BIOGRAPHICAL SKETCH

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NAME: Chen, Qi

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POSITION TITLE: Associate 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
Chongqing Medical University, Chongqing, China	MD	07/2006	Medicine
Institute of Zoology, Chinese Academy of Sciences, Beijing, China	PhD	07/2011	Reproductive and Developmental Biology

A. Personal Statement

I was broadly trained as a reproductive and developmental biologist since my PhD study, applying physiological, genetic and bioinformatic approaches to study sperm behavior (*Cell Res 2011*), early embryo development (Development 2015) and embryo implantation (*J Biol Chem 2011*) using mouse as model.

After series of curiosity-driven, serendipitous discoveries, my lab is currently focusing on the fact that some environmental exposure-induced phenotypes can be “memorized” in the sperm and inherited to the offspring, a process involving epigenetic inheritance via the sperm (*Nat Rev Genet 2016*). The search for the identities of sperm “epigenetic carriers” that respond to paternal environment changes and transmit the intergenerational phenotype remains the central concern of this rapidly evolving field. Our group first discovered that tRNA-derived small RNAs (tsRNAs) are highly enriched in mature sperm with evolutionary conservation (*Cell Res 2012*), and further showed in a high-fat diet (HFD) model, that sperm tsRNAs exhibit changes in both expression profiles and RNA modifications, and that injection of sperm tsRNA fractions from a HFD male into normal zygotes generated metabolic disorders in the F1 offspring, mimicking the HFD father (*Science 2016*). We also found that RNA modifications in tsRNAs are important for RNA stabilization and are sensitive to HFD exposure (*Science 2016*). In addition, we further demonstrated that a RNA methyltransferase, Dnmt2, can shape the sperm RNA ‘coding signature’ by regulating the biogenesis of both tsRNA and rRNA-derived small RNAs (rsRNAs) (*Nat Cell Biol 2018*). These data promote the concept that sperm RNAs and associated RNA modifications composed a 'sperm RNA code' - a type of epigenetic information beyond DNA sequence that mediate intergenerational inheritance of certain paternally acquired traits (*Nat Rev Endocrinol 2019*). My lab is currently actively exploring how the sperm RNA code (a combination of modified small RNAs) could influence embryo development such as by regulating cell fate decision that contribute to offspring health.

Because both tsRNAs and rsRNAs are highly modified, some of their RNA modifications will prevent their detection by using traditional RNA-seq, thus generating substantial bias in their discovery and following bioinformatic analysis. To conquer this problem, we recently developed a new method, *PANDORA-seq* (*Nat Cell Biol 2021*) to overcome RNA modifications that prevent small RNA detection in traditional RNA-seq, and developed a software *SPORTS* (*Genomics Proteomics Bioinformatics 2018*) to facilitate the systematic discovery and identification of tsRNAs/rsRNAs, especially those carry RNA modifications and could not be detected by using traditional RNA-seq. These novel tools have expanded our understanding on the diversity of small RNAs, especially those highly modified ones that are previously undetectable using traditional methods, this has also opened the opportunity to study tsRNAs/rsRNAs in a wide range of different biological systems and disease conditions (*Trends Biochem Sci 2021; Nat Cell Biol 2022*). I see great opportunities to apply these innovative tools in many biochemical and clinical investigations.

B. Positions and Honors

Positions and Employment

2023.2- Associate Professor/PI, University of Utah School of Medicine, UT, USA
2022.7-2023.2 Associate Professor/PI, University of California, Riverside, School of Medicine, CA, USA
2019.2-2022.6 Assistant Professor/PI, School of Medicine, University of California, Riverside, CA, USA
2015.10-2019.1 Assistant Professor/PI, University of Nevada, Reno School of Medicine, Reno, NV, USA
2011.7-2015.9 Assistant Professor/Co-PI, Institute of Zoology, Chinese Academy of Sciences, Beijing, China

Scientific Appointments

2021-present: Editorial Board Member, *Cell Research*
2018-present: Editorial Board Member, *Cell Discovery*
2017-present: Editorial Board Member, *Biology of Reproduction*
Ad hoc reviewer for journals including *Nature, Nat Cell Biol, Nat Genet, Nat Methods, Nat Neurosci, Nat Struc Mol Biol, Nat Commun, Cell Metab, Mol Cell, Dev Cell, Cell Rep, EMBO J, Sci Adv, PNAS, Genome Res, PLoS Biol, PLoS Genet, eLife, Development, Biol Reprod,* etc.

Charting member of NIH study section: CMIR (07/01/2022-06/30/2026)
Ad hoc panel member and reviewer for NIH study section: SIEE (02/2020)
Ad hoc panel member and reviewer for NIH study section: SBIR (06/2020)
Ad hoc panel member and reviewer for NIH study section: SIEE (10/2020)
Ad hoc panel member and reviewer for NIH study section: CMIR (02/2021)
Ad hoc mail reviewer for NIH Director's Pioneer Award Program: DP1 (03/2021)
Ad hoc mail reviewer for Wellcome Trust, MRC, and European Science Foundation etc

Honors

2019: Highly Cited Researcher (Cross-field) by Web of Science
2013: Fellow of Youth Innovation Promotion Association, Chinese Academy of Science
2011: Dean's Outstanding Award of Chinese Academy of Sciences

C. Contributions to Science

1. Epigenetic inheritance mediated by sperm tsRNAs and RNA modifications

The search for sperm epigenetic factors that could transmit acquired phenotypes is the key question for the rapidly developing field of transgenerational epigenetic inheritance. Our group was the first to report the existence of abundant tRNA-derived small RNAs (tsRNAs) in mammalian mature sperm (*Cell Res 2012*), and also provided the first functional evidence that sperm tsRNAs contribute to the intergenerational transmission of acquired metabolic disorder from father to offspring (*Science 2016*). Our findings thus strongly indicate that sperm tsRNAs is a type of paternal information carrier that mediate intergenerational epigenetic inheritance via shaping early embryo development. Importantly, we also found that RNA modifications in sperm tsRNAs are important for their stabilization after entering the oocytes, and are essential for tsRNAs' function as epigenetic information carrier (*Science 2016*). We further demonstrated that a RNA methyltransferase, *Dnmt2*, is required for sperm RNA-mediated epigenetic inheritance, which exert its function by shaping the sperm RNA 'coding signature' by regulating both tsRNA and rRNA-derived small RNAs (rsRNA) biogenesis (*Nat Cell Biol 2018*). These data promote the concept that sperm RNAs and associated RNA modifications composed a 'sperm RNA code' - a type of epigenetic information beyond DNA sequence that mediate intergenerational inheritance of certain paternally acquired traits (*Nat Rev Endocrinol 2019*).

(*Co-first authors; #Corresponding authors)

a) Zhang Y, Shi J, Rassoulzadegan M, Tuorto F, Chen Q#. Sperm RNA code programmes the metabolic health of offspring. ***Nature Reviews Endocrinology*** (2019) Aug;15(8):489-498. PMCID: PMC6626572

b) Zhang Y*, Zhang X*, Shi J*, Tuorto F*, Li X*, Liu Y, Liebers R, Zhang L, Qu Y, Qian J, Pahima M, Liu Y, Yan M, Cao Z, Lei X, Cao Y, Peng H, Liu S, Wang Y, Zheng H, Woolsey R, Quilici D, Zhai Q, Li L, Zhou T, Yan W, Lyko F, Zhang Y#, Zhou Q#, Duan E#, Chen Q#. Dnmt2 mediates intergenerational transmission of paternally acquired metabolic disorders through sperm small non-coding RNAs. ***Nature Cell Biology*** (2018); 20(5):535-540. PMCID: PMC5926820

c) Chen Q*,#, Yan M*, Cao Z*, Li X*, Zhang Y*, Shi J*, Peng H, Zhang X, Zhang Y, Duan E#, Zhai Q#, Zhou Q#, Sperm tsRNAs contribute to intergenerational inheritance of an acquired metabolic disorder. ***Science*** (2016), 351; 6271:397-400

d) Peng H, Shi J, Zhang Y, Zhang H, Liao S, Li W, Lei L, Han C, Ning L, Cao Y, Zhou Q, Chen Q[#], Duan E[#]. A novel class of tRNA-derived small RNAs extremely enriched in mature mouse sperm. ***Cell Research*** (2012), 22: 1609-1612. PMCID: PMC3494397

