Research highlights

Cardiac Snail family of transcription factors directs systemic lipid metabolism in Drosophila
Y Liu et al (Lim lab)

- Tetraspanin CD82 Interaction with Cholesterol Promotes Extracellular Vesicle-mediated Release of Ezrin to Inhibit Cell Movement
C Huang et al (Zhang lab)

- CD82-TRPM7-Numb Signaling mediates Age-related Cognitive Impairment
Y Zhao et al (Zhang lab)

- Critical evaluation of animal models of visceral pain for therapeutic development: A focus on irritable bowel syndrome
A Johnson et al (Greenwood-van Meerveld lab)

Successful Thesis defense
Gavin Pharaoh (Van Remmen lab)

Happy Retirement
Becky Mosley

Christmas Party
Tetraspanin CD82 interaction with cholesterol promotes extracellular vesicle–mediated release of ezrin to inhibit tumour cell movement

Chao Huang, a,b Franklin A. Hays, c James J. Tomasek, d Sinhbinya Benyajati, b and Xin A. Zhang a,b

ABSTRACT

Tumour metastasis suppressor KAI1/CD82 inhibits tumour cell movement. As a transmembrane protein, tetraspanin CD82 bridges the interactions between membrane microdomains of lipid rafts and tetraspanin-enriched microdomains (TEMs). In this study, we found that CD82 and other tetraspanins contain cholesterol recognition/interaction amino-acid consensus (CRAC) sequences in their transmembrane domains and revealed that cholesterol binding of CD82 determines its interaction with lipid rafts but not with TEMs. Functionally, CD82 needs cholesterol binding to inhibit solitary migration, collective migration, invasion and infiltrative outgrowth of tumour cells. Importantly, CD82–cholesterol–lipid raft interaction not only promotes extracellular release of lipid raft components such as cholesterol and gangliosides but also facilitates extracellular vesicle (EV)–mediated release of ezrin–radixin–moesin (ERM) protein Ezrin. Since ERM proteins link actin cytoskeleton to the plasma membrane, we show for the first time that cell movement can be regulated by EV-mediated releases, which disengage the plasma membrane from cytoskeleton and then impair cell movement. Our findings also conceptualize that interactions between membrane domains, in this case converge of lipid rafts and TEMs by CD82, can change cell movement. Moreover, CD82 coalescences with both lipid rafts and TEMs are essential for its inhibition of tumour cell movement and for its enhancement of EV release. Finally, our study underpins that tetraspanins as a superfamily of functionally versatile molecules are cholesterol-binding proteins.
Dr. Beverley Greenwood-van Meerveld (senior author) and Dr. Johnson (first author) were co-authors on a recently accepted position paper in Neurogastroenterology and Motility entitled

**CRITICAL EVALUATION OF ANIMAL MODELS OF VISCERAL PAIN FOR THERAPEUTICS DEVELOPMENT: A FOCUS ON IRRITABLE BOWEL SYNDROME**

**AUTHORS**


The focus of this paper was chronic abdominal pain, which is the major complaint in patients with disorders of the gut-brain interaction, also referred to as functional gastrointestinal disorders, such as irritable bowel syndrome (IBS). Models for IBS are faced with challenges including a complex clinical phenotype, which is co-morbid with other conditions including anxiety, depression, painful bladder syndrome and chronic pelvic pain. Based upon the multifactorial nature of IBS with complicated interactions between biological, psychological and sociological variables, no single experimental model recapitulates all the symptoms of IBS. This position paper contextualized chronic visceral pain using the example of IBS and focussed on its pathophysiology while providing a critical review of current animal models that are most relevant, robust and reliable in which to screen promising therapeutics to alleviate visceral pain and delineate the gaps and challenges with these models. We also highlighted, prioritized, and came to a consensus on the models with the highest face/construct validity.
Successful Ph.D. thesis defense

Gavin Pharaoh, Physiology doctoral candidate in Dr. Holly Van Remmen’s lab, successfully defended his dissertation on December 5, 2019.

