

# Martha Stipanuk

## Web Bio

### Information

### Biography

#### Biographical Statement

Martha Stipanuk is the James Jamison Professor in Nutrition in the Division of Nutritional Sciences at Cornell University, where she has been a faculty member since 1977. She received her B.S. from the University of Kentucky, her M.S. from Cornell University, and her Ph.D. from the University of Wisconsin-Madison in nutritional biochemistry.

Dr. Stipanuk's professional career has focused on the study of amino acid metabolism, particularly the metabolism of the sulfur-containing amino acid cysteine. Her work has contributed to an understanding of the intermediary pathways of cysteine metabolism in mammalian cells and of the role of various tissues in cysteine metabolism, including glutathione synthesis and taurine production, within the whole body. The Stipanuk laboratory has played a major role in elucidating the physiological function, regulation, structure, and protein coenzyme formation of cysteine dioxygenase, an iron-dependent enzyme that catalyzes the first step in the cysteinesulfinate-dependent pathway of cysteine catabolism. Cysteine dioxygenase plays a crucial role in regulating cysteine levels, in promoting taurine biosynthesis, and in restricting the metabolism of cysteine through the intermediate hydrogen sulfide, preventing sulfide toxicity and facilitating hydrogen sulfide signaling. The regulation of cysteine dioxygenase abundance and activity state occurs specifically in response to cysteine levels. The Stipanuk laboratory is also interested in elucidating the mechanism(s) by which the concentrations of other amino acids are sensed by cells and how cells respond to changes in amino acid availability.

Dr. Stipanuk has a long-standing interest in teaching and course development in the area of nutrient metabolism. She has developed a multi-authored advanced textbook entitled "Biochemical, Physiological and Molecular Aspects of Human Nutrition" published by Saunders/Elsevier with the 3rd edition released in 2012. Most recently, she has led efforts to develop and teach a graduate course on "Regulation of Macronutrient Metabolism." She also teaches a specialized graduate course on "Nutritional Regulation of Mammalian Protein Synthesis and Degradation."

### Teaching

#### Teaching and Advising Statement

My current teaching is primarily at the graduate student level. In this context, I try to focus classwork and assignments on topics relevant to major contemporary research questions in molecular nutrition and metabolism, incorporating use of the literature and development of conceptual mapping of topics to facilitate an understanding of multiple and complex pathways and physiological processes involved in particular research areas. In advising and mentoring both undergraduates and graduate students, I encourage students to pursue a range of areas of study and experiential learning relevant to their interests and to consider various possibilities for future study and careers.

## **Professional**

### **Current Professional Activities**

Cornell University Graduate Field Membership: Nutrition

Member of American Society for Nutrition

Member of the American Society for Biochemistry and Molecular Biology

Member of the American Society for Physiology

## **Research**

### **Current Research Activities**

Mechanisms of molecular regulation of key enzymes of cysteine metabolism in response to dietary changes; development and characterization of tissue-specific cysteine dioxygenase "knockout" mice; structure-function studies of thiol dioxygenases (cysteine dioxygenase, cysteamine dioxygenase); tissue-specific expression and function of enzymes in taurine and hydrogen sulfide biosynthetic pathways; amino acid deprivation and response to stress; role of amino acids in sensing of nutrient deprivation and activation of stress response pathways.

## **Extension**

## **Education**

### **Education**

- PhD 1977 - University of Wisconsin, Madison; Nutrition and Biochemistry
- MS 1972 - Cornell University, Nutrition and Biochemistry
- BS 1970 - University of Kentucky, Home Economics/Education

## **Courses**

### **Courses Taught**

NS 6100 - Nutritional Regulation of Mammalian Protein Synthesis and Degradation

NS 6320 - Regulation of Macronutrient Metabolism

Mentor for graduate student NS 7030 presentation

Research mentor for undergraduate research

Research mentor for graduate research

## **Websites**

### **Related Websites**

[DNS Home Page](#)

[Stipanuk Lab](#)

## **Administration**

## **Publications**

### **Selected Publications**

Jurkowska H., Roman H.B., Hirschberger L.L., Sasakura K., Nagano T., Hanaoka K., Krijt J., Stipanuk M.H. (2014) Primary hepatocytes from mice lacking cysteine dioxygenase show increased cysteine concentrations and higher rates of metabolism of cysteine to hydrogen sulfide and thiosulfate. *Amino Acids* 46:1353-1365.