2. Developing novel tools to explore the expanding world of small RNAs

To decode the RNA code, we developed a small RNA analyzing software *SPORTS1.0* with Dr. Tong Zhou (*Genomics Proteomics Bioinformatics 2018*) to facilitate the systematic analyses of tsRNAs and rsRNAs. More recently, we develop *PANDORA-seq* to overcome RNA modifications that prevent small RNA detection in traditional RNA-seq (*Nat Cell Biol 2021*). *PANDORA-seq* uncovers a new and surprising small RNA landscape that is in fact, dominated by tsRNA/rsRNA, rather than miRNA in many tissues/cells. *PANDORA-seq* facilitated the discovery of tissue/cell specific tsRNAs/rsRNAs in mouse and human, and lead to the functional discovery of tsRNAs/rsRNAs in stem cell differentiation (*Nat Cell Biol 2021*). I'm also very excited to participate in developing a new tool *MLC-Seq*, a mass spectrometry-based direct sequencing method, which enables simultaneously unraveling the sequences and full map of RNA modifications of tRNAs/tsRNAs with stoichiometric precision (*Preprint 2021*). These advanced tools aim to systematically analyze novel small RNAs such as tsRNAs and rsRNAs along with RNA modification, which is perquisite for revealing their functionality (*Trends Biochem Sci 2021*).

([#]Corresponding authors)

a) Shi J, Zhou T[#], Chen Q[#]. Exploring the expanding universe of small RNAs. ***Nature Cell Biology*** (2022) Apr;24(4):415–423.

b) Shi J, Zhang Y, Tan D, Zhang X, Yan M, Zhang Y, Franklin R, Shahbazi M, Mackinlay K, Liu S, Kuhle B, James ER, Zhang L, Qu Y, Zhai Q, Zhao W, Zhao L, Zhou C, Gu W, Murn J, Guo J, Carrell DT, Wang Y, Chen X, Cairns BR, Yang XL, Schimmel P, Zernicka-Goetz M, Cheloufi S[#], Zhang Y[#], Zhou T[#], Chen Q[#]. PANDORA-seq expands the repertoire of regulatory small RNAs by overcoming RNA modifications. ***Nature Cell Biology*** (2021) Apr;23(4):424-436. PMCID: PMC8236090

c) Yuan X, Su Y, Zhang X, Turkel SJ, Shi S, Wang X, Choi EJ, Wu W, Liu H, Viner R, Russo JJ, Li W, Bao X, Chen Q, Zhang S[#]. MLC-Seq: de novo sequencing of full-length tRNAs and quantitative mapping of multiple RNA modifications. ***Researchsquare*** (2021) doi:10.21203/rs.3.rs-1090754/v1 (preprint)

d) Shi J[#], Ko EA, Sanders KM, Chen Q[#], Zhou T[#]. SPORTS1.0: a tool for annotating and profiling non-coding RNAs optimized for rRNA- and tRNA- derived small RNAs. ***Genomics Proteomics Bioinformatics*** (2018) Apr;16(2):144-151. PMCID: PMC6112344

