BIOGRAPHICAL SKETCH

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NAME: Walter, Peter

eRA COMMONS USER NAME (agency login): WALTERP

POSITION TITLE: Principal Investigator

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Freie Universität, Berlin	BA	1976	Chemistry
Vanderbilt University, Nashville, TN	MS	1977	Organic Chemistry
The Rockefeller University, New York, NY	PHD	1981	Cell Biology

A. Personal Statement

A. Personal Statement Science Overview: Our laboratory seeks a molecular understanding of how cells control the quality of their proteins and organelles during homeostasis and stress. We are identifying the machinery and mechanisms that ensure proper protein synthesis, folding, and targeting, as well as the pathways that allow organelles to communicate and regulate their abundance. Additionally, we aim to understand how the rewiring of these processes leads to, or prevents, the progression of disease. Our laboratory uses a diverse array of approaches, ranging from biochemical reconstitution to genetics, to fuel our search for fundamental discoveries in cell biology.

B. Positions and Honors

Positions and Employment

1976 - 1977	Direct Exchange Fellow, Vanderbilt University, laboratory of Dr. T.M. Harris
1977 - 1981	Graduate Fellow, The Rockefeller University, laboratory of Dr. G. Blobel
1981 - 1982	Postdoctoral Fellow, The Rockefeller University, laboratory of Dr. G. Blobel
1982 - 1983	Assistant Professor, Laboratory of Cell Biology, The Rockefeller University
1983 -	Programs in Biological Sciences, Cell Biology, Biochemistry & Molecular Biology, Chemistry and Chemical Biology, Biophysics, UCSF
1983 - 1986	Assistant Professor, Dept of Biochemistry & Biophysics, UCSF
1986 - 1991	Associate Professor, Dept of Biochemistry & Biophysics, UCSF
1991 -	Professor, Dept of Biochemistry & Biophysics, UCSF
1997 -	Investigator, Howard Hughes Medical Institute
2001 - 2008	Chair, Department of Biochemistry & Biophysics, UCSF
2010 -	Distinguished Professor of Biochemistry and Biophysics, UCSF

Other Experience and Professional Memberships

1983 -	Member, American Society for Cell Biology
1998 -	Member, American Academy of Microbiology
2001 -	Member, American Academy of Arts and Sciences
2002 - 2004	Counselor, ASCB Council
2003 -	Member, National Academy of Sciences
2004 - 2007	Member, ASCB International Affairs Committee
2006 -	Member, Leopoldina Academy of Scientists
2007 - 2007	Member, ASCB Early Career Award Committee
2010 -	Member, ASCB E.B. Wilson Award Committee
2013 -	Member, DKFZ-ZMBH Alliance Scientific Advisory Board
2014 -	Member, ERC Panel Member, Cellular and Developmental Biology Grant Evaluation

2016 - ASCB President

Honors

1983 Searle Scholar Award, Kinship Foundation
1988 Passano Award, Passano Foundation
1988 Eli Lilly Award for Fundamental Research in Biological Chemistry, Eli Lilly Foundation
1989 Alfred P. Sloan Award, Alfred P. Sloan Foundation
1993 NIH MERIT Award, NIH
1996 Harvey Lecturer, Rockefeller University
1998 American Academy of Microbiology (elected Fellow), AAM
2001 American Academy of Arts & Sciences (elected Fellow), AAAS
2004 National Academy of Sciences (elected Member), NAS
2004 Virchow Award and Lecture, Universität Würzburg
2004 European Molecular Biology Organization (elected Associate Member), EMBO
2005 Wiley Prize in Biomedical Sciences (with Kazutoshi Mori), The Wiley Foundation
2006 47th Stadtler Lecturer, Baylor, Rice, and University of Texas
2006 George E. Palade Medal and Distinguished Lecture, Wayne State University
2007 50th Faculty Research Lecturer, University of California, San Francisco
2007 Opening Lecturer, 21st Symposium of the Protein Society, The Protein Society
2008 TY Shen Lecturer, MIT, Cambridge
2008 Rolf Sammet Preis, Goethe Universität Frankfurt
2009 Gairdner International Award (with Kazutoshi Mori), Gairdner Foundation
2009 E.B. Wilson Medal, American Society for Cell Biology
2009 Stein and Moore Award, The Protein Society
2011 Otto-Warburg Prize, German Society for Biochemistry and Molecular Biology
2011 Glenn Award for Research in Biological Mechanisms of Aging, Glenn Foundation
2012 Ernst Jung Prize for Medicine, The Jung Foundation
2012 Paul Ehrlich and Ludwig Darmstaedter Prize, Ehrlich Foundation
2014 Shaw Prize, Shaw Foundation
2014 Lasker Award, Lasker Foundation
2015 Vilcek Prize, Vilcek Foundation

