Plenary Session Proposal

SfRBM 2017 Meeting

Submitted by:

Maret G. Traber, Ph.D. Ava Helen Pauling Professor Linus Pauling Institute Oregon State University Corvallis, OR 97331-6512 541-737-7977 fax: 541-7375077 E-Mail: maret.traber@oregonstate.edu	Dr. Manfred Eggersdorfer Professor for Healthy Aging SVP Nutrition Science & Advocacy DSM Nutritional Products Wurmisweg 567 4303 Kaiseraugst, Switzerland T +41 61 815 8196 M +41 79 244 9006 Email: manfred.eggersdorfer@dsm.com

Session Chairs: Maret G. Traber, Manfred Eggersdorfer

Topic: Ferroptosis: lipid peroxidation-driven programmed cell death

Background: For decades, it has been appreciated that vitamin E and selenium-dependent Phospholipid Glutathione Peroxidase (GPx4) work in concert, that deletion of either vitamin E or selenium from the diet yields rather mild symptoms, but that deletion of both results in almost immediate death. Recent advances in evaluation of non-apoptotic mechanisms of programmed cell death have shown that ferroptosis is a mechanism of programmed cell death mediated by increased lipid peroxidation that can be important in cancer prevention and treatment. In contrast, GPx4 and GSH, along with Vitamin E can prevent ferroptotic cell death. Notably, Vitamin E may function as a 12-lipoxygenase inhibitor, thereby preventing the generation of oxidized arachidonic or adrenic phosphatidyl ethanolamine, which have been identified as lipid signaling molecules for ferroptosis. Additionally, endothelium specific *Gpx4* depletion in mice showed that Vitamin E was necessary not only for endothelial function but also mouse viability. Studies in mice with a *Gpx4* deletion in hematopoietic cells showed that GPx4 is essential for preventing receptor interacting protein 3 (RIP3)-dependent necroptosis in erythroid precursor cells, a process that could be ameliorated by Vitamin E . In a zebrafish model of vertebrate embryogenesis, vitamin E deficiency depleted cellular antioxidants, NADPH, and led to dysregulation of energy metabolism. Thus, there are a number of pathways involving lipid peroxidation, GPx4 and Vitamin E that lead to programmed cell death and emphasize the necessity for further studies to elucidate the signaling pathways involved in these cell-death mechanisms.

Title: Ferroptosis, a form of regulated necrotic cell death

Speaker: Marcus Conrad, Ph.D.
Helmholtz Zentrum München - German Research Center for Environmental Health
Institute of Developmental Genetics
Ingolstädter Landstrasse 1
85764 Neuherberg
Munich, Germany,
Email: marcus.conrad@helmholtz-muenchen.de
Phone: +49 89 3187-4608
https://www.helmholtz-muenchen.de/idg/research/neuropsychiatric-diseases/redox-signaling-disease/research/index.html

Dr. Conrad Marcus is a pioneer in the field of ferroptosis, which is a form of regulated necrotic cell death controlled by glutathione peroxidase 4 (GPX4). Acyl-CoA synthetase long-chain family member 4 (ACSL4) is an essential component for ferroptosis execution. Mechanistically, ACSL4 enriched cellular membranes with long polyunsaturated ω6 fatty acids (e.g. arachidonic

acid) and increased ferroptosis. Moreover, ACSL4 expression in basal-like breast cancer cell lines predicted their sensitivity to ferroptosis.
Reference: Doll S, Proneth B, Tyurina YY, Panzilius E, Kobayashi S, Ingold I, Irmler M, Beckers J, Aichler M, Walch A, Prokisch H, Trümbach D, Mao G, Qu F, Bayir H, Füllekrug J, Scheel CH, Wurst W, Schick JA, Kagan VE, Angeli JP, Conrad M. ACSL4 dictates ferroptosis sensitivity by shaping cellular lipid composition. Nat Chem Biol. 2017 Jan;13(1):91-98. doi: 10.1038/nchembio.2239. PubMed PMID: 27842070.