3. Molecular and cellular mechanisms in early mammalian embryo cell fate decision.

In mammalian preimplantation embryo development, when the first asymmetry emerges and how it develops to direct distinct cell fates are two longstanding questions. It remains debatable whether the first bifurcation of cell fate emerges randomly at morula stage, or has been predetermined at earlier stages before morphological distinction. Combining single-cell RNA-seq analysis and mathematical modeling, we recently showed that the very first symmetry-breaking process involves both chance separation and defined transcriptional circuits. From our single-embryo transcriptome analysis, small biases at molecular level will inevitably emerge at the 2-cell embryo stage, following a binomial distribution due to the cleavage division. At this stage, the blastomere-to-blastomere distribution seems random but during subsequent zygotic transcriptional activation, a "bistable pattern" emerges in some genes. Several lineage specifiers show a strong bias between different blastomeres thus providing potential for further increased asymmetry subsequently (*Development 2015*). These observations suggest a scenario of how order is created from a seemingly random process through the differential triggering of existing master regulators by the emergence of their small bias. As a triumph of our model and hypothesis, we showed symmetry breaking driven by heterogeneous LincGET expression since 2-cell mouse embryo (*Cell 2018*). Recently, we further propose that compartmentalized intracellular reactions, such as those mediated by cell-cell contact and cell geometry, generate micro-scale inhomogeneity, which is amplified in the developing embryo, driving pattern formation (*Nat Commun 2018*). Our studies provide the framework in explaining how small biases in RNA contents such as delivered by sperm and epigenetic modifiers in oocytes can change the trajectory of development and embryo developmental potential (*Nat Rev Genet 2016*).

(*Co-first authors; [#]Corresponding authors)

e) Chen Q*, Shi J*, Tao Y, Zernicka-Goetz M[#]. Tracing the origin of heterogeneity and symmetry breaking in the early mammalian embryo. ***Nature Communications*** (2018) May 8;9(1):1819. PMCID: PMC5940674

f) Wang J, Wang L, Feng G, Wang Y, Li Y, Li X, Liu C, Jiao G, Huang C, Shi J, Zhou T, Chen Q, Liu Z, Li W#, Zhou Q#. Asymmetric Expression of LincGET Biases Cell Fate in Two-Cell Mouse Embryos. ***Cell*** (2018) Dec 13;175(7):1887-1901.e18

g) Chen Q#, Yan W#, Duan E#, Epigenetic inheritance of acquired traits through sperm RNAs and sperm RNA modifications. ***Nature Reviews Genetics*** (2016) 17(12):733-743. PMCID: PMC5441558

h) Shi J*, Chen Q*,#, Li X*, Zheng X*, Zhang Y, Qiao J, Tang F, Tao Y#, Zhou Q#, Duan E#. Dynamic transcriptional symmetry-breaking in pre-implantation mammalian embryo development revealed by single-cell RNA-seq. ***Development.*** (2015), 15;142(20):3468-77.

4. Molecular mechanisms for embryo-uterine interactions and early pregnancy loss.

Mammalian blastocysts show remarkably consistent distribution pattern and embryo orientation with respect to the uterine structure. These long-time evolved patterns bear great biological significance and the disruption of which would lead to adverse effects on pregnancies (*Mol Aspect Med 2013*). The molecular mechanisms responsible for these traits involve an intricate interplay between the embryo and uteri, which are the continuous interests of both reproductive and developmental biologists. We recently provided strong evidence demonstrating the importance of myometrium peristalsis and fluid dynamics in intrauterine embryo localization and implantation, including defining the role of sympathetic activation through β2-Adrenoceptor (β2-AR) signaling for intrauterine embryo location and its profound link with ongoing pregnancy (*J Biol Chem 2011*); and defining the role of Aquaporin-mediated excessive intrauterine fluid as a major contributor in hyper-estrogen induced aberrant embryo implantation and pregnancy loss (*Cell Res 2015*). Both discoveries shed new light on the biomechanical and molecular mechanisms that govern intrauterine embryo localization, as well as the profound effects on successful pregnancy. We also provided the first genetic evidence that normal mammalian embryo-uterine orientation and subsequent embryo development require stage-specific uterine RBPJ signaling (*Cell Res 2014*), substantiating the concept that normal mammalian embryo-uterine orientation requires proper guidance from developmentally controlled uterine signaling to ensure normal post-implantation embryo development.