C. Contribution to Science

1. Molecular Mechanism of Protein Targeting: Our work over the last three decades on the structure and function of the signal recognition particle (SRP) and its receptor established the universal paradigm that governs our current understanding of signal sequence recognition and protein sorting in all cells, from bacteria to multicellular eukaryotes. This work ranges from the discovery of the apparatus' components, their functional analyses in vitro and in vivo, to their biophysical and crystallographic characterization. Our research has led to an increasingly precise and detailed understanding of both the molecular mechanism and the physiological context of the protein sorting and translocation. Initially as a graduate student with Günter Blobel and later in my own lab we: • Discovered, purified, and functionally characterized the SRP from canine pancreas. • Demonstrated a direct role of SRP in signal sequence binding. Discovered "elongation arrest", which assures that polypeptide chains emerging from the ribosome are kept short and prevented from folding before engaging in translocation. • Discovered that SRP contains an RNA subunit. Walter later showed that SRP in all cells – even bacteria – contains an obligate RNA subunit. • Purified (with Reid Gilmore) the SRP receptor using SRP affinity chromatography. • Showed that eukaryotic SRP receptor is a heterodimeric ER membrane protein complex. • Determined the functional roles of individual SRP subunits, using powerful in vitro disassembly and reconstitution systems. • Determined that SRP contains a GTPase domain that is structurally related to a GTPase domain in the SRP receptor, defining together a GTPase subfamily with unique properties. Most remarkably, the GTPase domains of SRP and SRP receptor directly interact and activate each other's GTPase activities in a reciprocally symmetrical reaction. • Discovered that the SRP receptor-subunit also contains a required GTPase domain. • Determined (with Robert Stroud) crystal structures of the SRP and SRP receptor GTPase domains alone and in complex with one another. • Demonstrated that prokaryotic SRP and SRP receptor can efficiently replace their mammalian counterparts to catalyze a complete co-translational protein targeting reaction. • Proposed the "Methionine Bristle Hypothesis" to explain how SRP can bind selectively to

different signal sequences despite their structural diversity. We now know from structural analyses that the hypothesis is correct: signal sequence binding occurs in a conserved pocket lined with flexible methionine side chains that accommodates ligands of different shapes. • Discovered that SRP RNA acts catalytically to promote protein targeting: SRP and SRP receptor associate and dissociate faster in the presence of the RNA. This activity is regulated: SRP RNA functions as an unprecedented kinetic switch that governs SRP/SRP receptor interaction in response to the occupancy of the SRP with signal sequences, explaining elegantly why SRP retained an RNA subunit throughout evolution. • Established a complete kinetic framework of the central interaction between the two GTPases. • Determined the crystal structure of the SRP/SRP receptor GTPase core-complex (with Bob Stroud). Remarkably, the two GTPases, in their complex, position their bound nucleotides so that the 3' OH group of one GTP hydrogen-bonds to the amma-phosphate group of the other, and vice versa. These symmetrical interactions in the quasi-symmetric heterodimer are important for reciprocal GTPase activation. • Recorded in collaboration with Jodi Puglisi first single-molecule real-time movies of SRP engaging with actively translating ribosomes. • Discovered a role for E. coli SRP in the prokaryotic heat shock response.

