Dear Author,

Please, note that changes made to the HTML content will be added to the article before publication, but are not reflected in this PDF.

Note also that this file should not be used for submitting corrections.

ARTICLE IN PRESS

Experimental Eye Research xxx (2015) 1-10



Contents lists available at ScienceDirect

Experimental Eye Research

journal homepage: www.elsevier.com/locate/yexer

Review

Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina

Ruth Bejarano-Escobar^a, Guadalupe Álvarez-Hernán^a, Ruth Morona^b, Agustín González^b, Gervasio Martín-Partido^a, Javier Francisco-Morcillo^{a, *}

^a Departamento de Biología Celular, Facultad de Ciencias, Universidad de Extremadura, 06071 Badajoz, Spain ^b Departamento de Biología Celular, Facultad de Biología, Universidad Complutense, 28040 Madrid, Spain

ARTICLE INFO

Article history: Received 6 October 2014 Received in revised form 24 June 2015 Accepted in revised form 25 June 2015 Available online xxx

Keywords: Transcription factor LIM-homeobox Eye development Neural retina Islet-1 Retinogenesis

ABSTRACT

The LIM-homeodomain transcription factor Islet-1 (Isl1) has been widely used as a marker of different subtypes of neurons in the developing and mature retina of vertebrates. During retinal neurogenesis, early Isl1 expression is detected in the nuclei of neuroblasts that give rise to ganglion, amacrine, bipolar, and horizontal cells. In the mature retina, Isl1 expression is restricted to the nuclei of ganglion cells, cholinergic amacrine cells, ON-bipolar cells, and subpopulations of horizontal cells. Recent studies have explored the functional mechanisms of Isl1 during specification and differentiation of these retinal cell types. Thus, conditional inactivation of *Isl1* in the developing mouse retina disrupts retinal function, and also results in optic nerve hypoplasia, marked reductions in mature ganglion, amacrine, and bipolar cells, and substantial increase in horizontal cells. Furthermore, conditional knockout shows delayed ganglion cell axon growth, ganglion cell axon guidance error, and ganglion cell nerve fiber defasciculation. These data together suggest a possible role for Isl1 in the early differentiation and maintenance of different vertebrate retinal cell types. This review examines whether the expression pattern of Isl1 during vertebrate retinal development is conserved across vertebrate species, and discusses current understanding of the developmental functions of Isl1 in retinogenesis.

© 2015 Published by Elsevier Ltd.

1. Development of the vertebrate retina

Embryonic retinal neurogenesis in vertebrates begins with an apparently uniform population of neuroepithelial cells, the retinal progenitor cells. After cell division on the apical (ventricular) side, post-mitotic cells that are committed to a certain precursor lineage are thought to detach their end-feet and migrate towards a specific lamina where they will start their morphological development. This is not valid for horizontal cells which can be generated by nonapical mitosis in the zebrafish (Godinho et al., 2007) and chick retina (Edqvist and Hallböök, 2004, 2008; Boije et al., 2009). The generation of the different cell types is under temporal control. Thus, retinal ganglion cells are generated first, followed in overlapping phases by horizontal cells, cone photoreceptor cells, amacrine cells, rod photoreceptor cells, bipolar cells, and, finally, Müller glial cells (Young, 1985; Cepko et al., 1996; Rapaport et al., 2004;

* Corresponding author.

E-mail address: morcillo@unex.es (J. Francisco-Morcillo).

http://dx.doi.org/10.1016/j.exer.2015.06.021 0014-4835/© 2015 Published by Elsevier Ltd.

Lamb et al., 2007).

Many genetic and molecular studies have revealed that genes controlling retinal cell fate are remarkably conserved among vertebrates, and, in some cases, even across the animal kingdom. It has been proposed that these genes encode intrinsic and extrinsic factors that control the multipotency of retinal progenitors, the generation of cell diversity, and the establishment of the clock that determines the ordered generation of retinal cell types. Thus, extrinsic factors are presumed to activate signaling pathways that often result in the expression of particular transcription factors that act in distinct combinations to either define a certain competence/ specification state of retinal progenitors or determine retinal cell types. During recent years, the search for intrinsic factors has led to the identification of many transcription factors of the homeodomain (HD) and activator-type basic helix-loop-helix (bHLH) protein families that play a pivotal role in the control of cell cycle exit and cell fate determination. Combinatorial transcription factor coding based on the differential expression of these transcription factors has been identified as a common mechanism underlying neuronal cell type diversity in the vertebrate retina (for reviews, see

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62

63

64

65

Ohsawa and Kageyama, 2008; Xiang, 2013). In the present communication, we provide an overview of the expression and function of Islet-1 (Isl1), a member of the LIM-HD family of transcription factors with a prominent role in retinogenesis in different vertebrate species.

