BIOGRAPHICAL SKETCH

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NAME: Wühr, Martin

eRA COMMONS USER NAME (credential, e.g., agency login): martinwuehr

POSITION TITLE: Visiting Scholar

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)	END DATE MM/YYYY	FIELD OF STUDY
Technical University of Munich, Munich	BS	05/2004	Biochemistry
Harvard University, Systems Biology, Cambridge, MA	PHD	05/2010	Systems Biology
Harvard Medical School, Boston, MA	Postdoctoral Fellow	06/2016	Proteomics

A. Personal Statement

I received my undergraduate training in Biochemistry from the Technical University of Munich. During my graduate studies in Systems Biology at Harvard, I investigated how the cell division machinery scales with rapidly changing cell size in early development. As a postdoc I wanted to combine the molecular resolution of a Biochemist with the Systems-Biology point of view I learned to appreciate during my Ph.D. Mass spectrometry-based proteomics promises this combination. To this end, I worked jointly between the Kirschner and Gygi laboratories. There I developed novel quantitative proteomics techniques which drastically increased measurement accuracy and sensitivity. One successful application of these techniques was to dissect nucleocytoplasmic segregation in the oocyte. We measure both partitioning and protein-complex size on a proteome-wide scale. Based on this data, we found a simple rule, by which nearly all proteins smaller than 100 kDa are equidistributed between nucleus and cytoplasm while proteins that are entirely in the nucleus or the cytoplasm are part of larger complexes. Many researchers have previously looked at individual protein complexes and their subcellular localization, but only the global perspective allowed us to make this discovery. In 2016 I opened my laboratory in the Lewis-Sigler Institute for Integrative Genomics at Princeton University. The work in my group falls broadly into two categories. First, we aim to develop quantitative proteomics technology to improve sensitivity and measurement quality. Second, we use proteomics to obtain a systems-level understanding of cellular organization. Our long-term goal is to parameterize the central dogma of molecular biology on a genome-wide scale and elucidate how differences in the genome phenotypes. Our research integrates skills and methods from various disciplines: The graduate students I mentor have backgrounds in Chemistry, Molecular Biology, and Chemical and Biological Engineering. I am committed to promoting an inclusive, safe and supportive research environment and ensure the safety of all individuals while performing research. My key goal is to provide training to my students that enables them to design experiments in a rigorous and unbiased manner as well as the analysis and reporting of results. I will ensure that students in my laboratory graduate in a timely fashion and obtain the skills, credentials, and experiences that prepare them for a transition into careers in the biomedical research workforce.

Ongoing and recently completed projects that I would like to highlight include:

NIH NIGMS R35GM128813 Wuhr (PI) 07/01/2018-06/30/2023 Development of New Proteomics Technology and its Application to Study Cellular Organization

DOE DE-FOA-000165 Zhao (PI) Wuher Role: Co-PI 09/2017 – 08/2022 Genome-scale Design and Engineering of Non-model Yeast Organisms for Production of Biofuels and Bioproducts

DOE DE-FOA-0001540 DeLucia (PI) Wuhr role: Co-PI 12/01/17 – 11/30/22 Center for Advanced

Bioenergy and Bioproducts Innovation

The Eric and Wendy Schmidt Transformative Technology Fund E2359 Wuhr (Co-PI) 07/01/2020 – 06/30/2022 A Novel Proteomics Platform for Interrogating Emergent Cytoplasmic Structure

Princeton Catalysis Initiative Fund MacMillan (PI) Wuhr Role: Co-Investigator 07/01/2020-06/30/2022 New technology for high-resolution chromatin interaction mapping to decipher epigenetic regulations in health and disease

Princeton Catalysis Initiative Fund MacMillan (PI) Wuhr Role: Co-Investigator 07/01/2019-06/30/2022 Determining the Functions of Uncharacterized Genes Required for Photosynthesis through Application of Novel High-Throughput Proteomics Technology

Citations:

1. Keber,Felix,, Nguyen,Thao,, Brangwynne,Cliff,P, Wühr,Martin,. Evidence for widespread cytoplasmic structuring into mesoscopic condensates. bioRxiv [Preprint]. 2021 December 18. Available from: https://www.biorxiv.org/content/10.1101/2021.12.17.473234v1
2. Nguyen T, Costa E, Deibert T, Reyes J, Keber F, Stadlmeier M, Gupta M, Kumar C, Amodeo A, Gatlin J, Wühr M. Differential nuclear import sets the timing of protein access to the embryonic genome. bioRxiv. 2021 October 18; :2021.10.18.464816. Available from: http://biorxiv.org/content/early/2021/10/18/2021.10.18.464816.abstract DOI: 10.1101/2021.10.18.464816
3. Johnson A, Stadlmeier M, Wühr M. TMTpro Complementary Ion Quantification Increases Plexing and Sensitivity for Accurate Multiplexed Proteomics at the MS2 Level. J Proteome Res. 2021 Jun 4;20(6):3043-3052. PubMed Central PMCID: PMC8330405.
4. Peshkin L, Gupta M, Ryazanova L, Wühr M. Bayesian Confidence Intervals for Multiplexed Proteomics Integrate Ion-statistics with Peptide Quantification Concordance. Mol Cell Proteomics. 2019 Oct;18(10):2108-2120. PubMed Central PMCID: PMC6773559.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021 -	Visiting Scholar, Simons Foundation - Flatiron Institute, New York, NY
2016 -	Assistant Professor, Princeton University, Lewis-Sigler Institute for Integrative Genomics, Princeton, NJ
2011 - 2016	Postdoctoral Fellow, Harvard Medical School

Honors

2021 - 2021	Robert J. Cotter New Investigator Award, Human Proteome Organization
2014 - 2016	Scholarship, Charles King Trust
2005 - 2010	Scholarship, “e-fellows”
2004 - 2005	Scholarship, Friedrich Ebert Foundation

C. Contribution to Science

1. Quantitative analysis of cell division machinery in early embryos.

   During my PhD in Tim Mitchison’s lab I investigated how cell-division machinery changes during cleavage stages of frog and fish embryos. In these embryos, cell size changes by orders of magnitude. During embryogenesis, the underlying cell division machinery must be able to change from being able to find the center and longest axis in a millimeter-sized cell to accomplishing this same process in a 10 µm large cell. We showed that, in smaller cells, spindle length scales with cell

length, but in very large cells spindle length reaches an upper limit and is de-coupled from cell size. The localization and orientation of these small spindles, compared to cell size, are determined by location and orientation of sister centrosomes set by the anaphase microtubules asters of the previous cycle. Furthermore, during my PhD training, I disproved the model that dynein pulls on the cell cortex to orient the asters. I demonstrated that, instead, dynein-dependent pulling forces that center and orient the asters act before astral microtubules contact the cortex they are moving towards. I developed a model in which dynein pulling on bulk cytoplasm, operating in conjunction with microtubule-length limiting mechanisms, centers nascent spindles, and orients them along the long axis of the cell. This is the first model that fully explains cleavage plane geometry in early vertebrate embryos. Recent work suggests that it applies more generally and can also explain cleavage plane orientation in many invertebrates.

a. Wühr M, Obholzer ND, Megason SG, Detrich HW 3rd, Mitchison TJ. Live imaging of the cytoskeleton in early cleavage-stage zebrafish embryos. Methods Cell Biol. 2011;101:1-18. PubMed Central PMCID: PMC6551615.
b. Wühr M, Tan ES, Parker SK, Detrich HW 3rd, Mitchison TJ. A model for cleavage plane determination in early amphibian and fish embryos. Curr Biol. 2010 Nov 23;20(22):2040-5. PubMed Central PMCID: PMC3031131.
c. Wühr M, Dumont S, Groen AC, Needleman DJ, Mitchison TJ. How does a millimeter-sized cell find its center?. Cell Cycle. 2009 Apr 15;8(8):1115-21. PubMed Central PMCID: PMC2880816.
d. Wühr M, Chen Y, Dumont S, Groen AC, Needleman DJ, Salic A, Mitchison TJ. Evidence for an upper limit to mitotic spindle length. Curr Biol. 2008 Aug 26;18(16):1256-61. PubMed Central PMCID: PMC2561182.

