BIOGRAPHICAL SKETCH

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NAME: SOUDAMANI SINGH

eRA COMMONS USER NAME (credential, e.g., agency login): SOUDAMANI SINGH

POSITION TITLE: ASSISTANT PROFESSOR

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Andhra University, Visakhapatnam, Andhra Pradesh, India	B.Sc.	04/1994	Botany, Zoology & Chemistry
University of Madras, Chennai, India	M.Sc.	05/1999	Zoology
	M.Phil.	4/2000	Zoology
Dr. ALM Institute of Basic Medical Sciences University of Madras, Chennai, India	PhD	01/2008	Zoology-Endocrinology
Section of Digestive Diseases, Dept. of Medicine, WVU, Morgantown, WV 26505.	Post Doctorate Research	07/2013	Gastroenterology
Clinical and Translational Sciences, Marshall University, Huntington, WV 25701	Post Doctorate Research	06/2017	Gastroenterology

A. Personal Statement

I have been working in the area of intestinal epithelial nutrient/electrolyte transport for the past 10 years, including my postdoctoral training period, with a primary focus on the mechanisms of regulation of NaCl, glucose and amino acid absorption under normal physiology and their alterations in inflammatory bowel disease (IBD) and obesity. The extensive training I received during my postdoctoral training program has given me an in-depth understanding of the regulation of the intestinal nutrient and electrolyte transporters, specifically Na^+/H^+ exchanger 3 (NHE3), the Cl^-/HCO_3^- exchanger DRA (Down-Regulated in Adenoma), sodium-glucose co-transporter 1 (SGLT1), the neutral amino acid transporter B0AT1 and L-type amino-acid transporter 1 (LAT1). My previous studies have demonstrated that arachidonic acid metabolites (AAM) formed during inflammatory conditions, such as IBD, are responsible for regulating the inhibition of Na-glutamine co-transport (NGcT) in villus and crypt cells. These studies demonstrated that inhibition of cyclooxygenase, a key enzyme in the inflammatory cascade, reverses the inhibition of NGcT via B0AT1 in rabbit small intestine villus cells isolated from chronically inflamed intestines. In addition to above studies we also demonstrated that inhibiting the synthesis of leukotrienes by lipoxygenase with the drug MK886 reversed the stimulation of SN2 function in crypt cells. I was also involved in projects studying regulation of NaCl and glucose transport in obesity. Utilizing *in vivo* animal models, our studies demonstrated unique regulation of NHE3 and SGLT1 in obesity. I am also working in a project to determine the regulation of LAT1 in mTOR activation in *in vitro* models of inflammatory bowel disease in normal small intestinal and colonic cells and colon cancer cells. This study was done in collaboration with Dr. Salisbury. Given my lab's expertise in amino acid transport in epithelial cells, I am also collaborating with Dr. Salisbury on his RO1 project to study the regulation of LAT1 in breast epithelial and breast cancer cells. As a junior faculty, I have recently secured a pilot project funding from the COBRE ACCORD of Marshall University to study the

role of glutamine transport in obesity, which has clear relevance to the central theme of the COBRE ACCORD addressing cellular transport in a distinct obesity-driven health complication. During this project period, our studies demonstrated novel mechanisms of regulation of glutamine transport in obesity by the adipocyte secretome (ADS)-derived molecules. ADS conditioned media from obese Zucker rats, but not lean Zucker rats increased intestinal glutamine absorption by increasing B0AT1 activity. My extensive studies on the role of intestinal epithelial transporters in the pathogenesis of IBD and obesity have resulted 9 peer-reviewed publications in high impact journals. Therefore, my expertise and experience in this area clearly support my suitability to serve in the proposed project.

B. Positions and Honors

Positions and Employment

2010-2013 Postdoctoral Fellow, Section of Digestive Diseases, Department of Medicine, Health Sciences Centre, West Virginia University, Morgantown, WV.

2013-2017 Postdoctoral Fellow, Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine, Marshall University, 1600 Hal Greer Blvd. Huntington, WV.

2017- 2018 Research Assistant Professor, Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine, Marshall University, 1600 Hal Greer Blvd. Huntington, WV.

2018-Present Assistant Professor, Department of Clinical and Translational Sciences, Joan C. Edwards School of Medicine, Marshall University, 1600 Hal Greer Blvd. Huntington, WV.