2. LIM-HD transcription factors in vertebrate development

The LIM proteins are an evolutionarily conserved family of homeodomain-containing transcription factors that also contain two specialized zinc finger motifs named LIM domains after the founding members Lin-11, Islet-1, and Mec-3 (Liu et al., 2000). These domains are zinc fingers that coordinate two zinc ions and mediate protein-protein interactions (Bhati et al., 2008). Studies of diverse vertebrate models have established that the LIM-HD factors are critical for the development of specialized cells in multiple tissue types, including the nervous system (Ericson et al., 1992; Pfaff et al., 1996; Porter et al., 1997; Moreno et al., 2008a,b,c; 2010, 2012; Deng et al., 2014), the heart (Pandur et al., 2013), the urogenital system (Kobayashi et al., 2004; Kaku et al., 2013), and such endocrine organs such as the pituitary gland (Mullen et al., 2007) and the pancreas (Ahlgren et al., 1997). In the case of the developing vertebrate central nervous system, LIM-HD transcription factors play crucial roles in controlling cell fate specification, survival and differentiation, and axonal projection patterns (Tsuchida et al., 1994; Hobert and Westphal, 2000; Bach, 2000).

2.1. LIM-HD transcription factors and development of the retina

In the case of the developing and mature vertebrate visual system, several of the LIM-HD transcription factors are particularly important in the specification and maintenance of cellular phenotypes. Thus, Lim1 (or Lhx1) is expressed by differentiating horizontal cells throughout retinal development (Liu et al., 2000; Edqvist and Hallböök, 2004; Poche et al., 2007). Lhx2 is involved in the specification of the eye field, and, together with Rax, Pax6, Six3, Six6, ET/Tbx3, and tll/Nr2e1, is considered to be an eye-field transcription factor (EFTF) (Chow and Lang, 2001). Thus, the absence of *Lhx2* in mouse causes anophthalmia (Porter et al., 1997). It also plays a key role in the progressive morphogenesis of the developing eye, including patterning of the neuroretina (Yun et al., 2009; Roy et al., 2013). Lim3 (Lhx3) is specifically expressed by postmitotic bipolar cells in the developing chick retina (Edqvist and Hallböök, 2004) and in a subset of bipolar cells in the mature mouse retina (Kim et al., 2008). Fischer et al. (2008) have shown that Lim3 and Islet-2 (Isl2) are transiently expressed by differentiating photoreceptors in the developing chick retina. Isl2 is also expressed by ganglion cells in the retina (Edqvist et al., 2006) and contributes to the guidance of retinal ganglion cell axons (Pak et al., 2004). More recently, it has been reported that the expression of LHX9 and LHX2, LHX3 and LHX4, and LHX6 may identify many retinal progenitors and retinal cell types/subtypes in the developing and mature mouse retina (Balasubramanian et al., 2014).

3. The LIM-homeodomain Islet-1 transcription factor

Isl1 was identified as a protein that binds to enhancer elements, and Isl1 mRNA is expressed in insulin-producing cell lines and islet cells (Karlsson et al., 1990). During embryonic development, Isl1 is critical for the differentiation of many organs. Isl1 null mutations in mice are lethal, with the embryos dying at E10.5 with severe abnormalities in the pancreas, heart, limbs, and central nervous system (Pfaff et al., 1996; Ahlgren et al., 1997; Cai et al., 2003). Thus, Isl1 is expressed in all pancreatic islet cell types and is necessary for the development of the dorsal exocrine pancreas and for the

