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THE CARDIOPROTECTIVE AND ANTICANCER EFFECTS OF SGLT2 INHIBITORS

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Sodium-glucose co-transporter-2 (SGLT2) receptors, found only in proximal tubules in the Kidney. Originally are approved for Type-2 diabetes mellitus, they inhibit glucose reabsorption in proximal tubules leading to excretion through urine and subsequently decreased serum glucose concentrations. Also they have demonstrated efficacy in decreasing cardiovascular events, especially in patients of Heart failure independently of glycemic control. Currently 2 SGLT2 inhibitors, empagliflozin and dapagliflozin are approved for treating Heart failure with both reduced and preserved ejection fraction. Recently they have been shown to have anticancer properties in several malignancies, including breast, liver, pancreatic, thyroid, prostate and lung cancers. In the context of metabolic reprogramming observed in cells within Glucose-based model, the potential of SGLT2 inhibitors to impede the uptake of glucose by cancer cells emerges as an appealing therapeutic strategy.

SGLT2 inhibitors offer cardioprotective effects through various mechanisms, benefiting patients with diabetes and heart failure. The search of the literature revealed many possible cardioprotective mechanisms, because SGLT2 inhibitors work with (i) the diuretic hypothesis (ii) the blood pressure lowering hypothesis (iii) favor the production of ketones, which can act as a 'superfuel' in the cardiac and renal tissue (the 'thrifty substrate' hypothesis), (iv) the metabolic effects hypothesis, (v) the anti-inflammatory effects hypothesis, (vi) can act through the angiotensin II type II receptors in the context of simultaneous renin-angiotensin-aldosterone-system (RAAS) blockade leading to vasodilation and positive inotropic effects (the RAAS hypothesis), (vii) directly kdecrease the activity of the upregulated in heart failure Na+–H+ exchanger in myocardial cells leading to restoration of mitochondrial calcium handling in cardiomyocytes (the sodium hypothesis).

Trials like DAPA-HF and EMPEROR-Reduced, demonstrate the risk reduction of heart failure progression and cardiovascular death with dapagliflozin and empagliflozin, regardless of diabetes status. Also the Meta-analysis confirms consistent benefits, including reduced mortality, hospitalizations for heart failure, and improved renal function.

In vitro cell culture studies and preclinical in vivo studies have confirmed that SGLT-2 inhibitors exhibit antiproliferative effects on certain types of cancer. They disrupt cancer cell functions independently of SGLT-2 presence by targeting essential cellular processes like mitochondria, key pathways, and energy production, effectively halting tumor growth. They not only reduce inflammation and oxidative stress but also hinder glucose uptake in tumors. In breast cancer, canagliflozin demonstrates anti-proliferative effects by impacting mitochondrial complex-I. Similarly, dapagliflozin and canagliflozin induce cell cycle arrest and apoptosis through AMPK activation, while avoiding the undesirable side effects of current chemotherapy treatments.

Treatments like anthracyclines pose high risks of cardiotoxicity which leads to heart failure. Radiotherapy can lead to cardiac injury and also associated with serious cardiovascular adverse events, including hypertension, arrhythmias, coronary artery disease and cardiomyopathy's. Dapagliflozin enhances cardiomyocyte viability during exposure to doxorubicin and trastuzumab, boosting their anticancer effects in breast cancer cells. Its cardioprotective effects stem from reducing intracellular Ca2+ overload and lipid peroxidation. It also lowers pro-inflammatory cytokine expression, crucial in cardiotoxicity, by inhibiting p65-NF-kB activation and NLRP3 inflammasome. Additionally, it decreases mTORC1/Fox01/3a expression post-treatment, highlighting its multifaceted protective mechanisms.