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The SGLT2 Inhibitor Canagliflozin Reduces Androgen Receptor Expression and Nuclear Localization of Beta-Catenin in Human Prostate Cancer Cells

Abstract

Drugs that inhibit the protein sodium-glucose cotransporter-2 (SGLT2) are commonly used in the United States to treat type 2 diabetes. Recent studies suggest that SGLT2 inhibitors reduce growth of lung, liver, and breast cancer cells in vitro. Therefore, administration of SGLT2 inhibitors may also limit the growth of malignant tumors. Previous work from our laboratory has shown that one SGLT2 inhibitor, canagliflozin, reduces the proliferation of C4-2B cells, a castration-resistant human prostate cancer cell line. Concentrations of canagliflozin that reduce proliferation also lower levels of the androgen receptor (AR), a protein known to promote growth of prostate cancers. The goal of this study was to define the mechanism by which canagliflozin lowers AR protein levels. Since canagliflozin induces phosphorylation of adenosine monophosphate-activated protein kinase (AMPK), we initially investigated the effect of the AMPK pathway on this response. AMPK is a kinase that regulates cellular energy homeostasis. Western blot analyses demonstrated that the AMPK inhibitor Compound C does not prevent canagliflozin-mediated reductions in AR protein within the C4-2B cells. This suggests the AMPK pathway does not significantly contribute to these reductions in AR. We next explored whether canagliflozin might alter localization of beta-catenin, a transcription factor known to increase AR expression. Western blotting showed that canagliflozin reduces the amount of nuclear beta-catenin and AR within C4-2B cells. These data suggest that reductions in beta-catenin signaling may be the mechanism by which canagliflozin lowers AR in prostate cancer cells.

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