generation of all endocrine cells (Thor et al., 1991; Ahlgren et al., 1997). Isl1 is also involved in vertebrate heart development, and its expression has been detected in adult cardiac stem cells, suggesting a possible function in cardiac repair and regeneration (Moretti et al., 2007; Pandur et al., 2013). Lineage studies have also revealed that Isl1 progenitors contribute to a majority of hindlimb cells, but its expression is downregulated as these progenitor cells migrate into the hindlimb (Narkis et al., 2012). However, *Isl1* is best known for its role in diverse aspects of regional development and neuronal differentiation in the central nervous system. Shh induces its expression in the nuclei of cells in the ventral region of the spinal cord, lateral to the floor plate (Ericson et al., 1992). Thus, motor neurons express this transcription factor soon after their final mitotic division and before the appearance of other differentiated motor neuron features (Ericson et al., 1992; Tsuchida et al., 1994). It is also essential for motor neuron cell body localization, motor column formation, and axon growth (Pfaff et al., 1996; Liang et al., 2011). Isl1 and Brn3a act epistatically to regulate core gene expression program of developing sensory neurons of the trigeminal ganglion and dorsal root ganglia at all levels of the neural axis repressing early regulators of neurogenesis (Dykes et al., 2011). Isl1 is also required for the development of restricted forebrain cholinergic neurons (Ericson et al., 1992; Wang and Liu, 2001; Elshatory and Gan, 2008), and is involved in the control of axon guidance in the telencephalon of mammals (López-Bendito et al., 2006). It has been used as a marker of cell types, regional subdivisions, and specific nuclei during development of the central nervous system in different vertebrates (Moreno et al., 2008a,b,c; 2010, 2012). It also plays a role in differentiating inner ear neurons in conjunction with other transcription factors (Deng et al., 2014). Finally, Isl1 orchestrates the early differentiation and maintenance of various cell types in the retina of different vertebrates (Table 1). Here, we provide an overview of the expression and function of Isl1 during retinogenesis in different vertebrate species.

4. Isl1 expression in the mature and developing retina across vertebrate phylogeny: its role in retinogenesis

The pattern of Isl1 expression is very similar in the mature and developing retinas of multiple vertebrate species (Figs. 1 and 2). Thus, Isl1 is detected in the nuclei of subpopulations of mature ganglion, amacrine, bipolar, and horizontal cells in different species of fish (Fig. 1A and B) (Shkumatava and Neumann, 2005; Bejarano-Escobar et al., 2009, 2010; 2012, 2014), amphibians (Fig. 1F) (Álvarez-Hernán et al., 2013), reptiles (Fig. 2A) (Francisco-Morcillo et al., 2006), birds (Fig. 2B) (Edqvist et al., 2006, 2008; Fischer et al., 2007; Boije et al., 2009; Okamoto et al., 2009; Suga et al., 2009; Shirazi Fard et al., 2013), and mammals (Fig. 2C) (Galli-Resta et al., 1997; Haverkamp et al., 2003; Elshatory et al., 2007a,b; Poche et al., 2007; Mu et al., 2008; Pan et al., 2008; Guduric-Fuchs et al., 2009; Li et al., 2014). During retinal development, the expression of Isl1 is consistent with that expected for a transcription factor involved in retinal neuroblast differentiation, following the gradients of maturation described during vertebrate retinogenesis (Figs. 1C-E, G, H and 2D-L) (Edqvist et al., 2006; Francisco-Morcillo et al., 2006; Elshatory et al., 2007a; Boije et al., 2008; Bejarano-Escobar et al., 2009, 2010; 2012; Guduric-Fuchs et al., 2009; Álvarez-Hernán et al., 2013). Because Isl1-null mice die at E10.5, before the onset of retinal neurogenesis (Pfaff et al., 1996), the role of Isl1 in retinogenesis is poorly understood. However, recent studies have shown that its conditional deletion in the developing retina induces variations in the numbers of ganglion, cholinergic amacrine, bipolar, and horizontal cells (Elshatory et al., 2007b; Mu et al., 2008; Pan et al., 2008; Whitney et al., 2011). Furthermore, some authors have described a transient expression

