Na^+-K^+-$2Cl^-$ cotransporter NKCC1 in regulation of glioma migration and progression

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The bumetanide-sensitive Na^+-K^+-$2Cl^-$ cotransporter 1 (NKCC1) maintains cell volume homeostasis by regulating intracellular K^+ and Cl^- content. NKCC1 expression is associated with high grade gliomas and increased NKCC1 activity was shown to promote glioma cell migration. The mechanisms underlying enhanced NKCC1 activity, and whether NKCC1 activity is modulated by the chemotherapeutic agent, temozolomide (TMZ), are unknown. We show that primary glioma cells (GCs) exhibit increased phosphorylation of NKCC1 as well as two upstream regulatory kinases, With-No-Lysine kinases 1 (WNK1) and oxidative stress-responsive kinase-1 (OSR1). NKCC1-meditaed Rb^+ (K^+) influx was detected in murine glioma cells via Ion Channel Reader (ICR8000, Aurora). siRNA-mediated silencing of WNK1 or OSR1 reduces the intracellular K^+ and Cl^- content of GCs and abolishes NKCC1-mediated regulatory volume increase. Surprisingly, TMZ causes robust activation of the WNK1/OSR1/NKCC1 signaling pathway in GCs and triggers glioma migration. Pharmacological inhibition of NKCC1 with bumetanide or siRNA knockdown of WNK1 or OSR1 significantly decreases basal GC migration even after TMZ treatment. We are investigating effects of combination of NKCC1 blockade with TMZ therapy on inhibiting glioma cell migration and growth.