The Graduate College and The Department of Physiology

Announces the Final Examination for the Defense of the Doctor of Philosophy Degree

Gavin A. Pharaoh
Doctoral Candidate
Advisor: Holly Van Remmen, Ph.D

TARGETING HYDROPEROXIDES IN NEUROGENIC ATROPHY

Sarcopenia is the age-related loss of skeletal muscle mass and function. There are many components that contribute to the development and progression of sarcopenia. The work described in this dissertation focuses specifically on loss of neuromuscular innervation, hydroperoxide production, and oxidative stress as factors involved in initiating and progressing neurogenic atrophy including sarcopenia. This work demonstrates a causal role for oxidative stress and specifically hydroperoxides in sarcopenia.

First, we examined the impact on sarcopenia in aged mice lacking the transcription factor Nrf2, which is the primary regulator of the antioxidant response. The Nrf2 antioxidant response protects against oxidative stress, and loss of the antioxidant response accelerates oxidative damage, atrophy, and weakness in aging muscle. This work provides evidence that increased oxidative stress contributes to sarcopenia progression.

Next, we examined how loss of innervation drives muscle atrophy through hydroperoxide production. Loss of neuromuscular innervation with age is a primary cause of sarcopenia (neurogenic atrophy). We have previously shown loss of innervation induces muscle reactive oxygen species (ROS) production in the form of hydroperoxide species, either lipid hydroperoxides (LOOHs) or hydrogen peroxide (H₂O₂). Here we show that loss of innervation primarily induces muscle LOOH production in the cytosolic phospholipase A2 (cPLA2) pathway in several models including aging. Increased scavenging of muscle H₂O₂ does not rescue muscle atrophy, while cPLA2 inhibition decreases LOOH production and protects muscle mass and fiber size. These experiments provide evidence that LOOHs produced in the cPLA2 pathway directly contribute to muscle atrophy after loss of innervation.

Finally, we examined potential mechanisms and treatments for adenosine diphosphate (ADP) insensitivity. Loss of sensitivity to ADP stimulation in aging human muscle causes increased production of mitochondrial H₂O₂. We show here that reduced ADP sensitivity in skeletal muscle mitochondria increases mitochondrial electron transport chain-derived H₂O₂ production in mouse models of aging and oxidative stress. However, denervation did not induce ADP insensitivity. Treatment with the mitochondrial-targeted peptide SS-31 improves ADP sensitivity and muscle fatigue resistance. This project describes how mechanisms including oxidative stress decrease sensitivity to ADP and result in increased mitochondrial H₂O₂ production and muscle fatigue in aging muscle.

The work provided in this dissertation provides evidence that oxidative stress and both hydroperoxide species (LOOH and H₂O₂) play a causal role in sarcopenia. We identify hydroperoxide species as clinically relevant targets with existing interventions and potential for pharmaceutical development to treat the loss of muscle mass and strength observed in sarcopenia.

Thursday, December 5th 9 – 10 a.m. (public seminar), BRC 109

You did it!
Look who’s retiring...

Becky Mosley

Come help us celebrate her 27 years of dedicated service with a retirement lunch reception.

December 6, 2019
11:00 a.m. – 1:00 p.m.
Department of Physiology
Biomedical Sciences Building
(BMSB) 6th floor

We hope you will come help make this a memorable event and wish her well in the next chapter of her life.
Retirement Luncheon for dear Becky
Retirement Luncheon for dear Becky
Retirement Luncheon for dear Becky
Retirement Luncheon for dear Becky
You will be dearly missed!
Department of Physiology

Christmas Party –
December 11, 2019

The Department of Physiology Cordially Invites You To Our

ANNUAL HOLIDAY
PARTY

- Catered lunches will be provided.
- Please bring your favorite dessert to share.
- December 11, 2019
  1:00 p.m. to 5:00 p.m.
- Location: The Department of Physiology, BMSB 6th Fl Lobby
Department of Physiology
Christmas Party
Department of Physiology Christmas Party
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We hope you have enjoyed reading the OUHSC Physiology newsletter. This publication is intended to share with everyone the latest events and developments within the Department. We welcome articles, thoughts and suggestions for our future issues. Please do so by emailing Dr. Hui-Ying Lim (hlim@ouhsc.edu).

All the lovely photos seen in this newsletter were generously provided by the following equally lovely ladies: