

BIOGRAPHICAL SKETCH

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NAME: Tracy G. Anthony

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

POSITION TITLE: Professor of Nutritional Sciences

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
Virginia Tech University, Blacksburg, VA	B.S.	08/93	Human Nutrition & Foods
University of Illinois, Urbana, IL	M.S.	05/95	Nutritional Sciences
University of Illinois, Urbana, IL	Ph.D.	05/98	Nutritional Sciences
Penn State College of Medicine, Hershey, PA	Postdoc	1998-2001	Cellular & Molecular Physiology

A. Personal Statement

The broad aim of my research program is to understand how altering the supply of amino acids, in total or individually, regulates protein homeostasis in the whole animal, with an emphasis on translational control of protein synthesis and gene expression. I have expansive training in nutrition, biochemistry, endocrinology, immunology, metabolism, molecular biology and physiology, and I hold deep experience in the design and use of diet studies and animal models to model the human condition. Over the years I have published molecular mechanisms of transcriptional and translational control by nutrition and exercise in many organ systems including liver, skeletal muscle, pancreas, adipose, immune tissues and brain. I am broadly interested in the cellular sensing of nutrients and how affiliated signal transduction networks such as the integrated stress response, the endoplasmic reticulum stress response/unfolded protein response and the mammalian target of rapamycin pathways integrate with each other to regulate proteostasis. My group has contributed to understanding the sensing and signaling mechanisms activated by increased and decreased dietary amino acid supply, as detailed below under Contributions to Science.

Recent example:

1. Nikonorova IA, Mirek ET, Signore CC, Goudie MP, Wek RC, Anthony TG. Time-resolved analysis of amino acid stress identifies eIF2 phosphorylation as necessary to inhibit mTORC1 activity in liver. *J Biol Chem.* 2018 Apr 6;293(14):5005-5015. doi: 10.1074/jbc.RA117.001625. Epub 2018 Feb 15. PMID: 29449374

B. Positions and HonorsPositions and Employment

1998-2001	American Diabetes Association Postdoctoral Research Fellow, Department of Cellular and Molecular Physiology, Penn State College of Medicine, Hershey, PA
2001-2005	Assistant Scientist/Assistant Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN.
2005-2010	Assistant Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN.
2010-2012	Associate Professor, Department of Biochemistry and Molecular Biology, Indiana University School of Medicine-Evansville, Evansville, IN.
2012-2018	Associate Professor, Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ.

July 2018-current Professor, Department of Nutritional Sciences, Rutgers University, New Brunswick, NJ.

Honors and Awards

- 2003 American Society for Nutritional Sciences *Peter J. Reeds Young Investigator Award* for recognition of research which focuses on the regulation of somatic growth and the unique roles of amino acids in protein metabolism.
- 2010 Indiana University School of Medicine *Trustees Teaching Award*
- 2014 *Fellow*, Dannon Institute Academic Mid-Career Nutrition Leadership Institute
- 2013-2018 Standing Member, Integrative Nutrition and Metabolic Processes Scientific Review Group, NIH

Other Experiences and Professional Memberships

- 1994 – current Member, American Society for Nutrition
- 1997 – current Member, American Physiological Society
- 2004 – current Member, American Society for Biochemistry and Molecular Biology
- 2010 – current Editorial Board, *American Journal of Physiology Endocrinology and Metabolism*
- 2015 – current Editorial Board, *Advances in Nutrition*
- 2016 – current Editorial Board, *Annual Reviews in Nutrition*
- 2017 – current Editorial Board, *Journal of Biological Chemistry*

C. Contribution to Science

1. Identified and characterized mechanisms by which dietary protein or leucine after exercise or fasting stimulates recovery of muscle protein synthesis and mRNA translation initiation *in vivo*. Our group was the first to show that the feeding protein after endurance exercise stimulates muscle protein synthesis recovery via activation of mRNA translation initiation and then described how the leucine content of a complete meal is a determining factor for initiating but not sustaining the anabolic response to dietary protein. Our group was also the first to show that the branched chain amino acid leucine was unique in its potency to stimulate mTORC1 *in vivo* and were the first to show control of mRNA translation initiation by leucine in mammalian tissue. I was involved in all aspects of these works and took a lead or supporting role in manuscript preparation.

- a) **Gautsch TA**, Anthony JC, Kimball SR, Paul GL, Layman DK, Jefferson LS. Availability of eIF4E regulates skeletal muscle protein synthesis during recovery from exercise. *Am J Physiol.* 1998 Feb;274(2 Pt 1):C406-14. PMID: 9486130
- b) Anthony JC, **Anthony TG**, Kimball SR, Vary TC, Jefferson LS. Orally administered leucine stimulates protein synthesis in skeletal muscle of post-absorptive rats in association with increased eIF4F formation. *J Nutr.* 2000 Feb;130(2):139-45. PMID: 10720160
- c) Anthony JC, Yoshizawa F, **Anthony TG**, Vary TC, Jefferson LS, Kimball SR. Leucine stimulates translation initiation in skeletal muscle of postabsorptive rats via a rapamycin-sensitive pathway. *J Nutr.* 2000 Oct;130(10):2413-9. PMID: 11015466
- d) **Anthony TG**, Anthony JC, Yoshizawa F, Kimball SR, Jefferson LS. Oral administration of leucine stimulates ribosomal protein mRNA translation but not global rates of protein synthesis in the liver of rats. *J Nutr.* 2001 Apr;131(4):1171-6. PMID: 11285321

2. Identified and characterized sensing and signaling events to amino acid insufficiency in mice, rats and pigs. Our group uncovered early and seminal evidence revealing how reduced dietary amino acid supply is sensed by GCN2 and signals via phosphorylation of eIF2 and mTORC1 in tissues of mammals. These findings were correlated with key physiological responses in the liver, skeletal muscle and brain. I was involved in all aspects of these works and took a lead or supporting role in manuscript preparation.

- a) **Anthony TG**, Reiter AK, Anthony JC, Kimball SR, Jefferson LS. Deficiency of dietary EAA preferentially inhibits mRNA translation of ribosomal proteins in the liver of meal-fed rats. *Am J Physiol Endocrinol Metab.* 2001 Sep;281(3):E430-9. PMID: 11500297
- b) Kobayashi H, Børsheim E, **Anthony TG**, Traber DL, Badalamenti J, Kimball SR, Jefferson LS, Wolfe RR. Reduced amino acid availability inhibits muscle protein synthesis and decreases activity of initiation factor eIF2B. *Am J Physiol Endocrinol Metab.* 2003 Mar;284(3):E488-98. PMID: 12556349
- c) **Anthony TG**, McDaniel BJ, Byerley RL, McGrath BC, Cavener DR, McNurlan MA, Wek RC. Preservation of liver protein synthesis during dietary leucine deprivation occurs at the expense of skeletal muscle mass in mice deleted for eIF2 kinase GCN2. *J Biol Chem.* 2004 Aug 27;279(35):36553-61. Epub 2004 Jun 22. PMID: 15213227

- d) Hao S, Sharp JW, Ross-Inta CM, McDaniel BJ, **Anthony TG**, Wek RC, Cavener DR, McGrath BC, Rudell JB, Koehnle TJ, Gietzen DW. Uncharged tRNA and Sensing of Amino Acid Deficiency in Mammalian Piriform Cortex. *Science*. 2005 Mar 18;307(5716):1776-8. PMID: 15774759

3. Identified and characterized mechanisms of metabolic toxicities by the anti-cancer drug L-asparaginase. Asparaginase is used to treat acute lymphoblastic leukemia, the most common childhood cancer, but unpredictably causes adverse metabolic toxicities that lead to treatment failure. Our group was the first to show that asparaginase activates GCN2 in mammalian tissues. We also revealed the protective function of GCN2 during asparaginase treatment and described the mechanism by which GCN2 null mice treated with asparaginase are predisposed to immunosuppression, hepatic failure and pancreatitis, providing the first genetic evidence for predisposition to adverse events by asparaginase. I directed these works and was deeply involved in all aspects including manuscript preparation.

- a) Wilson GJ, Lennox BA, She P, Mirek ET, Al Baghdadi RJ, Fusakio ME, Dixon JL, Henderson GC, Wek RC, **Anthony TG**. GCN2 is required to increase fibroblast growth factor 21 and maintain hepatic triglyceride homeostasis during asparaginase treatment. *Am J Physiol Endocrinol Metab*. 2015 Feb 15;308(4):E283-93. doi: 10.1152/ajpendo.00361.2014. Epub 2014 Dec 9. PMID: 25491724; PMC4329494
- b) Phillipson-Weiner L, Mirek ET, Wang Y, McAuliffe WG, Wek RC, **Anthony TG**. General control nonderepressible kinase 2 (GCN2) deletion predisposes to asparaginase-associated pancreatitis in mice. *Am J Physiol Gastrointest Liver Physiol*. Mar 11:ajpgi.00052.2016. doi: 10.1152/ajpgi.00052.2016. PMID: 26968207
- c) Nikonorova IA, Al-Baghdadi RJT, Mirek ET, Wang Y, Goudie MP, Wetstein BB, Dixon JL, Hine C, Mitchell JR, Adams CM, Wek RC, **Anthony TG**. Obesity challenges the hepatoprotective function of the integrated stress response to asparaginase exposure in mice. *J Biol Chem*. 2017 Apr 21;292(16):6786-6798. doi: 10.1074/jbc.M116.768408. Epub 2017 Feb 27. PMID: 28242759, PMC5399125
- d) Al-Baghdadi RJT, Nikonorova IA, Mirek ET, Wang Y, Park J, Belden WJ, Wek RC, **Anthony TG**. Role of activating transcription factor 4 in the hepatic response to amino acid depletion by asparaginase. *Sci Rep*. 2017 Apr 28;7(1):1272. doi: 10.1038/s41598-017-01041-7. PMID: 28455513, PMCID: PMC5430736

4. Characterized key regulatory elements within the integrated stress response. Activation of eIF2 kinases to environmental stress triggers the integrated stress response to promote cellular adaptation. Our group described novel and key features of the integrated stress response and unfolded protein response, specifically the role of eIF2 kinases and ATF4 in regulating selective mRNA translation, antioxidant stress responses and cell fate decisions with novel applications to human diseases such as hepatic steatosis and leukodystrophy. I directed or co-directed these works and was deeply involved in all aspects.

- a) Teske BF, Wek SA, Bunpo P, Cundiff JK, McClintick JN, **Anthony TG**, Wek RC. The eIF2 kinase PERK and the integrated stress response facilitate activation of ATF6 during endoplasmic reticulum stress. *Mol Biol Cell*. 2011 Nov;22(22):4390-405. doi: 10.1091/mbc.E11-06-0510. Epub 2011 Sep 14. PMID: 21917591; PMC3216664
- b) Baird TD, Palam LR, Fusakio ME, Willy JA, Davis CM, McClintick JN, **Anthony TG**, Wek RC. Selective mRNA translation during eIF2 phosphorylation induces expression of IBTK α . *Mol Biol Cell*. 2014 May;25(10):1686-97. doi: 10.1091/mbc.E14-02-0704. Epub 2014 Mar 19. PMID: 24648495; PMC4019499
- c) She P, Bunpo P, Cundiff JK, Wek RC, Harris RA, **Anthony TG**. General control nonderepressible 2 (GCN2) kinase protects oligodendrocytes and white matter during branched-chain amino acid deficiency in mice. *J. Biol. Chem*. Oct 25;288(43):31250-60. doi: 10.1074/jbc.M113.498469. PMID: 24019515; PMC3829435
- d) Fusakio ME, Willy JA, Wang Y, Mirek ET, Al Baghdadi RJ, Adams CM, **Anthony TG**, Wek RC. Transcription factor ATF4 directs basal and select induced gene expression in the unfolded protein response and cholesterol metabolism in liver. *Mol Biol Cell*. 2016 May 1;27(9):1536-51. doi: 10.1091/mbc.E16-01-0039. Epub 2016 Mar 9. PMID: 26960794; PMC4850040

5. Uncovered key regulatory events that guide physiological responses to dietary sulfur amino acid restriction. Dietary methionine restriction leads to physiological responses that extend lifespan and confer protection against metabolic diseases by reducing visceral fat, increasing insulin sensitivity, and ameliorating hepatosteatosis by altering lipid metabolism. Our group explored the role of GCN2 and the integrated stress response in regulating FGF21-driven changes in body composition during dietary methionine restriction in mice. We found that hepatic phosphorylation of eIF2 by GCN2 influenced early changes in body composition but did not correlate with long term changes in fat or lean mass, suggesting the presence of auxiliary or redundant control mechanisms. I directed or co-directed these works and was deeply involved in all aspects.

