Cation-selective Transporters are Critical Determinants of the Anti-proliferative Effects of Metformin in Breast Cancer Cells

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INTRODUCTION

The anti-diabetic agent metformin exerts anticancer effects against several cancers, including breast cancer. Studies suggest that the direct effects of metformin are mediated via activation of its intracellular target, namely, adenosine monophosphate-activated protein kinase (AMPK), while its indirect effects are thought to occur through reduction of circulating insulin and glucose levels (Figure 1).

Because metformin is highly hydrophilic and positively charged at physiologic pH, it requires cation-selective transporters for entry into cells. Previous studies in the Thakker laboratory showed varying expression profiles of cation-selective transporters in human breast tumor tissue (Figure 2A) and human breast cancer cell lines (Figure 2B). This study aims to test the hypothesis that transporters are central to the anti-proliferative effects of metformin in breast cancer cells. To achieve this goal, organic cation transporter 3 (OCT3) was selected as a representative transporter (see Figure 2A), and OCT3 was expressed in the BT20 cell line, which is deficient in cation transporters that can transport metformin into the cell. Comparison of metformin uptake and anti-proliferative potency in wild-type and OCT3-stably expressing OCT3-BT20 cells would enable us to test the central hypothesis of this study.

RESULTS

Figure 3: Metformin Uptake into Wild-type BT20 and OCT3-BT20 (Human Breast Cancer) Cells

Figure 4: Anti-proliferative Effects of Metformin in Wild-type and OCT3-BT20 (Human Breast Cancer) Cells

Figure 5: Effect of Metformin on AMPK Activation in Wild-type BT20 and OCT3-BT20 (Human Breast Cancer) Cells

CONCLUSIONS AND DISCUSSION

- Transporter-competent OCT3-BT20 cells showed higher intracellular uptake of metformin compared to transporter-deficient BT20 cells, suggesting that intracellular uptake of metformin in human breast cancer cells is enhanced by cation-selective transporters.
- Metformin induced a greater anti-proliferative effect in transporter-competent OCT3-BT20 cells compared to transporter-deficient BT20 cells, indicating that a higher intracellular uptake of metformin results in more potent anti-proliferative effects in human breast cancer cells.
- The higher levels of phosphorylated AMPK in transport-competent OCT3-BT20 cells support our hypothesis that the presence of OCT3 (as a representative cation-selective transporter) is critical for metformin cellular uptake and subsequent anti-proliferative effects.
- The results provide a clear guidance for the design of xenograft mouse models, comprising tumors produced from metformin transporter-competent and transporter-deficient cells, in which the role of metformin transporters can be evaluated for anti-tumor efficacy of metformin. These studies are in progress.

REFERENCE


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