BIOGRAPHICAL SKETCH

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NAME: Chen, Elizabeth H.

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POSITION TITLE: Professor of Molecular Biology and Cell Biology

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
Peking University	B.S.	1986-1990	Biochemistry
University of California at Los Angeles	M.S.	1990-1992	Biochemistry
Stanford University	Ph.D.	1992-1998	Developmental Biology
University of Texas Southwestern Medical Center	Postdoc	1998-2004	Molecular Biology

A. Personal Statement

My laboratory studies mechanisms underlying myoblast fusion, an indispensable process in skeletal muscle development and regeneration. We use a multifaceted approach including genetics, molecular biology, biochemistry, biophysics, live imaging, super-resolution microscopy and electron microscopy to dissect the mechanism of myoblast fusion. We have shown that myoblast fusion is an asymmetric process in which one cell invades its fusion partner using actin-propelled membrane protrusions to promote fusion pore formation. Building on insights we learned from myoblast fusion *in vivo*, we have reconstituted high-efficiency cell-cell fusion in an otherwise non-fusogenic, non-muscle cell line and uncovered a novel function for invasive membrane protrusions in fusogen engagement. Furthermore, we have discovered dynamic mechanosensory responses to the invasive forces in the receiving fusion partner and demonstrated that mechanical tension is a driving force for myoblast fusion. Our work to date has established a biophysical framework for understanding cell-cell fusion – the interplay between the pushing forces and the resisting forces from the two fusion partners at the fusogenic synapse brings the apposing cell membranes into close proximity to facilitate fusogen engagement and membrane fusion. This new conceptual framework has fundamentally changed our understanding of cell fusion and has become a widely accepted paradigm in the field.

1. Shilagardi, K., Li, S., Luo, F., Marikar, F, Duan R., Jin, P., Kim, J.H., Murnen, K., and **Chen, E.H.** (2013) Actin-propelled invasive membrane protrusions promote fusogenic protein engagement during cell-cell fusion. ***Science*** 340, 359-63. PMCID: PMC3631436
2. Kim, J.H., Ren, Y., Ng, W.P., Li, S., Son, S., Kee, Y., Zhang, S., Zhang, G., Fletcher, D.A., Robinson, D.N., and **Chen, E.H.** (2015) Mechanical tension drives cell membrane fusion. ***Dev Cell*** 32:561-73. PMCID: PMC4357538
3. Duan, R., Kim, J.H., Shilagardi, K., Schiffhauer, E., Lee, D., Son, S., Li, S., Thomas, C., Luo, T., Fletcher, D.A., Robinson, D.N., and **Chen, E.H.** (2018) Spectrin is a mechanoresponsive protein shaping fusogenic synapse architecture during myoblast fusion. ***Nat Cell Biol*** 20, 688-698. PMCID: PMC6397639.
4. Zhang, R., Lee, D.M., Jimah, J.R., Gerassimov, N., Yang, C., Kim, S., Luvsanjav, D., Winkelman, J., Mettlen, M., Abrams, M.E., Kalia, R., Keene, P., Pandey, P., Ravaux, B., Kim, J.H., Ditlev, J.A., Zhang, G., Rosen, M.K., Frost, A., Alto, N.M., Gardel, M., Schmid, S.L., Svikina, T., Hinshaw, J.E., and **Chen, E.H.** (2020) Dynamin regulates the dynamics and mechanical strength of the actin cytoskeleton as a multifilament actin-bundling protein. ***Nat Cell Biol*** 22, 674-688. PMCID: pending.

B. Positions and Honors

Positions and Employment

2004-2011	Assistant Professor of Molecular Biology and Genetics, Johns Hopkins University School of Medicine
2011-2016	Associate Professor of Molecular Biology and Genetics (primary appointment) and Cell Biology (secondary appointment), Johns Hopkins University School of Medicine
2012-2016	Center for Cell Dynamics, Johns Hopkins University School of Medicine
2016	Professor of Molecular Biology and Genetics (primary appointment) and Cell Biology (secondary appointment), Johns Hopkins University School of Medicine
2016-present	Professor of Molecular Biology (primary appointment) and Cell biology (secondary appointment), University of Texas Southwestern Medical Center
2016-present	Hamon Center for Regenerative Science and Medicine, University of Texas Southwestern Medical Center

Other Experience and Professional Memberships

2008	Editor, Cell Fusion. In the Methods in Molecular Biology Series. The Humana Press Inc., New Jersey, USA.
2009	Platform Session Chair (Cell Biology & Signal Transduction), 50th Annual Drosophila Research Conference
2009	Session Chair, Gordon Research Conference on Cell-Cell Fusion
2013	Scientific Committee, EMBO Workshop on Cell-Cell Fusion
2013-present	French AFM-Telethon grant review
2013-present	US-Israel Binational Science Foundation grant review
2013	Review Panel, Combined Site Visit, Program in Physical Biology & Program on Pediatric Imaging and Tissue Science, NICHD, NIH
2013	Session Co-Chair, ASBMR Symposium: Cutting Edge Discoveries in Muscle Biology, Disease and Therapeutics
2014	American Heart Association Established Investigator Award peer review study group
2015-present	Editorial Board Member, Journal of Cell Science
2016-present	Director, UT Southwestern Hamon Center for Regenerative Science and Medicine (CRSM) Postdoctoral Fellows Program
2017	Ad hoc member, NIAMS Board of Scientific Counselors Annual Meeting
2017	Co-organizer, Cellular Dynamics: Membrane-Cytoskeleton Interface, Journal of Cell Science and the Company of Biologists
2017	Organizer, Special Interest Group on Cell-Cell Fusion, ASCB/EMBO 2017 Meeting
2017-2019	Election Committee of the *Drosophila* Board
2018	Scientific Committee, EMBO Symposium on Membrane Fusion in Health and Disease, Cambridge, UK
2018	Israel Science Foundation grant review
2018	French National Research Agency grant review
2018	NIH COBRE Center in Protein Structure and Function grant review
2018	Co-Chair, Minisymposium on Cytoskeleton, Motility, and Cell Mechanics, ASCB/EMBO 2018 Meeting
2019	Session Co-Chair, Cell Biology: Cytoskeleton, Organelles, Trafficking, 60th Annual *Drosophila* Research Conference
2019	Co-Organizer, American Society for Cell Biology (ASCB) and Chinese Biophysical Society joint session on *Membrane Fusion and Fission*, the 17th Chinese Biophysics Congress, Tianjin, China
2019	Human Frontier Science Program (HFSP) grant review
2019-2020	*Drosophila* Image Award Committee
2019-2021	President, Society for Muscle Biology
2019-2022	NIAMS Advisory Council, NIH
2020	Selection Committee, ASCB Awards (EB Wilson Medal, Günter Blobel Early Career Award, and Merton Bernfield Memorial Award)
2021	Co-Organizer and President, Frontiers in Myogenesis, Skeletal Muscle: Development, Regeneration and Disease

2022 Chair, Gordon Research Conference on Cell-Cell Fusion, Diverse Systems and Common Mechanisms in Cell Fusion

Honors

2000-2003 The Helen Hay Whitney Foundation Postdoctoral Fellowship
2003 UT Southwestern Medical Center Postdoctoral Research Award
2005-2008 Edward Mallinckrodt, Jr. Foundation Young Investigator Award
2005-2009 National Scientist Development Award, American Heart Association
2005-2010 David and Lucile Packard Fellowship for Science and Engineering
2006-2008 Basil O'Connor Starter Scholar Research Award, March of Dimes
2006-2009 Searle Scholar, The Chicago Community Trust
2010 Plenary Lecture, 51st Annual *Drosophila* Research Conference, Washington, D.C.
2012-2017 National Established Investigator Award, American Heart Association
2014 New and Notable Symposium Lecture, Biophysical Society 58th Annual Meeting
2016-2021 HHMI Faculty Scholar
2018 WICB Mid-Career Award for Excellence in Research, American Society for Cell Biology

C. Contribution to Science

1. Revealing a function for the actin cytoskeleton in myoblast fusion.

To systematically study mechanisms underlying cell-cell fusion, I designed and conducted the first genome-wide screen for *Drosophila* myoblast fusion mutants as a postdoctoral fellow. This screen led to the identification of 11 new loci required for myoblast fusion. The first two loci that I characterized, *antisocial* and *loner*, encode proteins that link the muscle-specific cell adhesion molecules to regulators of the actin cytoskeleton. Antisocial (a scaffold protein) biochemically links the founder cell-specific adhesion molecule Duf to a subunit of a guanine nucleotide exchange factor (GEF) for the Rac GTPase, and Loner (an ARF6 GEF) is required for the proper localization of Rac. Given the well-established function for Rac in regulating actin cytoskeletal dynamics, these studies provided the first hint for the involvement of the actin cytoskeleton in myoblast fusion. In a subsequent study published in my own lab, we showed a genetic requirement for an actin nucleation-promoting factor and its binding protein (WASP and WIP) in myoblast fusion and revealed colocalization between WIP and an actin-enriched focus at the site of fusion. This was the first evidence for a direct link between the actin polymerization machinery and the site of fusion, demonstrating a role for the actin cytoskeleton in promoting myoblast fusion.