Honors

2004-2006 **Project fellow** in project entitled “Molecular approach to reproductive toxicity of aflatoxin.” funded by the University with Potential for Excellence (UWPFE), under the University Grants Commission (UGC) of the Government of India.

2007-2010 **Women Scientists** award in project entitled “Effects of experimental diabetes and insulin replacement on epididymal structure and function” funded by the Department of Science and Technology (DST) Women Scientist Scheme – A (WOS-A)

C. Contributions to Science

1. **Unique regulation of glutamine absorption in chronically inflamed intestinal cells**. In my recent publications, I studied the regulation of nutrient transport in *in-vitro* systems during inflammation. My focus includes the brush border membrane transporters B0AT1 and SN2/SNAT5. Glutamine, an essential primary nutrient, is assimilated through Na^+-dependent co-transport (B0AT1/SLC6A19) on the brush border membrane (BBM) of enterocytes in the small intestine. In villus cells glutamine is absorbed by B0AT1 (SLC6A19), but in crypt cells it is absorbed by SN2/SNAT5 (SLC38A5). In the inflamed small intestine, a physiological switch occurs, where B0AT1 is inhibited and SN2 is stimulated, thus becoming the main transporter for glutamine. The goal of the project was to determine whether AAM formed during inflammatory conditions like IBD could play a role in this observed phenomenon. To this end, experiments were conducted to study whether prostaglandin E2 (PGE2), or leukotriene D4 (LTD4), both present in inflamed gut mucosa, can alter the absorption of glutamine. We found that PGE2 regulates B0AT1, while LTD4 regulates SN2. This revealed that the COX pathway is more important at the level of villus, but the LOX pathway metabolites are important in the crypts. Next, we

studied whether inhibiting PG and LT formation by COX or LOX could reverse the transporter effects noted. To this end, we utilized piroxicam, an inhibitor of COX activity, and MK886, an inhibitor of LOX, to observe whether we could reverse alterations in B0AT1 and SN2. Piroxicam was found to restore normal B0AT1 function in villus and MK886 restored normal function of SN2 in crypts. Collectively, I have uncovered from in-vitro studies that B0AT1 regulation in inflammation is primarily driven by the COX pathway, whereas, SN2 is primarily regulated by the LOX pathway. As a result of my expertise in amino acid transport in intestinal epithelial cells, my collaborators and I were invited to present a comprehensive review of the regulation of amino acid transporters in IBD recently by the journal Comprehensive Physiology.

Singh S, Arthur S, and Sundaram U. Mechanisms of Regulation of Transporters of Amino Acid Absorption in Inflammatory Bowel Diseases. Comp Phys, 2020 c190016. V2. (In Press)

Arthur S, **Singh S**, Sundaram U. Cyclooxygenase pathway mediates the inhibition of Na-glutamine co-transporter B0AT1 in rabbit villus cells during chronic intestinal inflammation. PLoS One. 2018 Sep 7;13(9): e0203552. PMID: 30192835

Singh S, Arthur S, and Sundaram U. Unique regulation of Na-glutamine co-transporter SN2/SNAT5 in rabbit intestinal crypt cells during chronic enteritis. Under Revision Journal of Cellular and Molecular Medicine 2018 Mar;22(3):1443-1451. PMID: 29271063

Singh S, Arthur S, Talukder J, Palaniappan B, Coon S, Sundaram U. Mast cell regulation of Na-glutamine co-transporters B0AT1 in villus and SN2 in crypt cells during chronic intestinal inflammation. BMC gastroenterology. 2015; 15(1):47. PMID: 25884559

2. **Deregulation of glucose and sodium (Na)-chloride (Cl) homeostasis during obesity.** In FASEB, we have shown that during obesity SGLT1 and DRA are stimulated, whereas NHE3 was unaffected. The mechanism of stimulation of SGLT1 was due to increased affinity (K_m) while the mechanism of stimulation of DRA was increased transporter number (V_{max}). These observations provide the pathophysiologic basis for obesity mediated dysregulation of glucose and NaCl homeostasis, an underlying cause for diabetes and hypertension.

