BIOGRAPHICAL SKETCH

NAME: ESPENSHADE, PETER JOHN

eRA COMMONS USER NAME: pespens2

POSITION TITLE: PROFESSOR OF CELL BIOLOGY AND ONCOLOGY

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	YEAR(s)	FIELD OF STUDY
Princeton University	B.A.	1986-1990	Molecular Biology
Massachusetts Institute of Technology	Ph.D.	1991-1998	Biology
UT-Southwestern Medical Center, Dallas, TX	Postdoc	1998-2002	Molecular Cell Biology

A. Personal Statement

I have 30 years of experience in studies of yeast and mammalian molecular cell biology. As a doctoral student with Chris Kaiser at MIT, I studied protein trafficking in the secretory pathway, specifically mechanisms of COPII vesicle formation at the ER (Publications 1-4). Since 1998, I have focused on the regulation of sterol regulatory element-binding protein (SREBP) by lipid and oxygen supply. SREBP is a membrane-bound transcription factor that is the central regulator of cellular fatty acid and cholesterol synthesis. As a postdoctoral fellow with Dr. Michael Brown and Dr. Joseph Goldstein at UT-Southwestern, I described the sterol-regulated mechanism of SREBP proteolytic activation in mammals (Publications 5-8).

As an independent investigator, my lab has made several high impact discoveries including that fungal SREBP is a conserved hypoxic transcription factor that utilizes a novel cleavage mechanism for activation (Publications 9-12). We discovered a novel 2-oxoglutarate-Fe(II)-dioxygenase Ofd1 that functions as an oxygen sensor to regulate the degradation and DNA binding activity of yeast SREBP (Publications 13-16). Our studies of Ofd1 described a new paradigm for oxygen sensing and control of hypoxic gene expression.

Recently, we shifted our research interests back to that of mammalian SREBP as many important questions remain unanswered. Our yeast work demonstrated that SREBP is required for adaptation to low oxygen, conditions under which lipid synthesis becomes limiting. In preliminary studies, we have demonstrated that the SREBP pathway, and more specifically the SREBP cleavage activating protein (SCAP), is required for pancreatic ductal adenocarcinoma (PDAC) tumor growth in mouse subcutaneous and orthotopic xenograft models, and most recently in a genetically engineered mouse model of pancreas cancer.

In collaboration with Dr. Tim Osborne, we demonstrated that a derivative of dipyridamole, N2,N2,N6,N6-tetrakis[2-methoxyethyl]-4,8-di[piperidin-1-yl]pyrimido[5,4-d]pyrimidine-2,6-diamine (TMDP), is the first specific inhibitor of SCAP (reference below). TMDP, which lacks dipyridamole's phosphodiesterase inhibitory activity, directly binds SCAP and prevents its ER exit, thereby blocking SREBP proteolytic activation.

Esquejo RM, Roqueta-Rivera M, Shao W, Phelan PE, Seneviratne U, Am Ende CW, Hershberger PM, Machamer CE, **Espenshade PJ**, Osborne TF. Dipyridamole inhibits lipogenic gene expression by retaining SCAP-SREBP in the endoplasmic reticulum. 2021. ***Cell Chem. Biol.*** 28:169-179.

B. Positions and Honors

Positions and Employment

1990-1991 Research Assistant, Princeton University, Department of Molecular Biology
1991-1997 Graduate Student, Lab of Chris Kaiser, Massachusetts Institute of Technology
1997-2002 Postdoctoral Fellow, Lab of Brown and Goldstein, UT-Southwestern Medical Center at Dallas
2002-2008 Assistant Professor, Department of Cell Biology, Johns Hopkins University School of Medicine
2008-2013 Associate Professor, Department of Cell Biology, Johns Hopkins University School of Medicine
2013-date Professor, Department of Cell Biology, Johns Hopkins University School of Medicine
2014-date Associate Dean for Graduate Biomedical Education
2016-date Professor, Department of Oncology, secondary appointment
2016-date Member, Sidney Kimmel Comprehensive Cancer Center (GI Cancer Program)

Other Experience

2008	INMP NIH Study Section, Ad hoc member for two meetings
2009 – 2012	INMP NIH Study Section, Permanent Member
2014	American Heart Association, Microbiology BSc 2 Study Section
2014	NIH ZRG1 CB-C Study Section
2016	NIH ZRG1 EMNR F Study Section, November 2016
2019 - 2022	NIH NIGMS Advisory Council, Member

Honors

1990	Summa cum laude, Department of Molecular Biology, Princeton University
1990	Phi Beta Kappa Honor Society, Princeton University
1992	National Science Foundation Pre-Doctoral Fellowship
1998	National Research Service Award Postdoctoral Fellowship, NIH
2001	Career Award in the Biomedical Sciences, Burroughs Wellcome Fund
2006	Investigator in Pathogenesis of Infectious Disease Award, Burroughs Wellcome Fund
2007	Dean's Fund Award, Johns Hopkins University School of Medicine
2008	Established Investigator, American Heart Association
2012	ASBMB Avanti Young Investigator Award in Lipid Research
2014	Fellow of the American Association for the Advancement of Science

C. Contributions to Science (from 65 peer-reviewed publications)

Defined SEC16 as a peripheral ER membrane protein that scaffolds COPII coat protein assembly

SEC16 was an uncharacterized gene required for ER vesicle formation in *S. cerevisiae*. As a graduate student, I performed a comprehensive characterization of *SEC16* function, demonstrating that Sec16p bound directly to COPII subunits and nucleated COPII protein assembly.

1. **Espenshade P**, Gimeno RE, Holzmacher E, Teung P, Kaiser CA. 1995. Yeast *SEC16* gene encodes a multidomain vesicle coat protein that interacts with Sec23p. ***J. Cell Biol.*** 131:311-324. PMCID: PMC2199983

2. Gimeno RE, **Espenshade P**, Kaiser CA. 1995. *SED4* encodes a yeast endoplasmic reticulum protein that binds Sec16p and participates in vesicle formation. ***J. Cell Biol.*** 131:325-338. PMCID: PMC2199979

3. *Gimeno RE, ***Espenshade P**, Kaiser CA. 1996. COPII coat subunit interactions: Sec24p and Sec23p bind to adjacent regions of Sec16p. ***Mol. Biol. Cell*** 7:1815-1823. *Co-first author. PMCID: PMC276028

4. Shaywitz DA, **Espenshade P**, Gimeno RE, Kaiser CA. 1997. COPII subunit interactions in the assembly of the vesicle coat. ***J. Biol. Chem.*** 272:25413-25416.

Described the mechanism for sterol-regulated proteolytic activation of SREBP transcription factors

The ER membrane-bound transcription factor sterol regulatory element-binding proteins (SREBP) are central transcriptional regulators of cellular lipid homeostasis. As a postdoc with Brown and Goldstein at UT-Southwestern, I determined that the Site-1 protease, which first cleaves SREBP, is localized in the Golgi and that SREBP cleavage requires ER-to-Golgi transport. I demonstrated that cholesterol exerts negative feedback regulation on SREBP by controlling its incorporation into COPII, ER transport vesicles. In addition, I showed that the SREBP cleavage activating protein bound an unknown factor in the presence of sterols, leading to the identification of INSIG proteins, key negative regulators of the SREBP pathway.

5. **Espenshade PJ**, Cheng D, Goldstein JL, Brown MS. Autocatalytic processing of Site-1 protease removes propeptide and permits cleavage of sterol regulatory element-binding proteins. 1999. ***J. Biol. Chem.*** 274:22795-227804.

6. DeBose-Boyd RA, Brown MS, Li WP, Nohturfft A, Goldstein JL, **Espenshade PJ**. 1999. Transport-dependent proteolysis of SREBP: relocation of Site-1 protease from Golgi to ER obviates the need for SREBP transport to Golgi. ***Cell*** 99:703-712.

7. Nohturfft A, Yabe D, Goldstein JL, Brown MS, **Espenshade PJ**. 2000. Regulated step in cholesterol feedback localized to budding of SCAP from ER membranes. ***Cell*** 102:315-323.

8. Yang T, **Espenshade PJ**, Wright ME, Yabe D, Gong Y, Aebersold R, Goldstein JL, Brown MS. Crucial step in cholesterol homeostasis: sterols promote binding of SCAP to INSIG-1, a membrane protein that facilitates retention of SREBPs in the ER. 2002. ***Cell*** 110:489-500.

Discovered that fungal SREBP functions as an oxygen responsive transcription factor

Prior to this work, the SREBP transcription factors were thought to function only as regulators of systemic lipid homeostasis. As an independent investigator, I asked the question: What then is this transcription factor doing in a unicellular organism? We discovered that SREBP is an oxygen-responsive transcription factor required for growth in hypoxic environments. These findings created the field of fungal SREBP research and led to our discovery that SREBP is required for virulence in the fungal pathogen *Cryptococcus neoformans*. Subsequently, others showed this to be true for *Aspergillus fumigatus* and other pathogens. Our studies of yeast SREBP activation revealed a novel mechanism for SREBP cleavage activation that requires the multi-subunit Golgi Dsc E3 ligase and the rhomboid serine protease Rbd2. In addition, these studies prompted the search for additional SREBP functions in mammals, which now include roles in the inflammatory response and autophagy.

9. Hughes AL, Todd BL, **Espenshade PJ**. 2005. SREBP pathway responds to sterols and functions as an oxygen sensor in fission yeast. ***Cell*** 120:831-842.

10. Chang YC, Bien CM, Lee H, **Espenshade PJ*,** Kwon-Chung KJ*. 2007. Sre1p, a regulator of oxygen sensing and sterol homeostasis, is required for virulence in *Cryptococcus neoformans*. ***Mol. Microbiol.*** 64:614-629. *Corresponding authors.

11. Stewart EV, Nwosu CC, Tong Z, Roguev A, Cummins TD, Kim DU, Hayles J, Park HO, Hoe KL, Powell DW, Krogan NJ, **Espenshade PJ**. 2011. Yeast SREBP cleavage activation requires the Golgi Dsc E3 ligase complex. ***Mol. Cell*** 42:160-171. PMCID: PMC3083633

12. Hwang J, Ribbens D, Raychaudhuri S, Cairns L, Gu H, Frost A, Urban S, **Espenshade PJ**. 2016. A Golgi rhomboid protease Rbd2 recruits Cdc48 to cleave yeast SREBP. ***EMBO J.*** 35:2332-2349. PMCID: PMC5090219

Discovered the 2-oxoglutarate-Fe(II)-dioxygenase Ofd1 that functions as an oxygen sensor to regulate SREBP activity in fungi

Prior to this work, known eukaryotic mechanisms for control of oxygen-regulated transcription factors included expression (Rox1 in *S. cerevisiae),* coactivator binding (hypoxia-inducible factor - HIF), degradation (HIF), and proteolytic activation (yeast SREBP). In this series of studies, we demonstrated that Ofd1 is a prolyl hydroxylase which regulates both DNA binding and degradation of activated yeast SREBP Sre1. Mathematical modeling studies showed that both mechanisms are critical for the cellular response to hypoxia. In a recent *eLife* paper, we demonstrated that Ofd1 hydroxylates the small ribosomal protein Rps23 prior to ribosome assembly and that unassembled Rps23 regulates Sre1 activity by competing for binding to Ofd1. Collectively, this work defined a new mechanism for hypoxic gene regulation.

13. Hughes BT and **Espenshade PJ**. 2008. Oxygen-regulated degradation of fission yeast SREBP by Ofd1, a prolyl hydroxylase family member. ***EMBO J.*** 27:1491-1501. PMCID: PMC2396400
14. Lee CY, Stewart EV, Hughes BT and **Espenshade PJ**. 2009. Oxygen-dependent binding of Nro1 to the prolyl hydroxylase Ofd1 regulates SREBP degradation in yeast. ***EMBO J.*** 28:135-143. PMCID: PMC2634736

15. Lee CSY, Yeh TL, Hughes BT, **Espenshade PJ**. 2011. Regulation of the Sre1 hypoxic transcription factor by oxygen-dependent control of DNA binding. ***Mol. Cell*** 44:225-234. PMCID: PMC3208185

16. Clasen, SJ, Shao W, Gu H, **Espenshade PJ**. 2017. Prolyl dihydroxylation of unassembled uS12/Rps23 regulates fungal hypoxic adaptation. ***eLife*** 6:e28563. PMCID: PMC5690285

Complete List of Published Work (NCBI MyBibliography):
http://www.ncbi.nlm.nih.gov/sites/myncbi/peter.espenshade.1/bibliography/40609512/public/?sort=date&direction=ascending

D. Research Support
Ongoing Research Support

R01 HL77588 National Heart, Lung, Blood Institute – NIH 07/01/04 – 12/31/22
Espenshade - PI
Title: Regulation of Cellular Cholesterol Homeostasis
The goal is to identify new regulators of the SREBP pathway in yeast and cultured mammalian cells.

R01 GM126088 National Institute of General Medical Sciences – NIH 08/01/18 – 04/30/22
Espenshade - PI
Title: Lipid Regulation of Hypoxia-inducible Factors
The goal of this project is to determine the mechanism by which lipid regulates HIF signaling.

Emerson Collective (Agreement No 644565) 08/19/19 – 08/18/21
Espenshade - PI
Title: Targeting the SREBP Pathway in Pancreatic Cancer
The goals of this project are (1) to test the requirement for SCAP in PDAC development, metastasis, and survival using the KPC genetically engineered mouse model of pancreatic cancer and (2) to test whether atorvastatin and dipyridamole combination therapy is a novel, targeted therapy for PDAC using the KPC mouse model.