2. Development of technology for quantitative multiplexed proteomics.

Quantification of proteins on a genome-wide scale is important to study cells in health and disease. However, proteomics capabilities are still lagging other omics approaches like RNA-seq. A recent major advancement was the invention of multiplexed proteomics that allows the quantification of thousands of proteins among multiple conditions in a single experiment. In its standard implementation a major inherent artifact called interference distorts nearly all measurements. I invented the complement reporter-ion quantification strategy that enables interference-free multiplexed proteomics, which generates data with superb measurement precision, accuracy and sensitivity. As a major benefit, this method does not require higher order scans (MS3) and is therefore compatible with most proteomics mass spectrometers. Using these methods, we routinely measure ~9k proteins among multiple conditions with median coefficience of variation of ~5%. Additionally, we have made significant progress on developing statistical tools, which integrate ion-statistics with peptide quantification concordance, that help us obtain biological meaning from quantitative proteomics data.

a. Johnson A, Stadlmeier M, Wühr M. TMTpro Complementary Ion Quantification Increases Plexing and Sensitivity for Accurate Multiplexed Proteomics at the MS2 Level. J Proteome Res. 2021 Jun 4;20(6):3043-3052. PubMed Central PMCID: PMC8330405.
b. Peshkin L, Gupta M, Ryazanova L, Wühr M. Bayesian Confidence Intervals for Multiplexed Proteomics Integrate Ion-statistics with Peptide Quantification Concordance. Mol Cell Proteomics. 2019 Oct;18(10):2108-2120. PubMed Central PMCID: PMC6773559.
c. Pappireddi N, Martin L, Wühr M. A Review on Quantitative Multiplexed Proteomics. Chembiochem. 2019 May 15;20(10):1210-1224. PubMed Central PMCID: PMC6520187.
d. Sonnett M, Yeung E, Wühr M. Accurate, Sensitive, and Precise Multiplexed Proteomics Using the Complement Reporter Ion Cluster. Anal Chem. 2018 Apr 17;90(8):5032-5039. PubMed Central PMCID: PMC6220677.

3. Analysis of proteomes in early embryonic development.

   We have used multiplexed proteomics to study protein-dynamics, phospho-dynamics, and protein-subcellular localization in early embryonic development. We devised a model that, based on maternal dowry and observed mRNA changes, predicts protein dynamics. Using the reliable nuclear isolation of the large Xenopus oocyte we were able to quantify the relative nuclear localization of~9,000 proteins with multiplexed proteomics. We found that the protein distribution was trimodal, with most proteins localizing exclusively to either the nucleus or the cytoplasm, and a third smaller subset equally distributed. We found that the maintenance of different nucleocytoplasmic localization is dominated by complex assembly and passive retention rather than by continuous active nuclear transport. When we measured protein and phospho-protein dynamics after fertilization with quantitative proteomics, we found that protein degradation is limited to very few low-abundance proteins. However, this degradation promotes extensive dephosphorylation that occurs over a wide range of abundances during meiotic exit. We also show that eggs release a large amount of protein into the medium just after fertilization, which is likely related to the slow block of polyspermy.

   a. Nguyen T, Costa E, Deibert T, Reyes J, Keber F, Stadlmeier M, Gupta M, Kumar C, Amodeo A, Gatlin J, Wühr M. Differential nuclear import sets the timing of protein access to the embryonic genome. bioRxiv. 2021 October 18; :2021.10.18.464816. Available from: http://biorxiv.org/content/early/2021/10/18/2021.10.18.464816.abstract DOI: 10.1101/2021.10.18.464816
   b. Yeung E, McFann S, Marsh L, Dufresne E, Filippi S, Harrington HA, Shvartsman SY, Wühr M. Inference of Multisite Phosphorylation Rate Constants and Their Modulation by Pathogenic Mutations. Curr Biol. 2020 Mar 9;30(5):877-882.e6. PubMed Central PMCID: PMC7085240.
   c. Gupta M, Sonnett M, Ryazanova L, Presler M, Wühr M. Quantitative Proteomics of Xenopus Embryos I, Sample Preparation. Methods Mol Biol. 2018;1865:175-194. PubMed Central PMCID: PMC6564683.
   d. Peshkin L, Wühr M, Pearl E, Haas W, Freeman RM Jr, Gerhart JC, Klein AM, Horb M, Gygi SP, Kirschner MW. On the Relationship of Protein and mRNA Dynamics in Vertebrate Embryonic Development. Dev Cell. 2015 Nov 9;35(3):383-94. PubMed Central PMCID: PMC4776761.

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/martin.wuehr.1/bibliography/public/