BIOGRAPHICAL SKETCH

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NAME: Xin Zhang, Ph.D.

eRA COMMONS USER NAME (credential, e.g., agency login): XZHANG4

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
Beijing University, Beijing, China	B.S.	1991	Physics
Johns Hopkins University, Baltimore	Ph.D.	1998	Biology
Harvard Medical School, Boston	Postdoc	2003	Mammalian Genetics

A. Personal Statement

The main focus of my independent research is the mechanism of cell signaling during eye development. I have taken a genetic approach to dissect signaling pathways which are not only essential for embryonic development but also functionally important for congenital syndrome and cancer biology. My long-term goal is to combine mouse genetics with biochemical approaches to determine how intracellular signaling is received and interpreted in eye development and homeostasis. I would like to understand how specific heparan sulfate modifications mediate the diffusion and stability of ligands in extracellular matrix and regulate receptor/ligand interaction at cell surface. Inside the cell, I would like to delineate the exact signaling cascade leading to the downstream pathways. In vision research, growth factors such as FGF have been shown to promote the survival of retinal neurons, showing promise as a therapeutic agent for retinal injury. We would like to see that our mechanistic insights into intercellular signaling will eventually lead to therapeutic application to protect human vision.

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

R01 EY031210
Zhang (PI)
02/01/2020 - 12/31/2023
Mechanism of Csk signaling in lacrimal gland morphogenesis

R01 EY018868
Zhang (PI)
12/01/2008 - 07/31/2024
Regulation of FGF signaling in lacrimal gland development

R01 EY025933
Zhang (PI)
08/01/2015-08/31/2024

Lens ectoderm-derived Wnt signaling regulates eye development

R01 EY017061
Zhang (PI)
1/1/2006 - 03/31/2025
Signaling Mechanisms of Lens Development

Citations:

1. Makrides N, Wang Q, Tao C, Schwartz S, Zhang X. 2022 Jack of all trades, master of each: the diversity of FGF signaling in eye development. **Open Biology**. 12: 210265.
2. Cvekl A, Zhang X. 2017. Signaling and Gene Regulatory Networks in Mammalian Lens Development. **Trends in Genetics.** 33(10):677-702.
3. Garg A, Zhang X. 2017. Lacrimal gland development: from signaling interactions to regenerative medicine. **Developmental Dynamics.** 246(12):970-980.
4. Balasubramanian R, Zhang X. 2016. Mechanisms of FGF gradient formation during embryogenesis. **Seminar in Cell and Development Biology.** 53:94–100.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2021-present Herbert and Florence Irving Professor, Departments of Ophthalmology, Pathology and Cell Biology, Columbia University, New York, NY

2021-present Member, Biology and Medicine Panel, Research Grants Council (RGC) of Hong Kong, China

2019-2020 Guest editor, *PLoS Genetics*, *PLoS Biology* and *PNAS*

2014-2020 Regular member, NIH BVS Biology of the Visual System

2013-2020 Associate Professor, Departments of Ophthalmology, Pathology and Cell Biology
Columbia University, New York, NY

2013 Professor, Department of Medical and Molecular Genetics
Indiana University School of Medicine, Indianapolis, IN

2011-Present Editorial board, *PLoS ONE*

2009-2017 Ad Hoc study section member, NIH AED, ZEY1 VSN, ZRG1 BDC and ZRG1 CBR

2009-2013 Associate Professor, Department of Medical and Molecular Genetics
Indiana University School of Medicine, Indianapolis, IN

2005-Present Member, Association for Research in Vision and Ophthalmology (ARVO)

2004-Present Ad Hoc reviewer
American Diabetes Association, Wellcome Trust (UK), the Dutch research council (Netherlands), Israel Science Foundation, Czech Science Foundation and National Medical Research (Singapore)

2003–2009 Assistant Professor, Department of Medical and Molecular Genetics
Indiana University School of Medicine, Indianapolis, IN

1997-2002 Postdoctoral Fellow, Department of Medicine, Division of Genetics
Brigham and Women's Hospital, Harvard Medical School, Boston, MA

Honors

2021-present Herbert and Florence Irving Professor, Departments of Ophthalmology, Pathology and Cell Biology, Columbia University, New York, NY

2014-2020 Jules and Doris Stein RPB Professorship
Research to Prevent Blindness, New York, NY

2011-2013 David D. Weaver Investigator, Department of Medical and Molecular Genetics
Indiana University School of Medicine, Indianapolis, IN

2005–2007 Basil O'Connor Scholar
March of Dimes Birth Defects Foundation, White Plains, NY
2001–2002 Postdoctoral position on the *Molecular Bases of Eye Diseases* Training Grant
Schepens Eye Research Institute, Harvard Medical School, Boston, MA
1987, 1991 Scholarship
Beijing University, Beijing, China

