BIOGRAPHICAL SKETCH

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NAME: LEVINE, EDWARD M

eRA COMMONS USER NAME (agency login): EDLEVINE

POSITION TITLE: Professor

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

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Middlebury College, Middlebury, VT		05/1984	Biology
SUNY Albany, Albany, NY	BS	05/1986	Biology
SUNY Stony Brook, Stony Brook, NY	PHD	05/1994	Biochemistry and Molecular Biology
University of Washington, Seattle, Washington	Postdoctoral Fellow	10/1999	Mammalian retinal development

A. Personal Statement

My laboratory addresses two areas of importance to vision. In the first, we study the cellular and molecular mechanisms governing mouse retinal development, from the initial patterning events of the optic neuroepithelium through specification of cell fate in the proliferative and multipotential retinal progenitor cells and their postmitotic progeny. Our work incorporates multiple genetic models that are helping us to identify the genetic circuitry driving these processes. The second topic is to understand how the resident retinal glia (Muller glia) contribute to the pathological changes associated with retinal disease and injury, and to discover ways to stimulate regeneration from these cells. We are particularly interested in understanding how the Muller glia alter their differentiation program in retinal injury and proliferative vitreoretinopathy as these situations best reveal the complexity of the barriers to regeneration. Through the Audacious Goals Initiative from the National Eye Institute, we have begun a screen to identify novel factors that promote regenerative properties in adult mouse Muller glia *in vivo.* Our research incorporates mouse genetics, cell and tissue culture, analyses of protein and nucleic acid expression, imaging, and examination of cellular behavior.

B. Positions and Honors

Positions and Employment

1986 - 1988 Research Assistant, W. Alton Jones Cell Science Center, Lake Placid, NY
1999 - 2007 Assistant Professor, Ophthalmology & Visual Sciences, University of Utah, Salt Lake City, UT
1999 - 2007 Adjunct Assistant Professor, Neurobiology & Anatomy, University of Utah
2007 - 2015 Associate Professor, Ophthalmology & Visual Sciences, University of Utah
2007 - 2016 Adjunct Associate Professor, Neurobiology & Anatomy, University of Utah
2015 - 2015 Professor, Ophthalmology & Visual Sciences, University of Utah
2015 - 2017 Adjunct Professor, Ophthalmology & Visual Sciences, University of Utah
2015 - present Professor, Cell & Developmental Biology, Vanderbilt University, Nashville, TN
2015- present Professor, Ophthalmology & Visual Sciences, Vanderbilt University Medical Center

Other Experience and Professional Memberships

Society for Neuroscience, Society for Developmental Biology, Association for Research in Vision and Ophthalmology, International Society for Eye Research
2003 - present Editorial Board Member, Developmental Dynamics
2005 onward ad hoc Reviewer, NIH Peer Review: NCF, BDPE, BVS

2006 - present Scientific Review Committee, Fight for Sight
2007 - 2012 Editorial Board Member, Journal of Ocular Biology, Diseases, and Informatics

Honors

1992 Travel Fellowship, EMBO
1992 Inductee, Sigma Xi
1993 Travel Fellowship, EMBO
1995 - 1998 National Research Scholar Award, NIH
2000 Travel Award, ISER/Alcon
2002 - 2005 Career Development Award, Research to Prevent Blindness, Inc
2007 Sybil H. Harrington Scholar, Research to Prevent Blindness, Inc
2015 - present William A. Black Endowed Chair in Ophthalmology, Vanderbilt University/Vanderbilt University Medical Center

C. Contribution to Science

1. My early studies centered on the factors associated with regeneration and adult neurogenesis in the goldfish visual system, a classical model for studying CNS regeneration and plasticity. I assisted on identifying intermediate filament proteins associated with retinal ganglion cell axon regeneration following optic nerve crush. For my primary research, I identified transcription factors that could drive adult neurogenesis in the retina. Through an RT-PCR based screen and subsequent expression analyses, I discovered the Vsx1 and Vsx2 homeobox genes and determined that these genes were expressed in the ciliary margin stem cell zone, during regeneration after retinal injury, and in differentiated bipolar cells. With a fellow graduate student, we showed that both genes are expressed in an evolutionarily conserved fashion during embryonic retinal development. Both genes are now known to have key roles in human ocular development and function: human Vsx1 mutations are linked to posterior polymorphous dystrophy and keratoconus; human Vsx2 mutations are linked to non-syndromic, bilateral microphthalmia.

    a. Glasgow E, Druger RK, Levine EM, Fuchs C, Schechter N. Plasticin, a novel type III neurofilament protein from goldfish retina: increased expression during optic nerve regeneration. Neuron. 1992 Aug;9(2):373-81. PubMed PMID: 1379821.
    b. Levine EM, Schechter N. Homeobox genes are expressed in the retina and brain of adult goldfish. Proc Natl Acad Sci U S A. 1993 Apr 1;90(7):2729-33. PubMed PMID: 8096640; PubMed Central PMCID: PMC46169.
    c. Levine EM, Hitchcock PF, Glasgow E, Schechter N. Restricted expression of a new paired-class homeobox gene in normal and regenerating adult goldfish retina. J Comp Neurol. 1994 Oct 22;348(4):596-606. PubMed PMID: 7836564.
    d. Passini MA, Levine EM, Canger AK, Raymond PA, Schechter N. Vsx-1 and Vsx-2: differential expression of two paired-like homeobox genes during zebrafish and goldfish retinogenesis. J Comp Neurol. 1997 Nov 24;388(3):495-505. PubMed PMID: 9368856.