   Palaniappan B, Arthur S, Sundaram VL, Butts M, Sundaram S, Mani K, **Singh S**, Nepal N, Sundaram U. Inhibition of intestinal villus cell Na/K-ATPase mediates altered glucose and NaCl absorption in obesity-associated diabetes and hypertension. FASEB J. 2019 Aug;33(8):9323-9333. PMID: 31107610

3. **Moderate dose of alcohol differentially regulates intestinal nutrient transporters.** I am also a co-author on a manuscript published in *The Journal of Nutrition.* In this work, we showed how a moderate dose of alcohol, equivalent to a drink a day for women and two drinks a day for men, significantly inhibits intestinal glucose absorption via the sodium-dependent glucose co-transporter SGLT1. In this manuscript, we determined this inhibition was present both in rat intestinal epithelial cells as well as at the intestinal villus cell brush border membrane of Sprague Dawley rats. In addition to this work we have also published an article in the journal *Nutrients* demonstrating moderate alcohol significantly inhibits glutamine absorption both *in vitro* and *in vivo.*

   Butts M, **Singh S**, Haynes J, Arthur S, Sundaram U. Moderate Alcohol Consumption Uniquely Regulates Sodium-Dependent Glucose Co-Transport in Rat Intestinal Epithelial Cells In Vitro and In Vivo. J Nutr. 2019 Nov 26. pii: nxz277. doi: 10.1093/jn/nxz277. PMID: 31769840.

Butts M, Singh Paulraj R, Haynes J, Arthur S, **Singh S**, Sundaram U. Moderate Alcohol Consumption Inhibits Sodium-Dependent Glutamine Co-Transport in Rat Intestinal Epithelial Cells in Vitro and Ex Vivo. Nutrients. 2019 Oct 18;11(10). pii: E2516. doi: 10.3390/nu11102516. PMID: 31635319

4. **Inimitable regulation of SGLT1 during inflammation in intestinal epithelial cells.** In *Cells*, we have shown that during chronic enteritis, peroxynitrite (OONO), a potent oxidant, inhibits SGLT1 while NHE3 activity was unaltered. The mechanism of inhibition of SGLT1 by OONO was secondary to reduction in the number of co-transporters (V_{max}) without an alteration in the affinity. We have further found out that the p38 mitogen-activated protein (MAP) kinase pathway mediates the OONO inhibition of SGLT1. In another study we have shown that chronic and specific inhibition of basolateral Na^+-K^+-ATPase in IEC-18 cells increases intracellular Na^+. In this study, we have shown that Na^+-K^+-ATPase stimulates entrance of glucose via the brush border membrane SGLT1, but not influx of Na^+ via NHE3. The mechanism of stimulation of SGLT1 is secondary to an increase in the affinity of the co-transporter for glucose. Na^+-K^+-ATPase regulates the brush border membrane SGLT1, possibly in a compensatory manner for the loss of trans-membrane Na^+, leading to its inhibition.

   Palaniappan B, Manoharan P, Arthur S, **Singh S**, Murughiyan U, Sundaram U. Stimulation of constitutive nitric oxide uniquely and compensatorily regulates intestinal epithelial cell brush border membrane Na absorption. Physiol Rep. 2019 May;7(9): e14086. PMID: 31074207.

   Manoharan P, Sundaram S, **Singh S**, Sundaram U. Inducible Nitric Oxide Regulates Brush Border Membrane Na-Glucose Co-transport, but Not Na:H Exchange via p38 MAP Kinase in Intestinal Epithelial Cells. Cells. 2018 Aug 19;7(8). pii: E111. doi: 10.3390/cells7080111. PMID: 30126234

   Manoharan P, Gayam S, Arthur S, Palaniappan B, **Singh S**, Dick GM, Sundaram U. Chronic and selective inhibition of basolateral membrane Na-K-ATPase uniquely regulates brush border membrane Na absorption in intestinal epithelial cells. Am J Physiol. Cell Physiol. 2015 Apr 15;308 (8):C650-6. PMID: 25652450

Complete list of publications in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/soudamani.singh.1/bibliography/public/

D. Additional Information: Research Support and/or Scholastic Performance

Ongoing research support:

Title: Regulation of amino acid absorption in the mammalian small intestine
Role: Faculty investigator
PI: Uma Sundaram, MD
Type: R01 DK108054; Agency: NIH/NIDDK
Effort 6 calendar months
Period: 07/01/16 – 06/30/2021

Title: Appalachian Center for Cellular transport in Obesity Related Disorders
Role: Pilot investigator, Project: *Adipose derived secretome regulation of Na-glutamine co-transport during obesity*
PI: Uma Sundaram, MD
Type: 1P20GM121299-01; Agency: NIH/NIGMS
Effort: 0.6 calendar months
Period 07/01/20198 – 06/30/2023