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

ARTICLE IN PRESS

R. Bejarano-Escobar et al. / Experimental Eye Research xxx (2015) 1–10

Table 1

Species	Bibliography	Most relevant events described
Fish		
Zebrafish (Danio rerio, Hamilton 1822)	Korzh et al., 1993	Onset of Isl1 immunoreactivity in the retina
	Link et al. 2000	 IsI1-Immunoreactive neurons appear after 24hpf. IsI1 immunoreactivity in the mature retina
	Link et al., 2000	- Expressed in ganglion, amacrine, bipolar, and horizontal cell precursors.
	Masai et al., 2000	Isl1 expression in the developing retina
		- Isl1 mRNA expression is initiated at 27 hpf in the ventronasal retina.
		 Ine expression progressively spreads to the dorsal and temporal retina. Isl1 mRNA is expressed in the CCL and in the INI
	Shkumatava et al., 2004	Isl1 immunoreactivity in the developing and mature retina
		- Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar,
Tarah (Tinas tinas Lingana 1759)	Bejarano-Escobar et al., 2009	and horizontal cells in the differentiating and mature retina.
Tench (Tinca tinca, Linnaeus 1758)		- Expressed in the first newborn ganglion cells in the undifferentiated neural
		retina.
		- Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar,
	Reissen Fresher et al. 2010	and horizontal cells in the differentiating and mature retina.
(Solea senegalensis, Kaup 1858)	Bejarano-Escobar et al., 2010	- Expressed in the first newborn ganglion cells in the undifferentiated neural
(soled senegulensis, Ruup 1050)		retina.
		- Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar,
	Pointano Frankar et al. 2012	and horizontal cells in the differentiating and mature retina.
Sinaii-spotted Catsnark (Scyliorhinus canicula Linnaeus 1758)	bejarano-Escobar et al., 2012	- Expressed in migrating neuroblasts and in the first newborn ganglion cells in
(Scyliorninus canicula, Linnaeus 1758)		the undifferentiated neural retina.
		- Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar
		and horizontal cells in the developing and mature retina.
South African clawed frog	Álvarez-Hernán et al. 2013	Isl1 immunoreactivity in the developing and mature retina
(Xenopus laevis, Daudin 1802)	Alvarez Herman et al., 2015	- Expressed in migrating neuroblasts and in the first newborn ganglion cells in
		the undifferentiated neural retina.
		- Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar,
Reptiles		and norizontal cens in the differentiating and mature retina.
Reptiles Mediterranean turtle (<i>Mauremys leprosa</i> , Schweigger 1812)	Francisco-Morcillo et al., 2006	Isl1 immunoreactivity in the developing and mature retina
		- Expressed in the first postmitotic neuroblasts.
		 Expressed in migrating neuroblasts and in the first newborn ganglion cells in the undifferentiated neuroblastical
		- Expressed in many differentiated ganglion cells subsets of amacrine bipolar
		and horizontal cells in the differentiating and mature retina.
		- Expressed in the nuclei of a subset of photoreceptors.
Birds	Austin et al. 1005	Patinal determination by Notch coloction
CHICK (Guilus guilus, Lillideus 1758)	AUSUII et al., 1990	- Used as a ganglion cell-specific marker throughout chick retinal development
	Fischer et al., 2002	Production of ganglion cells in the retinal margin
		- In the post-hatch retina, Isl1 is expressed in differentiating neurons located in
		the progenitor zone.
		 in the post-match returnation is expressed in choinergic anactine cells, many bipolar cells, and most ganglion cells.
	Francisco-Morcillo et al., 2005	Molecular mechanisms involved in retinal cell differentiation
		- Expressed in migrating neuroblasts and in the first newborn ganglion cells in
		the undifferentiated neural retina.
		and horizontal cells in the differentiating and mature retina
		- Fgf19-positive horizontal cells and Isl1-positive cells never overlap.
	Edqvist et al., 2006	Isl1 immunoreactivity in the developing retina
		- Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal
		- Expressed in the nuclei of a subset of photorecentors probably due to
		antibody cross-reactivity with Isl2.
	Fischer et al., 2007	Identification of different subsets of horizontal cells
		 Most of the Isl1-positive horizontal cells also express trkA, but only a few of them also express calentinin
	Boije et al 2008	mRNA expression of different transcription factors in the developing retina
	2010 Ct al., 2000	- Isl1 mRNA expression is first detected by HH20.
		- Isl1 mRNA expression is detected in ganglion, amacrine, bipolar, and
		horizontal cells, but not in photoreceptors.
	Edqvist et al., 2008	Molecular mechanisms involved in horizontal cell differentiation
		- The birth of Isl1-positive horizontal cells neaked between F4 and F5
		- Expressed in the axonless horizontal cell subtype.
	Fischer et al., 2008	Isl1 immunoreactivity in the developing retina
		- Isl1 is not expressed by differentiating photoreceptors.
		(continued on next page)

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

R. Bejarano-Escobar et al. / Experimental Eye Research xxx (2015) 1–10

Table 1 (continued)