a. Lim B, Miyazaki R, Neher S, Siegele DA, Ito K, Walter P, Akiyama Y, Yura T, Gross CA. Heat shock transcription factor σ32 co-opts the signal recognition particle to regulate protein homeostasis in E. coli. PLoS Biol. 2013 Dec;11(12):e1001735. PubMed PMID: 24358019; PubMed Central PMCID: PMC3866087.
b. Noriega TR, Tsai A, Elvekrog MM, Petrov A, Neher SB, Chen J, Bradshaw N, Puglisi JD, Walter P. Signal recognition particle-ribosome binding is sensitive to nascent chain length. J Biol Chem. 2014 Jul 11;289(28):19294-305. PubMed PMID: 24808175; PubMed Central PMCID: PMC4094042.
c. Elvekrog M, Walter P. Dynamics of co-translational membrane targeting. *Curr Opin Chem Biol.* 2015.

2. Regulation of Organelle Abundance: Over the last 20 years we deciphered the mechanism through which proliferation of the ER is controlled according to physiological needs of a cell. Using genetic approaches in S. cerevisiae as an entry point, we determined the mechanism of an intracellular signal transduction pathway that mediates communication between the ER lumen (where a sensor determines the need for more ER) and the nucleus (where transcription of genes encoding specific ER proteins is induced). This pathway, termed the "Unfolded Protein Response" or UPR, coordinately regulates expression of ER resident proteins and key enzymes in lipid biosynthesis. Characterization of the UPR revealed many surprising steps, including a non-conventional cytoplasmic mRNA splicing pathway and control of translation elongation by an mRNA intron. Importantly, the lessons learned from the yeast system are directly applicable to mammalian cells, and dysregulation of the UPR is an emerging contributor to human diseases, including diabetes, neurodegeneration diseases, viral infections, and cancer. In particular, we: • Discovered in 1993 (concomitant with Katzutoshi Mori) the transmembrane kinase Ire1 as the first known component of the UPR pathway. Ire1 is the signal transduction device that monitors conditions inside the ER and transmits this information across the membrane. Isolated the transcription activator Hac1 that controls transcription of UPR target genes. • Discovered that control of Hac1 synthesis occurs by regulated splicing of HAC1 mRNA. Splicing removes an intron that inhibits translation of unspliced mRNA. • Discovered that the splicing reaction occurs by an unprecedented, non-conventional mechanism that does not utilize the spliceosome involved in the processing of other mRNAs. • Discovered that Ire1 is a bifunctional enzyme that in addition to a kinase activity also exhibits endoribonuclease activity. Ire1 cleaves HAC1 mRNA specifically at both splice junctions, and thus directly carries out the first step of the splicing reaction. Remarkably, HAC1 mRNA is the only mRNA in yeast cleaved by Ire1. • Identified tRNA ligase as an additional component required for HAC1 mRNA splicing. Prior to this discovery, tRNA ligase was only known for its role in tRNA processing. • Reconstituted HAC1 mRNA splicing in vitro with purified components and characterized the mechanism of the reaction. • Discovered (with Kevan Shokat) that Ire1's kinase function can be entirely bypassed if the nucleotide binding site is occupied by cognate ligands, demonstrating that the kinase module provides a conformational module required to activate the RNase activity of the same protein. The kinase domain of Ire1 provided a new paradigm of how a kinase domain can function in signal transduction: ligand binding rather than phosphorylation provides the conformational switch that propagates the signal. • Showed that the salient feature of the unusual mechanism of UPR signaling are conserved in eukaryotic cells. Yeast HAC1 mRNA is accurately spliced in mammalian cells in response to UPR induction. The mammalian ortholog of Hac1 is the transcription factor XBP-1. • Discovered (with Jonathan Weissman) that Hac1 also controls transcription of genes encoding key enzymes in phospholipid biosynthesis. The UPR thus coordinates the biosynthesis of the ER membrane and proteins. • Showed that ER volume expansion without concomitant up-regulation of UPR target genes helps cells cope with ER stress. • Showed that the UPR controls 5% of the genes in the yeast genome, including many genes with known or predicted functions in the secretory pathway.• Identified synthetic defects in genetic screens and genome-wide e-map analyses to elucidate physiologically important connections between the UPR and secretory/membrane protein