Title: Oxidized arachidonic-phosphatidyl ethanolamine, key player navigating cells to ferroptosis

Speaker: Valarian Kagan, Ph.D.
Environmental and Occupational Health
University of Pittsburgh
Pittsburgh, PA 15219
E-mail: kagan@pitt.edu
Primary Phone: 412-624-9479, Secondary Phone: 412-624-9700
Fax: 412-624-9361
Web site: http://www.pitt.edu/~kagan/

Dr. Valerian E. Kagan is known for his innovated studies integrating oxidative stress, antioxidants, tissue and cell acute and chronic injury. He has founded a new field of research "Oxidative Lipidomics" and demonstrated its research power in investigations of cell death mechanisms. Most recently, he has identified key oxidized lipids that direct cells to ferroptosis.
Reference: Kagan VE, Mao G, Qu F, Angeli JP, Doll S, Croix CS, Dar HH, Liu B, Tyurin VA, Ritov VB, Kapralov AA, Amoscato AA, Jiang J, Anthonymuthu T, Mohammadyani D, Yang Q, Proneth B, Klein-Seetharaman J, Watkins S, Bahar I, Greenberger J, Mallampalli RK, Stockwell BR, Tyurina YY, Conrad M, Bayır H. Oxidized arachidonic and adrenic PEs navigate cells to ferroptosis. Nat Chem Biol. 2017 Jan;13(1):81-90. doi: 10.1038/nchembio.2238. PubMed PMID: 27842066.

Title: Ferroptosis during tumor suppression

Speaker: Wei Gu, PhD.
Professor of Pathology and Cell Biology
Institute for Cancer Genetics, Department of Pathology and Cell Biology, and Herbert Irving Comprehensive Cancer Center
College of Physicians and Surgeons, Columbia University
1130 Nicholas Avenue, New York, NY 10032, USA
phone: 212-851-5282
Email: wg8@cumc.columbia.edu
http://icg.cumc.columbia.edu/research-faculty/Wei-Gu-research

Wei Gu has identified most of the molecules and pathways that regulate p53 activity, including 1) acetylation and deacetylation of the p53 polypeptide, 2) "dynamic ubiquitination" which determines the stability and subcellular localization of p53 protein and 3) that the three canonical functions of p53 in apoptosis, cell growth arrest and senescence are dispensable functions of p53 as a tumor suppressor. He further demonstrated that p53-mediated ferroptosis is critically involved in tumor suppression, representing the first evidence that p53 can suppress tumor growth in the absence of its canonical functions.
Reference:
Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015 Apr 2;520(7545):57-62. doi: 10.1038/nature14344. PubMed PMID: 25799988; PubMed Central PMCID: PMC4455927.

Title: Ferroptosis, mechanism of cell death in vitamin E deficiency during embryogenesis?
Speaker: Maret G. Traber, Ph.D
See contact information above

Dr. Maret Traber is one of the leading experts on vitamin E with research efforts focused on the physiological properties of vitamin E, especially human vitamin E kinetics and the factors that modulate human vitamin E requirements, such as bioavailability, lipid peroxidation and metabolism. Her laboratory has been focusing on identifying lipids susceptible to damage as a result of inadequate vitamin E using untargeted lipidomics. These outcomes led to metabolomics assessments, which identified dysregulated metabolism in vitamin E deficient zebrafish embryos, pointing to the potential role of ferroptosis in embryonic development.

Melissa McDougall, Jaewoo Choi, Hye-Kyeong Kim, Gerd Bobe, J. Frederik Stevens, Enrique Cadenas, Robert Tanguay, Maret G. Traber Lethal Dysregulation of Energy Metabolism During Embryonic Vitamin E Deficiency. Free Radical Biology and Medicine
http://dx.doi.org/10.1016/j.freeradbiomed.2017.01.020