell adherence and leads to detachment-induced cell death in HCT116 colon cancer cells [9]. In renal cancer (CaKi-1) cells, DAPA reduces SGLT2 expression, causes G1-phase arrest, and induces apoptosis [14].

Both DAPA and CANA have been reported to suppress the AMPK/mTOR axis and inhibit proliferation in breast cancer cell lines such as MCF-7 and T-47D [8]. Interestingly, because DAPA is inactivated by UDP-glucuronyltransferase Family 1 Member A9 (UGT1A9) conjugation, its efficacy may depend on cellular UGT1A9 expression levels, a potential determinant of tumor sensitivity [7].

These context-dependent effects highlight that SGLT2 inhibitors might require molecular profiling for optimized oncologic application. As such, SGLT2 inhibitors may hold the greatest therapeutic promise when integrated into a personalized oncology framework guided by molecular profiling.

2.4. Empagliflozin: Combination Synergy and Cytokine Modulation

Empagliflozin (EMPA), a highly selective SGLT2 inhibitor, has been shown to inhibit tumor proliferation in cervical cancer models [15]. More notably, EMPA in combination with metformin suppressed diethyl nitrosamine-induced HCC in mice, reducing tumor size and normalizing serum levels of tumor necrosis factor α (TNF- α), transforming growth factor (TGF)- β , and VEGF [16,17]. The

combination synergy likely arises from convergent effects on energy metabolism and inflammatory cytokine signaling. Such findings support exploring SGLT2 inhibitors as adjuncts to existing metabolic or chemotherapeutic regimens.

2.5. Ipragliflozin and Tofogliflozin: Emerging Preclinical Data

Ipragliflozin (IPRA) has been found to inhibit Na⁺ and glucose co-transport in breast cancer cells, leading to membrane hyperpolarization and mitochondrial instability that promote cell death [18]. Downregulation of SGLT2 via siRNA similarly suppressed tumor growth, confirming a direct role for SGLT2 in tumor cell viability.

Tofogliflozin (TOFO) has been shown to attenuate early neoplastic lesions and reduce proinflammatory cytokines (IL-1 β , IL-6, TNF- α) in HCC and colorectal cancer models [19]. In adult T-cell leukemia, TOFO decreased ATP and NADPH levels and impaired glucose uptake, leading to growth inhibition [20]. Though preclinical, these findings reinforce the concept that SGLT2 blockade can induce metabolic collapse in high-glucose-dependent tumors.

3. Discussion

3.1. Translational Challenges and Research Gaps

While preclinical data are compelling, the translation of SGLT2 inhibitors into oncologic therapy faces several barriers. First, SGLT2 expression is heterogeneous across tumor types and even within tumor subclones, limiting the generalizability of these agents [5,7]. Second, their anticancer effects may depend on indirect metabolic changes such as insulin lowering, which could differ between metabolic states (e.g., obesity vs cachexia) [7]. Third, most evidence derives from murine models and cell lines; only one small clinical study in pancreatic carcinoma has shown tumor size reduction [21].

Moreover, the specific molecular mechanisms: whether direct metabolic toxicity, AMPK/mTOR modulation, or immune microenvironment alteration, remain to be clarified. Emerging studies suggest that SGLT2 inhibitors may also influence macrophage polarization and tumor immunity, but systematic investigation is lacking [22,23].

3.2. Future Research Directions

To advance this field, several approaches are recommended:

- a. Molecular Profiling: Map SGLT2 expression across tumor types and stages to identify responsive cancers and possible biomarkers of drug sensitivity.
- b. Mechanistic Clarification: Dissect the relative contribution of glucose restriction versus signaling pathway modulation (e.g., AMPK/mTOR/ERK axis).
- c. Combination Therapies: Investigate synergistic effects with metformin, immune checkpoint inhibitors, or standard chemotherapies as suggested by preclinical studies [16].
- d. Clinical Trials: Design early-phase studies using repurposed SGLT2 inhibitors in specific metabolic-oncology contexts (e.g., NASH-HCC).
- e. Safety Evaluation: Monitor potential oncologic off-targets, as chronic glycosuria and ketogenesis may have unintended effects in cancer patients [24].

3.3. Conclusion

SGLT2 inhibitors represent a promising therapeutic bridge between metabolic regulation and oncology. By restricting glucose uptake and disrupting tumor cell energetics, these agents demonstrate a range of anticancer effects in preclinical models, including AMPK activation, mTOR and ERK1/2 suppression, cell cycle arrest, apoptosis induction, and inhibition of angiogenesis. Notably, compounds such as canagliflozin, dapagliflozin, and empagliflozin have shown efficacy across multiple cancer types *in vitro* and *in vivo*. However, clinical validation remains limited, and several translational uncertainties persist. These include challenges in dose translation, tumor-

specific pharmacokinetics, and variability in SGLT2 expression across cancers. Additionally, the differing selectivity profiles among available inhibitors may influence therapeutic response and safety. To realize their full potential in oncology, SGLT2 inhibitors must be evaluated in well-designed clinical trials, guided by molecular profiling and metabolic context. We propose that with systematic investigation and patient stratification, these agents could offer a novel and personalized strategy in cancer therapeutics.

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