Ables GP, Brown-Borg HM, Buffenstein R, Church CD, Elshorbagy AK, Gladyshev VN, Huang TH, Miller RA, Mitchell JR, Richie JP, Rogina B, Stipanuk MH, Orentreich DS, Orentreich N. The first international mini-symposium on methionine lifespan. *Front Genet.* 2014 May 9;5:122.

Sikalidis A.K., Mazor K.M., Lee J.I., Roman H.B., Hirschberger L.L., Stipanuk M.H. (2014) Upregulation of capacity for glutathione synthesis in response to amino acid deprivation: regulation of glutamate-cysteine ligase subunits. *Amino Acids* 46:1285-1296.

Sikalidis A.K., Mazor K.M., Kang M., Liu H., and Stipanuk M.H. (2013) Total 4EBP1 is elevated in liver of rats in response to low sulfur amino acid intake. *J Amino Acids* 2013:864757. doi: 10.1155/2013/864757.

Driggers C.M., Cooley R.B., Sankaran B., Hirschberger L.L., Stipanuk M.H., Karplus P.A. (2013) Cysteine dioxygenase structures from pH4 to 9: consistent cys-persulfenate formation at intermediate pH and a Cys-bound enzyme at higher pH. *J Mol Biol.* 425:3121-3136.

Kerr T.A., Matsumoto Y., Matsumoto H., Xie Y., Hirschberger L.L., Stipanuk M.H., Anakk S., Moore D.D., Watanabe M., Kennedy S., Davidson N.O. (2014) Cysteine sulfinic acid decarboxylase regulation: A role for farnesoid X receptor and small heterodimer partner in murine hepatic taurine metabolism. *Hepatol Res.*44:E218-E228.

Roman H.B., Hirschberger L.L., Krijt J., Valli A., Kožich V., Stipanuk M.H. (2013) The cysteine dioxygenase knockout mouse: altered cysteine metabolism in nonhepatic tissues leads to excess H<sub>2</sub>S/HS<sup>-</sup> production and evidence of pancreatic and lung toxicity. *Antioxid Redox Signal.* 19:1321-1336.

Ueki, I., Roman, H.B., Hirschberger, L.L., Junior, C., Stipanuk, M.H. (2012) Extrahepatic tissues compensate for loss of hepatic taurine synthesis in mice with liver-specific knockout of cysteine dioxygenase. *Am. J. Physiol. Endocrinol. Metab.* 302: E1292-E1299.

Ueki, I., Roman, H.B. Valli, A. Fieselmann, K., Lam, J., Peters, R., Hirschberger, L.L., and Stipanuk, M.H. (2011) Knockout of the murine cysteine dioxygenase gene results in severe impairment in ability to synthesize taurine and an increased catabolism of cysteine to hydrogen sulfide. *Am. J. Physiol. Endocrinol. Metab.* 301: E688-E684.

Stipanuk, M.H., Simmons, C.R., Karplus, A. P., Dominy, J.E. Jr. (2011) Thiol dioxygenases: unique families of cupin proteins. *Amino Acids* 41:91-102.

Stipanuk, M.H., Ueki, I. (2011) Dealing with methionine/homocysteine sulfur: cysteine metabolism to taurine and inorganic sulfur. *J. Inherit. Metab. Dis.* 34:17-32.