C. Contributions to Science

1. Heparan sulfates regulates FGF signaling and basement membrane assembly

Proteoglycans are heavily glycosylated proteins with covalently linked glycosaminoglycan (GAG) side chains. We first showed N-sulfated heparan sulfate as a co-receptor of FGF ligand. We also generated genetic deletion mutants in heparan sulfate 2-O and 6-O transferases, and observed significant lacrimal gland budding defects in 6-O heparan sulfate sulfation mutants but not in 2-O sulfation mutants. On the other hand, combined deletion of both 2-O and 6-O sulfations completely abolished FGF-dependent lacrimal gland development. These studies demonstrated that the sulfation pattern of heparan sulfates plays an important role in mammalian eye development. We also show that mesenchymal glycosaminoglycan controls lacrimal gland induction by restricting the diffusion of Fgf10. The basement membrane is crucial for cell polarity, adhesion and motility, but how it is assembled on the cell surface is not well understood. We show that ablation of glycosaminoglycans in neuroretina disrupts the retinal basement membrane, which leads to arrest of astrocyte migration and subsequent failure of angiogenesis. By genetic deletion and time-lapse imaging, we show that retinal astrocytes require the retinal basement membrane as the migratory substrate and neuronal-derived PDGF as the chemoattractive cue for astrocytes.

Qu X, Carbe C, Tao C, Powers A, Lawrence R, van Kuppevelt TH, Cardoso WV, Grobe K, Esko JD, Zhang X. 2011. Lacrimal gland development and Fgf10-Fgfr2b signaling is controlled by 2-*O* and 6-*O* sulfated heparan sulfate. **Journal of Biological Chemistry.** 286(16):14435-14444.

Qu X, Pan Y, Carbe C, Powers A, Grobe K, Zhang X. 2012. Glycosaminoglycan-dependent restriction of FGF diffusion is necessary for lacrimal gland development. **Development.** 139:2730-2739.

Tao C, Zhang X. 2016. Retinal Proteoglycans Act as Cellular Receptors for Basement Membrane Assembly to Control Astrocyte Migration and Angiogenesis. **Cell Reports.** 17, 1832–1844.

Tao C, Makrides N, Chuang JZ, Wu Y, Brooks SE, Esko JD, Sung CH, Zhang X. 2022 Chondroitin sulfate enhances the barrier function of basement membrane assembled by heparan sulfate. **Development**. 149, dev200569.

2. FGF signaling is mediated by intracellular adaptor proteins

We investigated the adaptor protein Frs2α and its structurally related scaffolding proteins, Gab1 and Gab2, in FGF signaling. Genetic interaction experiments demonstrate that direct binding of Shp2 to Frs2α is necessary for activation of ERK signaling, whereas constitutive activation of either Shp2 or Kras signaling can compensate for the absence of Frs2α in lens and retinal development. By contrast, knockout of Gab1 and Gab2 failed to disrupt FGF signaling in vitro and lens development in vivo. We further demonstrated that adaptor proteins Crk and Crkl are recruited to the Frs2α complex to regulate cytoskeletal organization during lens fiber cell elongation. These results reveal the repertoire of adaptor proteins used in transmitting FGF signaling.

Cai Z, Tao C, Ladher R, Gotoh N, Feng G, Wang F, Zhang X. 2013. Deficient FGF signaling causes optic nerve dysgenesis and ocular coloboma. **Development**. 140:2711-2723.

Li H, Tao C, Cai Z, Hertzler-Schaefer K, Collins TN, Wang F, Feng GS, Gotoh N, Zhang X. 2014. Frs2α and Shp2 signal independently of Gab to mediate FGF signaling in lens development. **Journal of Cell Science** 127:571–582. (PMID: 24284065)

Collins TN, Mao Y, Li H, Bouaziz M, Hong A, Feng GS, Wang F, Quilliam LA, Chen L, Park T, Curran T, Zhang X. 2018. Crk proteins transduce FGF signaling to promote lens fiber cell elongation. **eLife.** 7:e32586.

3. FGF signaling requires Shp2 protein phosphatase to activate Ras pathway

We showed that Shp2 modulates Sprouty2 in a complex feedback loop to fine tune the activity of Ras-MAPK signaling in lens and lacrimal gland development. In retina development, loss of Shp2 prevented FGF-

induced transformation of the early eye primordia into the retinal tissues. Interestingly, we also showed that depletion of Shp2 after retina formation led to retinal degeneration in adult animals. In the neural crest, our study shows that Shp2 functions downstream to FGF signaling to induce Alx4 expression, which is required for lacrimal gland development. This mechanism is conserved in human as we identified bilateral lacrimal gland aplasia in a patient carrying *ALX4* mutation.

Pan Y, Carbe C, Powers A, Feng GS, Zhang X. 2010. Sprouty2 modulated Kras signaling rescues Shp2 deficiency during lens and lacrimal gland development. **Development.** 137:1085-1093.