a. **Chen, E.H.,** and Olson, E.N. (2001) Antisocial, an intracellular adaptor protein, is required for myoblast fusion in *Drosophila*. ***Dev Cell*** 1, 705-715.
b. **Chen, E.H.,** Pryce, B.A., Tzeng, J.A., Gonzalez, G.A., and Olson, E.N. (2003) Control of myoblast fusion by a guanine nucleotide exchange factor, Loner, and its effector ARF6. ***Cell*** 114, 751-762.
c. Kim, S., Shilagardi, K., Zhang, S., Hong, S., Sens, K., Bo, J., Gonzalez, G.A., and **Chen, E.H.** (2007) Characterization of *Drosophila* WIP reveals a critical function of the actin cytoskeleton in myoblast fusion. ***Dev Cell*** 12, 571-86.

2. Discovery of the asymmetric fusogenic synapse.

Next, we examined the precise localization, morphology, molecular composition and function of the F-actin focus at the site of fusion. Our analysis revealed a striking asymmetry of actin-enriched structures at the fusogenic synapse. We found that the F-actin focus is localized exclusively in the FCM. Electron microscopy revealed that each F-actin focus comprises multiple finger-like protrusions drilling into the apposing founder cell. We named this invasive structure “podosome-like structure” (PLS) due to its resemblance to a podosome, an actin-rich adhesive structure previously described in cultured cells. We further demonstrated that the formation of the PLS requires the actin nucleation-promoting factors WASP and Scar, and that PLS invasion is required for fusion pore formation. Our discovery of the invasive PLS at the site of fusion, which we named “fusogenic synapse”, has brought a major conceptual advance in the mechanistic understanding of cell fusion – cell fusion is not a symmetrical process as previously envisioned, but rather an asymmetric process in which one cell actively invades the other using an actin-propelled PLS to promote fusion pore formation.

a. Sens, K.L., Zhang, S., Jin, P., Duan, R., Zhang, G., Luo, F., Parachini, L., and **Chen, E.H.** (2010) An invasive podosome-like structure promotes fusion pore formation during myoblast fusion. ***J Cell Biol*** 191,1013-27. PMCID: PMC2995175

3. Dissecting the mechanisms underlying podosome invasion.

To further probe the central importance of PLS in myoblast fusion, we examined the molecular regulation of PLS. We identified an essential function for Blown fuse (Blow) in regulating the invasiveness of PLS. Blow promotes the dissociation of the WASP-WIP complex by competing with WASP for WIP binding. Dissociation of the WASP-WIP complex, in turn, leads to dynamic actin polymerization within the PLS. Our characterization of Blow revealed that the dynamics, rather than the accumulated level, of actin polymerization drives PLS invasion and fusion pore formation. We also identified an essential function for p21-activated kinases (PAKs) in myoblast fusion. We showed that PAKs act downstream of Rac to organize the actin filaments within the PLS into a dense focus. These studies further support our model that PLS invasion is critical for fusion pore formation and reveal two novel mechanisms controlling actin polymerization dynamics and PLS invasion.

a. Jin, P., Duan, R., Luo, F., Zhang, G., Hong, N., and **Chen, E.H.** (2011) Competition between Blown Fuse and WASP for WIP binding regulates the dynamics of WASP-dependent actin polymerization *in vivo*. ***Dev Cell*** 20, 623-38. PMCID: PMC3179271

b. Duan, R., Jin, P., Luo, F., Zhang, G., Anderson, N., and **Chen, E.H.** (2012) Group I PAKs function downstream of Rac to regulate podosome invasion during myoblast fusion *in vivo*. ***J Cell Biol*** 199, 169-85. PMCID: PMC3461515

c. Zhang, R., Lee, D.M., Jimah, J.R., Gerassimov, N., Yang, C., Kim, S., Luvsanjav, D., Winkelman, J., Mettlen, M., Abrams, M.E., Kalia, R., Keene, P., Pandey, P., Ravaux, B., Kim, J.H., Ditlev, J.A., Zhang, G., Rosen, M.K., Frost, A., Alto, N.M., Gardel, M., Schmid, S.L., Svikina, T., Hinshaw, J.E., and **Chen, E.H.** (2020) Dynamin regulates the dynamics and mechanical strength of the actin cytoskeleton as a multifilament actin-bundling protein. ***Nat Cell Biol*** 22, 674-688. PMCID: pending.