- a) **Anthony TG**, Morrison CD, Gettys TW. Remodeling of lipid metabolism by dietary restriction of essential amino acids. *Diabetes*. 2013 Aug;62(8):2635-44. doi: 10.2337/db12-1613. PMID: 23881190
- b) Wanders D, Stone KP, Forney LA, Cortez CC, Dille KN, Simon J, Xu M, Hotard EC, Nikonorova IA, Pettit AP, **Anthony TG**, Gettys TW. Role of GCN2-Independent Signaling Through a Noncanonical PERK/NRF2 Pathway in the Physiological Responses to Dietary Methionine Restriction. *Diabetes*. 2016 Jun;65(6):1499-510. doi: 10.2337/db15-1324. Epub 2016 Mar 2. PMID: 26936965, PMCID: PMC4878423
- c) Pettit AP, Jonsson WO, Bargoud AR, Mirek ET, Peelor FF 3rd, Wang Y, Gettys TW, Kimball SR, Miller BF, Hamilton KL, Wek RC, **Anthony TG**. Dietary Methionine Restriction Regulates Liver Protein Synthesis and Gene Expression Independently of Eukaryotic Initiation Factor 2 Phosphorylation in Mice. *J Nutr*. 2017 Jun;147(6):1031-1040. doi: 10.3945/jn.116.246710. Epub 2017 Apr 26. PMID: 28446632, PMCID: PMC5443467

NCBI My Bibliography URL:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/tracy.anthony.1/bibliography/40896220/public/?sort=date&direction=d&ascending>

D. Research Support

ACTIVE

1 R01DK109714-01A1 (MPI: Anthony/Wek)

01/01/17 – 12/31/21

NIH/NIDDK

Homeostatic Responses to Amino Acid Insufficiency

Define the contribution of the integrated stress response to the early molecular and physiological responses that function to maintain proteostasis during dietary amino acid insufficiency.

Role: Lead PI

2 R01DK096311-05A1 (Gettys)

04/01/2017 – 03/31/2019

NIH/NIDDK

The major goal of this project is to examine the impact of PERK deletion on the metabolic phenotype associated with dietary methionine restriction.

Role: Subcontract PI

Multistate NC1184

10/01/17 – 09/30/18

USDA NIFA

Molecular Mechanisms Regulating Skeletal Muscle Growth and Differentiation

My portion of this project examines the role of dietary protein and exercise on the skeletal muscle of horses and mice.

Role: NJ Station PI

COMPLETED:

1 R01 DK105032

12/01/15 – 11/30/2017

NIH/NIDDK (PI: Morrison)

FGF21 is an Endocrine Signal of Protein Restriction.

This project examines the role of the hepatokine FGF21 on mediating the metabolic responses to dietary protein restriction.

Role: Subcontract PI

1 R01 HD070487-06

7/25/2011 – 4/30/2016 (NCE to 4/30/2017)

NIH/NICHD

Molecular Mechanisms of Adverse Metabolic Events by Asparaginase

The major goal of this project is to investigate key molecular events that modulate hepatic dysfunction by the anti-leukemic agent, asparaginase.

Role: PI

R01HD070487-S1 NIH Eunice Kennedy Shriver National Institute of Child Health and Human Development

Supplement to Recover Losses from Hurricane Sandy

Title: Molecular Mechanisms of Adverse Metabolic Events by Asparaginase

12/03/2013 – 04/30/2015

Role: PI

This supplement was to aid in recovery efforts from lost reagents and resources caused by Hurricane Sandy.