biogenesis and quality control. • Discovered a novel, ER-specific form of autophagy (ER-phagy), which upon UPR activation selectively engulfs ER and delivers it to vacuolar degradation. • Demonstrated (with Hana El-Samad) that binding of the chaperone BiP to Ire1 in the ER lumen modulates the UPR by buffering the free pool of Ire1. • Extended (in collaboration with Shokat) the work into mammalian cells, showing that IRE1 signaling shuts off, if ER stress remains unmitigated for a prolonged time. These results suggest that IRE1is controlled by a "timer" that serves to switch the UPR from an initially cytoprotective response into apoptosis when ER stress cannot be remedied. • Discovered that activated Ire1 forms oligomeric clusters in the ER membrane. HAC1 mRNA is recruited to these clusters by a novel targeting signal encoded in its 3' UTR. • Determined (with Bob Stroud) a crystal structure of the Ire1 lumenal domain that, together with biochemical studies, revealed that Ire1 detects unfolded proteins by binding them directly. The structure showed that the Ire1 lumenal domain architecturally resembles the peptide-binding domain of major histocompatibility complexes. The structure also suggested that the lumenal domain forms oligomers upon activation. Both conjectures were supported by functional data. • Determined (with Bob Stroud) crystal structures of active, oligomeric Ire1 kinase/RNase domains. The structure and the accompanying kinetic characterization can nicely explain why oligomeric assemblies of more than four Ire1p subunits are required to activate the RNase. • Discovered that many kinase inhibitors including some FDA-approved drugs, function—paradoxically—as activators for Ire1 RNase. The crystal structure shows that these drugs bind to the ATP binding site in the kinase domain where they act as allosteric activators that can bypass the need for the phosphoryl-transfer reaction that is normally carried out by Ire1 and other protein kinases. • Developed with Kevan Shokat small molecule inhibitors and activators of human IRE1 and PERK • Determined that the UPR in S. pombe utilizes a completely different way of executing corrective actions that utilize a mechanism of Ire1-dependent mRNA decay to reduce the load of proteins entering the ER lumen. • Discovered a small, drug-like molecule, ISRIB, that renders cells insensitive to eIF2 phosphorylation by PERK and other eIF2 kinases. ISRIB enhances cognitive memory in rodents by releasing an intrinsic brake on long-term memory formation. The drug acts by activating eIF2's guanine nucleotide exchange factor, eIF2B, by stabilizing it as a dimer. • Discovered with Avi Ashkenazi that the UPR induces apoptosis via enhanced expression and intracellular activation of the death receptor DR5.

a. Walter P, Ron D. The unfolded protein response: from stress pathway to homeostatic regulation. Science. 2011 Nov 25;334(6059):1081-6. PubMed PMID: 22116877. Sidrauski C, Acosta-Alvear D,

b. Khoutorsky A, Vedantham P, Hearn BR, Li H, Gamache K, Gallagher CM, Ang KK, Wilson C, Okreglak V, Ashkenazi A, Hann B, Nader K, Arkin MR, Renslo AR, Sonenberg N, Walter P. Pharmacological brake-release of mRNA translation enhances cognitive memory. Elife. 2013 May 28;2:e00498. PubMed PMID: 23741617; PubMed Central PMCID: PMC3667625.

c. Sidrauski C, Tsai JC, Kampmann M, Hearn BR, Vedantham P, Jaishankar P, Sokabe M, Mendez AS, Newton BW, Tang EL, Verschueren E, Johnson JR, Krogan NJ, Fraser CS, Weissman JS, Renslo AR, Walter P. Pharmacological dimerization and activation of the exchange factor eIF2B antagonizes the integrated stress response. Elife. 2015. 4:e07314. PubMed PMID: 25875391; PubMed Central PMCID: PMC4426669.

d. Mendez AS, Alfaro J, Morales-Soto MA, Dar AC, McCullagh E, Gotthardt K, Li H, Acosta-Alvear D, Sidrauski C, Korennykh AV, Bernales S, Shokat KM, Walter P. Endoplasmic reticulum stress-independent activation of unfolded protein response kinases by a small molecule ATP-mimic. Elife. 2015 May 19;4 PubMed PMID: 25986605; PubMed Central PMCID: PMC4436593.

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