4. Reconstituting high efficiency cell-cell fusion in cultured cells.

To extrapolate the mechanisms we have uncovered in *Drosophila* myoblast fusion to generic cell-cell fusion events and to probe the mechanism of fusion more deeply, we developed a cell-based assay by reconstituting high efficiency cell-cell fusion in the normally non-fusing *Drosophila* cells. This was achieved by co-expressing the *Drosophila* FCM-specific adhesion molecule Sns and a *C. elegans* epithelial cell-derived fusogen Eff-1. Interestingly, cell fusion in this reconstituted system is mediated by a similar invasive PLS as in *Drosophila* myoblasts. Using this simple model, we showed that a specific function of the PLS is to promote fusogen engagement across two apposing membranes. This study represents a major advance in the cell-cell fusion field. It is the first reconstitution of high-efficiency cell-cell fusion using physiologically relevant components. The fact that similar actin-propelled membrane protrusions are used in the reconstituted cell-fusion model as in *Drosophila* embryos supports a general function for these protrusions in promoting cell-cell fusion.

a. Shilagardi, K., Li, S., Luo, F., Marikar, F, Duan R., Jin, P., Kim, J., Murnen, K., and **Chen, E.H.** (2013) Actin-propelled invasive membrane protrusions promote fusogenic protein engagement during cell-cell fusion. ***Science*** 340, 359-63. PMCID: PMC3631436

5. Discovery of a role for mechanical tension in driving cell membrane fusion.

Using both *Drosophila* myoblast fusion and the reconstituted fusion in cultured cells, we showed that the invasive protrusions from the attacking cell trigger mechanosensory responses of the actin motor myosin II and the membrane skeleton protein spectrin in the receiving fusion partner. While accumulated myosin II at the fusogenic synapse increases cortical tension and promotes fusion pore formation, the uneven spectrin network functions as a cellular fence to restrict the diffusion of cell adhesion molecules and a cellular sieve to constrict the invasive protrusions, thereby increasing the mechanical tension of the fusogenic synapse to promote cell membrane fusion. These studies fill a major gap in our understanding of cell-cell fusion by uncovering the cellular mechanics of the receiving cell and revealing mechanical tension as a driving force for cell membrane fusion.

a. Kim, J.H., Ren, Y., Ng, W.P., Li, S., Son, S., Kee, Y., Zhang, S., Zhang, G., Fletcher, D.A., Robinson, D.N., and **Chen, E.H.** (2015) Mechanical tension drives cell membrane fusion. ***Dev Cell*** 32(5):561-73. PMCID: PMC4357538

b. Duan, R., Kim, J.H., Shilagardi, K., Schiffhauer, E., Lee, D., Son, S., Li, S., Thomas, C., Luo, T., Fletcher, D.A., Robinson, D.N., and **Chen, E.H.** (2018) Spectrin is a mechanoresponsive protein shaping fusogenic synapse architecture during myoblast fusion. ***Nat Cell Biol*** 20, 688-698.

Complete List of Published Work in MyBibliography: http://www.ncbi.nlm.nih.gov/sites/myncbi/elizabeth.chen.1/bibliography/41144513/public/?sort=date&direction=ascending.

D. Research Support

Faculty Scholar Award (PI: Chen) 11/01/16-10/31/21
HHMI
"Cell-Cell Fusion in Development and Regeneration"
The goal of this project is to discover the overarching principles of cell-cell fusion in development and regeneration.

R01 AR053173 (PI: Chen) 07/01/06-03/31/23
NIH/NIAMS
"Molecular Mechanisms of Myoblast Fusion"
The goal of this project is to study the functions of calcium signaling and phospholipids in *Drosophila* myoblast fusion.

R35 GM136316 (PI Chen) 05/04/20- 04/30/25
NIH/NIGMS
Decoding the Mechanisms of Cell-Cell Fusion
The goal of this project is to study the fusogenic synapse of mouse myoblast fusion and to identify novel transmembrane proteins that promote cell-cell fusion.

R01 AR075005 (PI Chen) 08/01/20 – 05/31/25
NIH/NIAMS
Investigating mechanisms of vertebrate myoblast fusion using zebrafish as a model
The goal of this project is to investigate the function of the actin cytoskeleton and the interactions between the actin cytoskeleton and the fusogenic proteins in zebrafish myoblast fusion.