(*Co-first authors; #Corresponding authors)

a) Zhang Y*, Chen Q*, Zhang H*, Wang Q*, Rong L, Jin Y, Wang H, Ma T, Qiao J, Duan E. Aquaporin-mediated excessive intrauterine fluid is a major contributor in hyper-estrogen induced aberrant embryo implantation. ***Cell Research.*** (2015); Jan,25(1):139-42.

b) Zhang S, Kong S, Wang B, Cheng X, Chen Y, Wu W, Wang Q, Shi J, Zhang Y, Wang S, Lu J, Lydon JP, DeMayo F, Pear WS, Han H, Lin H, Li L, Wang H, Wang YL, Li B, Chen Q#, Duan E#, Wang H#. Uterine Rbpj is required for embryonic-uterine orientation and decidual remodeling via Notch pathway-independent and -dependent mechanisms. ***Cell Research.*** (2014), 24:925-942.

c) Chen Q*, Zhang Y*, Elad D, Jaffa AJ, Cao Y, Ye X#, Duan E#. Navigating the site for embryo implantation: Biomechanical and molecular regulation of intrauterine embryo distribution. ***Molecular Aspects of Medicine.*** (2013) 34:1024-42.

d) Chen Q*, Zhang Y*, Peng H, Lei L, Kuang H, Zhang L, Ning L, Cao Y, Duan E#. Transient β2-Adrenoceptor activation confers pregnancy loss by disrupting embryo spacing at implantation. ***Journal of Biological Chemistry.*** (2011), 286: 4349-4356.

5. Sperm motility and postcopulatory sperm behavior

In the journey from the male to female reproductive tract, mammalian sperm experience a natural osmotic decrease (e.g., in mouse, from ~415 mOsm in the cauda epididymis to ~310 mOsm in the uterine cavity). On one hand, the hypotonic stress upon ejaculation is beneficial for mouse sperm motility “start-up” (evolutionary trait from fish sperm), but like a double-edged sword, the hypotonic stress could also cause potential harm to sperm function by inducing un-wanted cell swelling. To counteract this negative impact, mammalian sperm have acquired mechanisms to drive rapid transmembrane water movement towards efficient cell volume regulation. However, the specific sperm proteins responsible for this rapid osmoadaptation remain elusive. We discovered that Aquaporin-3 (AQP3) is an essential membrane protein for sperm regulatory volume decrease (RVD) upon physiological hypotonicity, balancing the “trade-off” between hypotonic induced sperm motility and cell swelling, thereby optimizing postcopulatory sperm behavior (*Cell Res, 2011*), implicating AQP3’s role in active membrane mechanosensing (*Acta Pharmacol Sin, 2011*). We also demonstrated that the postcopulatory sperm behavior involves cooperation-based sperm clusters that facilitate sperm oviduct entry and fertilization (*Protein Cell 2021*).

(*Co-first authors)

a) Qu Y*, Chen Q*, Guo S*, Ma C, Lu Y, Shi J, Liu S, Zhou T, Noda T, Qian J, Zhang L, Zhu X, Lei X, Cao Y, Li W, Plachta N, Matzuk MM, Ikawa M, Duan E, Zhang Y, Wang H. Cooperation-based sperm clusters

mediate sperm oviduct entry and fertilization. ***Protein & Cell*** (2021) 12(10):810-817. PMCID: PMC8464547

b) Chen Q, Duan EK. Aquaporins in sperm osmoadaptation: an emerging role for volume regulation. ***Acta Pharmacologica Sinica*** (2011), 32: 721-4. PMCID: PMC4009956

c) Chen Q*, Peng H*, Lei L*, Zhang Y, Kuang H, Cao Y, Shi QX, Ma T, Duan E#. Aquaporin3 is a sperm water channel essential for postcopulatory sperm osmoadaptation and migration. ***Cell Research*** (2011), 21: 922-933. PMCID: PMC3343308

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