Cai Z, Feng GS, Zhang X. 2010. Temporal requirement of the protein tyrosine phosphatase Shp2 in establishing the neuronal fate in early retinal development. **Journal of Neuroscience.** 30(11):4110–4119

Cai Z, Simons DL, Fu XY, Feng GS, Wu SM, Zhang X. 2011. Loss of Shp2-mediated MAPK signaling in Müller glial cells results in retinal degeneration. **Molecular and Cellular Biology.** 31:2973-2983.

Garg A, Bansal B, Gotoh N, Feng G, Zhong J, Wang F, Kariminejad A, Brooks S and Zhang X. 2017. Alx4 relays sequential FGF signaling to induce lacrimal gland morphogenesis. **PLoS Genetics**. 13(10):e1007047.

4. Downstream pathways of FGF signaling

Nf1 and Pten are negative regulators of Ras and PI3K signaling, respectively. We showed that lens induction required Nf1 function in vivo, which could be substituted by pharmacological inhibition of MEK-ERK signaling. We observed that deletion of Pten strongly elevated Fgf10 protein levels without increasing Fgf10 transcription in the periocular cutaneous squamous cell carcinoma (SCC). The translational activation of Fgf10 by Pten deletion was reversed by genetic disruption of the mTORC1 complex, which also prevented skin tumorigenesis in Pten mutants. We further reported that genetic and pharmacological inhibition of Ras-MAPK pathway impeded epidermal hyperplasia in Pten tumor. Finally, we showed that the Pea3 family transcription factors were direct downstream effector of FGF signaling in lacrimal gland development and they programed the genetic landscape of the lacrimal gland epithelial cells in fate determination.

Carbe C and Zhang X. 2011. Lens induction requires attenuation of ERK signaling by *Nf1*. **Human Molecular Genetics.** 20(7):1315–1323.

Hertzler-Schaefer K, Mathew G, Spandau DF, Somani A, Tholpady S, Chen Y, Zhang X. 2014. Pten loss induces autocrine FGF signaling to promote skin tumorigenesis. **Cell Reports** 6(5):818-26. (PMID: 24582960).

Mathew G, Hannan A, Hertzler-Schaefer K, Wang F, Feng GS, Zhong J, Zhao JJ, Downward J, Zhang X. 2016. Targeting of Ras-mediated FGF signaling suppresses Pten-deficient skin tumor. **Proc Natl Acad Sci U S A.** 113, 13156–13161.

Garg A, Hannan A, Wang Q, Collins T, Teng S, Bansal M, Zhong J, Xu K, Zhang X. 2018. FGF-induced Pea3 transcription factors program the genetic landscape for cell fate determination. **PLoS Genetics.** 14(9):e1007660.

5. Crosstalk of FGF signaling

In the lens, we show that FGF and PDGF antagonize each other through their intrinsic biases toward distinct downstream targets. FGF induces the Ras-MAPK axis to promote lens cell differentiation and activates Etv family transcription factors to stimulate expression of Notch ligand Jag1. In contrast, PDGF preferentially stimulates PI3K to enhance Notch signaling, which is necessary for maintaining the lens progenitor cell pool. In the lacrimal gland, we find that PI3K is activated by both the p85-mediated IGF and Ras-mediated FGF signaling and, together, they prevent expansion of EGF receptor expression from the lacrimal gland stalk to the bud region. In the optic cup, we performed single-cell analysis and showed that FGF signaling regulates the self-renewal, differentiation, and survival of ciliary margin progenitor cells. By stabilizing β-catenin in a GSK3β-independent manner, FGF cooperates with Wnt signaling to specify the retinal pigmented epithelium (RPE), ciliary margin and neural retina fate.

Li H, Mao Y, Bouaziz M, Yu H, Qu X, Wang F, Feng GS, Shawber C, Zhang X. 2019. Lens differentiation is controlled by the balance between PDGF and FGF signaling. **PLoS Biology.** 17(2):e3000133.

*Garg A, Hannan A, Wang Q, Makrides N, Zhong J, Li H, Yoon S, Mao Y, Zhang X. 2020.Etv transcription factors functionally diverge from their upstream FGF signaling in lens development. **eLife.** 9:e51915. **Selected for an eLife digest.*

Wang Q, Tao C, Hannan A, Yoon S, Min X, Peregrin J, Qu X, Li H, Yu H, Zhao J, Zhang X. 2021. Lacrimal gland budding requires PI3K-dependent suppression of EGF signaling. **Science Advances**. 7(27):eabf1068.

Balasubramanian R, Min X, Quinn PMJ, Giudice QL, Tao C, Polanco K, Makrides N, Peregrin J, Bouaziz M, Mao Y, Wang Q, Costa BL, Buenaventura D, Wang F, Ma L, Tsang SH, Pierre JF, Zhang X. 2021. Phase transition specified by a binary code patterns the vertebrate eye cup. **Science Advances.** 7(46):eabj9846.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/sites/myncbi/1bMOrJ6Ni4a5f/bibliography/53233055/public/?sort=date&direction=ascending