BIOGRAPHICAL SKETCH

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NAME: Lori L. Wallrath

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POSITION TITLE: Professor

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Michigan State University	B.S.	05/1986	Microbiology
Michigan State University	Ph.D.	03/1991	Genetics
Washington University, St. Louis	Postdoc	11/1994	Chromatin Structure/ Gene Expression

A. Personal Statement

Research in my laboratory is focused on molecular mechanisms of nuclear envelope related diseases. Mutations in the human *LMNA* gene cause a collection of diseases called laminopathies that includes rare types of muscular dystrophy. The *LMNA* gene encodes lamins, intermediate filaments that line the nuclear envelope. Lamins provide structural support for the nucleus, regulate gene expression, and participate in many nuclear processes. To understand the molecular pathology of laminopathies, my laboratory has developed Drosophila models of lamin-associated muscular dystrophy. Using these models, we have identified novel disease mechanisms that were then observed in human muscle biopsy tissue, demonstrating clinical relevance. For example, we discovered that specific mutant lamins cause cytoplasmic aggregation of nuclear pore proteins and activation of the Nrf2/Keap1 redox pathway. Given the similar defects in the fly and human muscles, we are using the fly models to take a genetic and pharmacological approach to identify conditions that suppress the muscle defects. The long-term goal is to identify potential therapies for these muscular dystrophies.

My interest in the nuclear envelope grew from years of research on heterochromatin, nuclear organization, and gene expression. I was a PhD student in the laboratory of Thomas B. Friedman, PhD (now at NIH) where I studied the evolution of gene expression among different Drosophila species. As a postdoctoral fellow in the laboratory of Sarah C.R. Elgin, PhD (Washington University in St. Louis), I studied chromatin structure and gene expression with emphasis on heterochromatin. I demonstrated that a classic phenomenon called Position Effect Variegation (PEV) was caused by association of Heterochromatin Protein 1a (HP1a) and an altered nucleosome organization. The juxtaposition of heterochromatin to the nuclear lamina sparked my interest in the nuclear envelope and its relation to human disease.

- **Wallrath, L.L.** and Elgin, S.C.R. (1995) Position effect variegation in *Drosophila* is associated with an altered chromatin structure. *Genes Dev*. 9:1263–1277. PMID: 7758950.
- Dialynas, G., Shrestha, O.K. Ponce, J.M., Zwerger, M., Thiemann, D.A., Young, G.H., Moore, S.A., Yu, L., Lammerding, J. and **Wallrath, L.L.** (2015). Myopathic lamin mutations cause reductive stress and activate the Nrf2/Keap-1 pathway. *PLoS Genet.* 11:e1005231.
- Bhide, S., Trujillo, A.S., O'Connor, M.T., Young, G.H., Cryderman, D.E., Chandran, S., Nikravesh, M., **Wallath, L.L.** and Melkani, G.C. (2018). Increasing autophagy and blocking Nrf2 suppress laminopathy-induced age-dependent cardiac dysfunction and shortened lifespan. *Aging Cell*: e12747.
- Earle, A.J., Kirby, T.J., Fedorchak, G.R., Isermann, P., Patel, J., Irubanti, S., Moore, S.A., Bonne, G. **Wallrath, L.L.** and Lammerding, J. (2020) Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells. *J. Nat. Mater.* 19:464-473 doi: 10.1038/s41563-019-0563-5.

B. Positions and Honors

Positions of Employment

1994–1996	Research Assistant Professor, Department of Biology, Washington University
1997–2003	Assistant Professor, Department of Biochemistry, University of Iowa
2003–2009	Associate Professor, Department of Biochemistry, University of Iowa
2009–Present	Professor, Department of Biochemistry, University of Iowa
2010–2020	Vice Chair, Department of Biochemistry, University of Iowa

Honors and Awards

1990–1991	College of Natural Science Fellowship, Michigan State University
1991–1994	National Institutes of Health Postdoctoral Research Fellowship
1995	*Genes & Dev.* paper selected as a "Milestone in Gene Expression" by *Nature*
1997	College of Medicine Bioscience Initiative Award, University of Iowa
1998–2000	Basil O' Connor March of Dimes Award
1998	Midwest Drosophila Research Conference, Co-organizer
2000	41st Annual Drosophila Research Conference, Co-organizer
2001	European Drosophila Conference, mini-symposium organizer
2001–2004	American Cancer Society, General Mechanisms of Cancer Study Section, permanent member
2005	Genetics paper highlighted by "Faculty of 1000"
2006–2010	NIH Molecular Genetics C Study Section, permanent member
2008	Guest Editor, journal *Mutation Research: Fundamental Mechanisms of Mutagenesis,* Special Issue on "Epigenetics of development and human disease"
2009	Midwest Breast Cancer Research Symposium, Iowa City, Iowa, Co-organizer
2009-Present	*Nucleus*, Editorial Board
2010	Chromatin and Chromosomes Mini-symposium, ASCB Annual Meeting, Philadelphia, Pennsylvania, Co-organizer
2011	Collegiate Teaching Award, University of Iowa
2011	Instructional Improvement Award: Perspectives on Science Writing, University of Iowa
2014	Midwest Chromatin and Epigenetics Meeting, Madison, Wisconsin, Co-organizer
2015	Mary Murphy Endowed Lecture, Clarke University, Dubuque, Iowa
2018	Summer Research Opportunities Program (SROP) for underrepresented minorities, Mentoring Award, honorable mention, Graduate College, University of Iowa
2019	SROP Mentoring Award, Graduate College, University of Iowa
2019	Summer Research Fellowship Outstanding Mentor in Basic Science Research, Carver College of Medicine
2020	ASCB Cell Bio virtual, Special Interest Group, Nuclear Envelope and Nuclear Pores, Co-Organizer

