University of Massachusetts UMASS Medical School

GRADUATE SCHOOL OF BIOMEDICAL SCIENCES

BIOCHEMISTRY AND MOLECULAR PHARMACOLOGY

Ph.D. THESIS DEFENSE

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MENTOR: Anthony Carruthers, PhD

THURSDAY, 12/21/2017 9:00 a.m.
LRB 816

"Small Molecule Modulation of GLUT1–Mediated Glucose Transport"

The Glucose transport protein, GLUT1, is highly expressed in rapidly proliferating cells, including cancer cells, while decreased GLUT1 levels are found in diseases such as GLUT1 deficiency syndrome and Alzheimer's. There is increased interest in developing GLUT1 inhibitors as novel anti-cancer therapeutics, and the discovery of compounds that directly stimulate GLUT1 function. This work investigates how small molecules stimulate and/or inhibit GLUT1-mediated glucose transport, either directly or through the AMPK pathway.

Using sugar transport assays and docking analyses to explore Ligand–GLUT1 interactions and specificity of binding, we show that: 1) Ligands inhibit GLUT1 by competing with glucose for binding to the exofacial or endofacial sugar binding sites; 2) Subsaturating inhibitor concentrations stimulate sugar uptake; 3) Ligands inhibit GLUT1–, GLUT3– and GLUT4–mediated sugar uptake in HEK293 cells; and 4) Inclusion of a benzonitrile head group on endofacial GLUT1 inhibitors confers greater inhibitory potency.

Furthermore, we investigated AMPK-regulated GLUT1 trafficking in cultured blood-brain barrier endothelial cells, and show that inhibition of GLUT1 internalization is not responsible for increased cell surface levels of GLUT1 observed with AMPK activation in these cells.

This study provides a framework for screening candidate GLUT1 inhibitors for specificity, and for optimizing drug design and delivery. Our data on transport stimulation at low inhibitor concentrations support the idea that GLUT1 functions as a cooperative oligomer of allosteric alternating access subunits.

Mentor(s)

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