Sikalidis, A.K., Stipanuk, M.H. (2010) Growing rats respond to a sulfur amino acid-deficient diet by phosphorylation of the alpha subunit of eukaryotic initiation factor 2 heterotrimeric complex and induction of adaptive components of the integrated stress response. *J. Nutr.* 140:1080-1085.

Stipanuk, M. H. (2009) Macroautophagy and its role in nutrient homeostasis. *Nutr. Rev.* 67:677-689.

Ueki, I. and Stipanuk, M.H. (2009) 3T3-L1 adipocytes and rat adipose tissue have a high capacity for taurine synthesis by the cysteine dioxygenase/cysteinesulfinate decarboxylase and cysteamine dioxygenase pathways. *J. Nutr.* 139:207-214..

Stipanuk, M.H., Ueki, I., Dominy, J.E. Jr., Simmons, C.R., and Hirschberger, L.L. (2009) Cysteine dioxygenase: a robust system for regulation of cellular cysteine levels. *Amino Acids* 37:55-63.

Stipanuk, M.H., Dominy, J.E., Jr., Ueki, I., and Hirschberger, L.L. (2008) Measurement of cysteine dioxygenase activity and protein abundance. *Curr. Prot. Toxicol.* 6.15.1-6.15.25.

Simmons, C.R., Krishnamoorthy, K., Granett, S.L., Schuller, D.J., Dominy, J.E. Jr., Begley, T.P., Stipanuk, M.H., and Karplus, P.A. (2008) A putative Fe<sup>2+</sup>-bound persulfenate intermediate in cysteine dioxygenase. *Biochemistry* 47:11390-11392.

Dominy, J.E. Jr., Hwang, J., Guo, S., Hirschberger, L.L., Zhang, S., and Stipanuk, M.H. (2008) Synthesis of amino acid cofactor in cysteine dioxygenase is regulated by substrate and represents a novel post-translational regulation of activity. *J. Biol. Chem.* 283:12188-12201.

Lee, J-I., Dominy, J.E., Jr., Sikalidis, A. K., Hirschberger, L.L., Wang, W., and Stipanuk, M.H. (2008) HepG2/C3A cells respond to cysteine-deprivation by induction of the amino acid deprivation/integrated stress response pathway. *Physiol. Genomics* 33:218-229.

Dominy, J. E. Jr., Simmons, C.R., Hirschberger, L.L., Hwang, J., Coloso, R.M., Stipanuk, M.H. (2007) Discovery and characterization of a second mammalian thiol dioxygenase: Cysteamine dioxygenase. *J. Biol. Chem.* 282:25189-25198.

Ueki, I., and Stipanuk, M.H. (2007) Enzymes of the taurine biosynthetic pathway are expressed in rat mammary gland. *J. Nutr.* 137:1887-1894.

Dominy, J.E., Jr., Hwang, J., and Stipanuk, M.H. (2007) Overexpression of cysteine dioxygenase reduces intracellular cysteine and glutathione pools in HepG2/C3A cells. *Am. J. Physiol. Endocrinol. Metab.* 293:E62-E69.

Stipanuk, M.H., Dominy, J.E. Jr., Lee, J-I., and Coloso, R.M. (2006) Mammalian cysteine metabolism: new insights into regulation of cysteine metabolism. *J. Nutr.* 136:1652S-1659S.

Dominy, J.E. Jr., Simmons, C.R., Karplus, P.A., Gehring, A.M., and Stipanuk, M.H. (2006) Identification and characterization of bacterial cysteine dioxygenases: a new route of cysteine degradation for eubacteria. *J. Bacteriol.* 188:5561-5569.

Simmons, C.R., Liu, Q., Huang, Q., Hao, Q., Begley, T.P., Karplus, P.A., and Stipanuk, M.H. (2006) Crystal structure of mammalian cysteine dioxygenase: A novel mononuclear iron center for cysteine thiol oxidation. *J. Biol. Chem.* 281:18723-18733. [Issue cover is CDO structure]