2. The widely studied ocular retardation J (orJ) mouse harbors a Vsx2 null mutation and has become the definitive animal model for understanding the causes of microphthalmia due to defects in retinal development. We were the first to demonstrate that misregulation of cell cycle proteins is a major contributor to the microphthalmic phenotype in orJ, and that the alterations in retinal development are due to changes in intrinsically defined progenitor cell functions and to alterations in the environment, thus revealing the complex and central role of Vsx2 in retinal and ocular development. Once human genetic variants of Vsx2 were identified, we created knock-in mutant mice harboring mutations to match those found in humans. We determined that Vsx2 has a gatekeeper function; to allow the retinal developmental program to proceed without interference from other tissue programs. We also uncovered the first reported function for the CVC domain, a highly conserved sequence in the Vsx gene family. We also showed that neurogenic progenitors/glia persist in the adult retina of orJ mice, to date the only genetic mouse model known to support adult neurogenesis without additional manipulation.

a. Green ES, Stubbs JL, Levine EM. Genetic rescue of cell number in a mouse model of microphthalmia: interactions between Chx10 and G1-phase cell cycle regulators. Development. 2003 Feb;130(3):539-52. PubMed PMID: 12490560.

b. Dhomen NS, Balaggan KS, Pearson RA, Bainbridge JW, Levine EM, Ali RR, Sowden JC. Absence of chx10 causes neural progenitors to persist in the adult retina. Invest Ophthalmol Vis Sci. 2006 Jan;47(1):386-96. PubMed PMID: 16384989; PubMed Central PMCID: PMC2423807.

c. Zou C, Levine EM. Vsx2 controls eye organogenesis and retinal progenitor identity via homeodomain and non-homeodomain residues required for high affinity DNA binding. PLoS Genet. 2012 Sep;8(9):e1002924. PubMed PMID: 23028343; PubMed Central PMCID: PMC3447932.

d. Sigulinsky CL, German ML, Leung AM, Clark AM, Yun S, Levine EM. Genetic chimeras reveal the autonomy requirements for Vsx2 in embryonic retinal progenitor cells. Neural Dev. 2015 Apr 27;10:12. PubMed PMID: 25927996; PubMed Central PMCID: PMC4450477.

3. Through genetic analysis of germline knockout and conditional knockout mouse models, we have identified key regulators and mechanisms governing optic cup regionalization, retinal identity, progenitor proliferation, and neurogenic output. Of note, we showed with germline knockout studies of the Lhx2 transcription factor that it acts as an organizer molecule for optic cup formation and regional patterning, in part through direct regulation of factors such as Vsx2, and through setting up the competence for optic neuroepithelial cells to respond in specific manners to key signaling factors. We also demonstrated a key role for Lhx2 in regulating retinal progenitor maintenance and transitions in competence states. Other works have shown similar properties for the cell cycle protein Cyclin D1 and Vsx2, with notable links to both cell autonomous molecular networks and signaling pathways such as the hedgehog pathway.

a. Sigulinsky CL, Green ES, Clark AM, Levine EM. Vsx2/Chx10 ensures the correct timing and magnitude of Hedgehog signaling in the mouse retina. Dev Biol. 2008 May 15;317(2):560-75. PubMed PMID: 18417110; PubMed Central PMCID: PMC2671289.

b. Das G, Choi Y, Sicinski P, Levine EM. Cyclin D1 fine-tunes the neurogenic output of embryonic retinal progenitor cells. Neural Dev. 2009 May 5;4:15. PubMed PMID: 19416500; PubMed Central PMCID: PMC2694796.

c. Yun S, Saijoh Y, Hirokawa KE, Kopinke D, Murtaugh LC, Monuki ES, Levine EM. Lhx2 links the intrinsic and extrinsic factors that control optic cup formation. Development. 2009 Dec;136(23):3895-906. PubMed PMID: 19906857; PubMed Central PMCID: PMC2778739.

d. Gordon PJ, Yun S, Clark AM, Monuki ES, Murtaugh LC, Levine EM. Lhx2 balances progenitor maintenance with neurogenic output and promotes competence state progression in the developing retina. J Neurosci. 2013 Jul 24;33(30):12197-207. PubMed PMID: 23884928; PubMed Central PMCID: PMC3721834.

