Cell Programs for Elimination of the Unnecessary: Fatal Role of Peroxidized Lipids

January 31

Thursday, 12:30 pm

Weekly Colloquium

Billings Building
Rosedale Conference Room

Speaker: Valerian E. Kagan, Ph.D., D.Sc
Professor, Department of Environmental and Occupational Health, School of Medicine,
Department of Pharmacology and Chemical Biology
Director, Center for Free Radical and Antioxidant Health
University of Pittsburgh

Speaker: Hülya Bayır, M.D.
Professor, Department of Critical Care Medicine
Department of Environmental and Occupational Health
Director of Research, Pediatric Critical Care Medicine
Associate Director, Center for Free Radical and Antioxidant Health, Pitt Public Health and
Safar Center for Resuscitation Research
University of Pittsburgh

Host: Rajiv R. Ratan, M.D., Ph.D.

For more information, please contact
Darlene White at
daw9085@med.cornell.edu

Burke Neurological Institute
Academic Affiliate of Weill Cornell Medicine
785 Mamaroneck Avenue
White Plains, NY 10605
burke.weill.cornell.edu

Abstract

Amphiphilc polyunsaturated lipids are essential for life as structural building blocks of biological membranes and as signaling molecules. Coordination of numerous metabolic reactions and pathways requires high diversification of lipids which is achieved, to a large extent, via oxygenation of polyunsaturated lipids. This fundamental role of oxygenated polyunsaturated lipids in regulation is associated with a risk of their injurious effects via aberrant reactions of hydrophobic electrophilic carbonyl compounds – aldehydes, ketones, epoxides – with essential nucleophilic sites in proteins. These secondary reactive lipid electrophiles are generated from the common hydroperoxy-precursors, the primary molecular products of lipid peroxidation reactions. Therefore, control of the hydroperoxy-lipids is operated by the key intracellular redox regulatory system – thiols and their discoordination may lead to different types of regulated cell death as exemplified by apoptosis and ferroptosis. In apoptosis, formation of a complex between an intermembrane space hemoprotein, cytochrome c (cyt c), and a mitochondrial-specific phospholipid, cardiolipin, results in the peroxidation of the latter leading to the release of cyt c into the cytosol and subsequent pro-apoptotic reactions. In ferroptosis, a newly identified iron dependent form of regulated cell death, hydroperoxy-phosphatidylethanolamines generated by 15-lipoxygenases have been identified as the proximate ferroptotic death signals in cells. The ferroptotic pathway is an evolutionarily conserved pathway employed by bacterial pathogens as a theft-ferroptotic mechanism hijacking the host phospholipids to generate HOO-AA-PE death signals in epithelial cells.

Publications

1. PEBP1 Wardens Ferroptosis by Enabling Lipoxygenase Generation of Lipid Death Signals. Wenzel SE, Tyurina YY, Zhao J, St Croix CM, Dar HH, Mao G, Tyurin VA, Anthonymuthu TS, Kapralov AA, Amoscato AA, Mikulska-Ruminska K, Shrivastava IH, Kenny EM, Yang Q, Rosenbaum JC, Sparvero LJ, Emlet DR, Wen X, Minami Y, Qu F, Watkins SC, Holman TR, VanDemark AP, Kellum JA, Bahar I, Bayır H, Kagan VE. Cell. 2017 Oct 19;171(3):628-641.
2. Pseudomonas aeruginosa utilizes host polyunsaturated phosphatidylethanolamines to trigger theft-ferroptosis in bronchial epithelium. Dar HH, Tyurina YY, Mikulska-Ruminska K, Shrivastava I, Ting HC, Tyurin VA, Krieger J, St Croix CM, Watkins S, Bayir E, Mao G, Armbruster CR, Kapralov A, Wang H, Parsek MR, Anthonymuthu TS, Ogunsola AF, Flitter BA, Freedman CJ, Gaston JR, Holman TR, Pilewski JM, Greenberger JS, Mallampalli RK, Doi Y, Lee JS, Bahar I, Bomberger JM, Bayır H, Kagan VE. J Clin Invest. 2018 Oct 1;128(10):4639-4653.
3. Empowerment of 15-lipoxygenase catalytic competence in selective oxidation of membrane ETE-PE to ferroptotic death signals, HpETE-PE. Anthonymuthu TS, Kenny EM, Shrivastava IH, Tyurina YY, Hier ZE, Ting HC, Dar H, Tyurin VA, Nesterova A, Amoscato AA, Mikulska-Ruminska K, Rosenbaum JC, Mao G, Jinming Z, Conrad M, Kellum JA, Wenzel SE, VanDemark AP, Bahar I, Kagan VE, Bayir H. J Am Chem Soc. 2018 Dec 7. doi: 10.1021/jacs.8b09913. [Epub ahead of print] PMID: 30525572

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