C. Contributions to Science

1. Determined molecular mechanisms of gene silencing by heterochromatin

As a postdoctoral fellow, I performed experiments to determine mechanisms of gene silencing by heterochromatin. I designed a clever genetic screen to recover transposon insertions in heterochromatin. These transgenic stocks were used to dissect the molecular basis of gene silencing by heterochromatin. I was the first to show that gene silencing by heterochromatin was caused by an altered chromatin structure that included regularly spaced nucleosomes. These stocks have been a valuable resource for the Drosophila research community and are now integrated into the Bloomington Stock Center, Bloomington Indiana.

My studies on heterochromatin continued into my independent career. My laboratory was the first to show that Heterochromatin Protein 1 (HP1a) was sufficient to nucleate the formation of heterochromatin at ectopic sites throughout the genome. My collaborator Michael Shogren-Knaak, PhD (Iowa State University) and I were the first to demonstrate that human HP1alpha bridged nucleosomes on the same and different DNA strands, resulting in chromatin compaction.

- **Wallrath, L.L**. and Elgin, S.C.R. (1995) Position effect variegation in *Drosophila* is associated with an altered chromatin structure. *Genes Dev*. 9:1263–1277. PMID: 7758950.
- Cryderman, D.E., Morris E.J., Biessmann, H., Elgin, S.C.R. and **Wallrath, L.L.** (1999) Silencing at *Drosophila* telomeres: nuclear organization and chromatin structure play critical roles. *EMBO J*. 18: 3724-3735. doiL 10.1007/s004120050144 PMID: 10393187. PMCID:PMC1171449.
- Danzer, J. and **Wallrath, L.L**. (2004) Mechanisms of HP1-mediated gene silencing in Drosophila. *Development* 131: 3571–3580. doi: 10.1242/dev.01223.
- Azzaz, A.M., Vitalini, M.W., Thomas, A.S., Price, J., Blacketer, M.J., Cruderman, D.E., Zirbel, .LN., Woodcock, C.L., Elcock, A.H., **Wallrath, L.L.** and Shogren-Knaak, M.A. (2014). HP1Hsa promotes nucleosome associations that drive chromatin condensation. *J. Biol. Chem.* 289:6850–6861.

2. Demonstrated that HP1alpha regulates breast cancer invasion/metastasis

Through a collaboration with Mary Hendrix, PhD (former Head of Anatomy and Cell Biology, University of Iowa), we determined that HP1alpha levels regulate *in vitro* invasion of breast cancer cells. Through a collaboration with Chris Stipp, PhD (Biology, Univ. of Iowa), we showed that HP1alpha regulates an epithelial to mesenchymal transition in a mouse model of triple negative breast cancer. In this context, over-expression of HP1alpha, a predictor of poor patient outcome, causes DNA methylation at the promoter of the gene encoding E-cadherin, a molecule required for intercellular adhesion. Thus, HP1alpha appears to regulate initial steps in the metastatic cascade.

- Kirschmann, D.A., Lininger, R.A., Gardner, L.M.G., Seftor, E.A., Odero, V.A., Ainsztein, A.M., Earnshaw, W.C., **Wallrath, L.L**. and Hendrix, M.J.C. (2000). Down-regulation of $HP1^{Hsa}$ expression is associated with the metastatic phenotype in breast cancer. *Cancer Res*. 60:3359–3363.
- Norwood, L.E., Moss, T.J., Margaryan, N.V., Cook, S., Wright, L., Seftor, E.A., Hendrix, M.J.C., Kirschmann, D.A. and **Wallrath L.L.** (2006) A requirement for dimerization of HP1-Hsalpha suppression of breast cancer invasion. *J. Biol. Chem*. 281: 18668–18676. doi:10.1074/jbc.M512454200.
- Moss, T.J. and **Wallrath, L.L.** (2007) Connections between epigenetic gene silencing and disease. *Mutation Research* 628: 163–174.
- Fagan, R.L., Cryderman, D.E., Kopelovich, L., **Wallrath, L.L**. and Brenner, C. (2013) Laccaic Acid A is a direct, DNA-competitive inhibitor of DNA methyltransferase 1. *J. Biol. Chem*. 288: 23858–23867.