4. We have developed and characterized several genetic mouse models that have benefited the vision research community and beyond. In addition to the Vsx2 knock-in missense mutant mice (described in Zou and Levine, 2012), the Hes1CreERT2 driver (described in Yun et al. 2009 and Gordon et al., 2013), we developed a GFP reporter line that is expressed in Muller glia and a tamoxifen inducible Cre line that can be used for lineage analysis or manipulating gene expression in Muller Glia. These lines have been used to study the roles of Muller Glia in retinal degeneration and regeneration. We openly distribute these lines to laboratories in the United States and abroad.

a. Wohl S, Jorstad N, Levine EM, Reh TA. Muller glial microRNAs are required for the maintenance of glial homeostasis and retinal architecture. Nature Communications. 2017 Nov;8(1):1603 PubMed PMID:29150673; PubMed Central PMCID: PMC5693933

b. Pollak J, Wilken MS, Ueki Y, Cox KE, Sullivan JM, Taylor RJ, Levine EM, Reh TA. ASCL1 reprograms mouse Muller glia into neurogenic retinal progenitors. Development. 2013 Jun;140(12):2619-31. PubMed PMID: 23637330; PubMed Central PMCID: PMC3666387.

c. Heynen SR, Meneau I, Caprara C, Samardzija M, Imsand C, Levine EM, Grimm C. CDC42 is required for tissue lamination and cell survival in the mouse retina. PLoS One. 2013;8(1):e53806. PubMed PMID: 23372671; PubMed Central PMCID: PMC3553133.

d. Vázquez-Chona FR, Clark AM, Levine EM. Rlbp1 promoter drives robust Müller glial GFP expression in transgenic mice. Invest Ophthalmol Vis Sci. 2009 Aug;50(8):3996-4003. PubMed PMID: 19324864.

5. Retinal regeneration occurs in fish from an intrinsic source, the Muller glia. The human and mouse retinas are non-regenerative, and the Muller glia respond to injury and pathologies by becoming reactive, which has both protective and deleterious effects. To better understand how to control Muller glia reactivity and promote regeneration, we have been studying the role of cyclin-dependent kinase inhibitors in Muller glia. We determined through genetic approaches that p27Kip1 acts in Muller glia to prevent reactive behavior when the retina is normal. We also determined that reactivity induced by p27Kip1 inactivation is compatible with retinal homeostasis, thereby suggesting that interventions that limit the detrimental properties of reactive glia will better support normal tissue function in pathological conditions. Controlling glial reactivity is also likely to be an important step in promoting regeneration from Muller glia.

   a. Vázquez-Chona FR, Swan A, Ferrell WD, Jiang L, Baehr W, Chien WM, Fero M, Marc RE, Levine EM. Proliferative reactive gliosis is compatible with glial metabolic support and neuronal function. BMC Neurosci. 2011 Oct 10;12:98. PubMed PMID: 21985191; PubMed Central PMCID: PMC3203081.
   b. Jones BW, Watt CB, Frederick JM, Baehr W, Chen CK, Levine EM, Milam AH, Lavail MM, Marc RE. Retinal remodeling triggered by photoreceptor degenerations. J Comp Neurol. 2003 Sep 8;464(1):1-16. PubMed PMID: 12866125.
   c. Cunningham JJ, Levine EM, Zindy F, Goloubeva O, Roussel MF, Smeyne RJ. The cyclin-dependent kinase inhibitors p19(Ink4d) and p27(Kip1) are coexpressed in select retinal cells and act cooperatively to control cell cycle exit. Mol Cell Neurosci. 2002 Mar;19(3):359-74. PubMed PMID: 11906209.
   d. Levine EM, Close J, Fero M, Ostrovsky A, Reh TA. p27(Kip1) regulates cell cycle withdrawal of late multipotent progenitor cells in the mammalian retina. Dev Biol. 2000 Mar 15;219(2):299-314. PubMed PMID: 10694424.

Complete List of Published Work in My Bibliography:
http://1.usa.gov/1MAb3FY

D. Research Support

Ongoing Research Support

U01 EY027265, National Eye Institute (NEI)
Levine, Edward M (PI), Patton, James G (PI), David Calkins (PI)
09/01/2016 - 08/31/2019
Novel Activators of Regeneration in Muller Glia
The goal of this grant is to discover new factors that activate regenerative properties in the Muller glia of the retina. This project is funded through the Audacious Goals Initiative at the National Eye Institute
Role: Contact PI

R01 EY013760
Levine, Edward M (PI), National Eye Institute (NEI)
12/01/01-04/30/18
Regulation of Retinal Progenitor Cell Properties
The goal of this grant is to determine how Lhx2 regulates the transition in competence states from the early to late phases of neurogenesis in retinal progenitor cells, and how Vsx2 regulates the timing of onset of retinal neurogenesis.
Role: PI

U01 EY027265-Supplement, National Eye Institute (NEI)
Levine, Edward M (PI), Patton, James G (PI), David Calkins (PI)

09/01/2017 - 08/31/2019
Novel Activators of Regeneration in Muller Glia
This supplement allows us to expand our *in vivo* screen underway in the parent U01 grant
Role: Contact PI

Completed Research Support (last 3 yrs)

P30-EY014800, National Eye Institute (NEI)
Marc, Robert (PI)
07/01/10-06/30/15
Vision Core Grant
This grant provides core research services to laboratories at the University of Utah that are directly engaged in vision research. Dr. Levine is the module director for the Histomics Core, which provides genotyping services, trains users on the departmental cryostats, and manages the cryostats and other core equipment.
Role: Co-Investigator