3. Developed Drosophila models of skeletal muscle and cardiac laminopathies that identified novel mechanisms of pathology

Studies of heterochromatin directed my interests to the nuclear envelope, where I have focused on lamins, intermediate filaments that form a meshwork along the inner nuclear membrane. Mutations in the human *LMNA* gene encoding A-type lamins cause a collection of diseases known as laminopathies. My laboratory has focused on skeletal muscle laminopathies, which are often accompanied by cardiac defects. To understand how mutant lamins cause muscle pathology, we developed Drosophila models of laminopathies. We showed that muscle-specific expression of patient-based mutant lamins activated the Nrf2/Keap-1 redox signaling pathway, leading to reductive stress. These findings were conserved in humans; patient muscle biopsy tissue showed mislocalization of nuclear envelope proteins and activation of the Nrf2/Keap1 pathway. Using muscle-specific RNAi and over-expression, we showed that the muscular dystrophy phenotypes were suppressed by lowering the reductive stress and increasing autophagy. We extended these studies to cardiac tissue through the development of Drosophila cardiac laminopathies models with Rolf Bodmer (Sanford Burnham Medical Research Institute) and Girish Melkani (San Diego State U). Collectively, our findings suggest novel targets for therapy, and have also developed induced pluripotent stem (iPS) cells from patient fibroblasts for drug screens in collaboration with Ivor Benjamin, MD (Medical College of Wisconsin).

In 2018, I was on sabbatical in the laboratory of my collaborator (Jan Lammerding, PhD, Cornell University), where we developed a novel micropipette harpooning assay and applied it to the Drosophila muscle laminopathy models. We learned that specific mutant lamins physically uncouple the cytoskeleton from the nucleoskeleton. We discovered that specific mutant lamins caused chromatin protrusions and transient nuclear ruptures that results in DNA damage, leading to muscle weakness and wasting.

- Dialynas, G., Shrestha, O.K., Ponce, J.M., Zwerger, M., Thiemann, D.A., Young, G.H., Moore, S.A., Yu, L., Lammerding, J. and **Wallrath, L.L.** (2015). Myopathic lamin mutations cause reductive stress and activate the Nrf2/Keap-1 pathway. *PLoS Genet.* 11:e1005231.
- Bhide, S., Trujillo, A.S., O'Connor, M.T., Young, G.H., Cryderman, D.E., Chandran, S., Nikravesh, M., **Wallath, L.L.** and Melkani, G.C. (2018). Increasing autophagy and blocking Nrf2 suppress laminopathy-induced age-dependent cardiac dysfunction and shortened lifespan. *Aging Cell.* e12747.
- Chandran, S., Suggs, J.A., Wang, B.J., Han, A., Bhide, S., Cryderman, D.E, Moore, S.A., Bernstein, S.I., **Wallrath, L.L**. and G.C. Melkani (2019). Suppression of myopathic lamin mutations by muscle-specific activation of AMPK and modulation of downstream signaling. *Hum. Mol. Genet*. 28:351–371. doi: 10.1093/hmg/ddy332.
- Earle, A.J., Kirby, T.J., Fedorchak, G.R., Isermann, P., Patel, J., Irubanti, S., Moore, S.A., Bonne, G. **Wallrath, L.L.** and Lammerding, J. (2020) Mutant lamins cause nuclear envelope rupture and DNA damage in skeletal muscle cells. *J. Nat. Mater.* 19:464-473 doi: 10.1038/s41563-019-0563-5.

List of published works can be found at:
https://www.ncbi.nlm.nih.gov/sites/myncbi/lori.wallrath.1/bibliography/45987722/public/?sort=date&direction=ascending.

D. Research Support

Ongoing

NIH R21 RAR075193A (Wallrath, PI; Darbro, collaborator) 3/01/2020-2/28/2022
Title: Smad signaling in skeletal muscle laminopathies
Goal: To determine the role of SMAD signaling in *LMNA* muscular dystrophy.
No overlap with proposed studies.

University of Iowa Foundation Award: Family Gift (Wallrath and Drack, Co-PIs) 10/01/2020-9/30/21
Title: Functional tests of a variant pre-mRNA splicing factor in eye disease
Goal: To test a variant of unknown significance in *SNRNP200* for loss of function in Drosophila.
No overlap with proposed studies. This is a small award to generate a single fly model for functional tests of a novel variant of unknown significance in *SNRNP2*00.

Undiagnosed Disease Network (Wallrath, PI) 07/01/2019–06/31/20
Title: The role of TMEM43 in skeletal muscle (no cost extension until 06/31/21)
Goal: To determine if specific mutations in *TMEM43* cause muscle defects using Drosophila.

Recently completed (past 3 years)

Muscular Dystrophy Association 44728 (Wallrath, PI) 02/01/2017–01/31/2020
Title: Suppression of lamin-induced muscle defects

Burroughs Wellcome Fund Collaborative Research Travel Grant (Wallrath, PI) 7/1/2017–6/30/2018
Title: Using microfluidic chips for *in vivo* analysis of subcellular defects associated with nuclear muscular dystrophy
Sabbatical Research, Cornell University, Ithaca, NY, laboratory of Jan Lammerding, PhD

NIH R21 AG049454 (Melkani, PI; Wallrath and Bodmer, collaborators) 8/15/2015–4/30/2017
Title: Genetic analysis and regulation of lamin-induced cardiac defects