1	
2	
3	
4 r	
5	
0 7	
/ 8	
9 9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24 25	
20 26	
20 27	
21 70	
20 20	
20	
30	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49 50	
5U 51	
51 52	
J∠ 52	
55 54	
55	
55 56	
57	
58	
59	
60	
61	
62	
63	
64	

Mammals Molecular mechanisms involved in macrine cell differentiation (EG) and into the mature return. Mammals Suga et al. 2009 Molecular mechanisms involved in horizontal cell differentiation (EG) and into the mature return. Mammals Suga et al. 2009 Molecular mechanisms involved in horizontal cell differentiation (EG) and into the mature return. Mammals Suga et al. 2009 Molecular mechanisms involved in horizontal cell differentiation (EG) and into the mature return. Mammals Suga et al. 2007 Elshatory et al. 2007a Mass musculus, linnaeus 1758) Elshatory et al. 2007a Elshatory et al. 2007a Muse musculus, linnaeus 1758) Elshatory et al. 2007a Elshatory et al. 2007b Muse musculus, linnaeus 1758) Elshatory et al. 2007a Elshatory et al. 2007b Muse et al. 2008 Molecular mechanisms involved in horizontal cells and holinergic macrine cells. Muse musculus, linnaeus 1758) Fun et al. 2007b Elshatory et al. 2007b Muse et al. 2008 Molecular mechanisms involved in mechanism involved in returnal gangion cell development Muse et al. 2014 Vittury et al. 2017 Notecular mechanisms involved in returnal gangion cell development Muse et al. 2018 Molecular mechanisms involved in retural ganglion cells et al. 2018	Species	Bibliography	Most relevant events described
Mammals - The chillengic amacrine cells cepress IsIl with the onset of differentiation Mammals - Suga et al, 2009 Molecular mechanisms involved in horizontal cell differentiation Mammals - Suga et al, 2009 Sint distribution cells in the onset of differentiation Mammals - Suga et al, 2009 Sint distribution cells in the onset of differentiation Mammals - Sint distribution cells in the onset of differentiation Musse - Suga et al, 2007 Sint distribution cells in the onset of differentiation Musse - Supressed tim the anomet of sint cells interess whyce change into Type II horizontal cells. Such not differentiation of Type III horizontal cells. Such not differentiation of popular cells. And large maintained in them. Musse - Eshatory et al, 2007a III inmunoractivity in the developing cells. III et al., 2014 - Eshatory et al, 2007a III inmunoractivity in the developing cells. Mus et al, 2008 - Eshatory et al, 2007a - Eshatory et al, 2007a - Eshatory et al, 2007a Mu et al, 2008 - Not expressed in differentiation and subtypes - Eshatory et al, 2007a - Supressed differentiation and subtype et al, 2007a Wu et al, 2012 - Supressed differenti		Stanke et al., 2008	Molecular mechanisms involved in amacrine cell differentiation
Okamoto et al. 2009 Moiecular mechanisms involved in hozicotal cell differentiation Suga et al. 2009 First detected immunobischemically at E3.5 in gangion cells. Ammunols Eist ad cell and cell are required for the subtype-specific morphogenesis of positive horizontal cells at elevelopmental sugaes. Mammols Eist actor equired for the subtype-specific morphogenesis of positive horizontal cells at elevelopmental sugaes. Mammols Eist actor equired for the subtype-specific morphogenesis of positive horizontal cells at elevelopmental sugaes. Mammols Eist actor equired for the subtype-specific morphogenesis of positive horizontal cells. In the developing retina Massee Eist actor et al. 2007a Eist actor et al. 2007a Bist actor et al. 2007a Eist actor et al. 2007a Eist actor et al. 2007a Massee Eist actor et al. 2007a Eist actor et al. 2007a Eist actor et al. 2007a Massee Eist actor et al. 2007a Eist actor et al. 2007a Eist actor et al. 2007a Massee Eist actor et al. 2008 Forerest for differentiation of tripal actor et al. 2008 Forerest for differentiation of tripal actor actor et al. 2008 Mu et al. 2008 Whitrey et al. 2017 Fore third agrafion cell development. Eist actor et al. 2008 Whitrey et al. 2016 Whitrey et al. 2018 Eist actor et			- The cholinergic amacrine cells express Isl1 with the onset of differentiation (E6) and into the mature retina.
Animals - Chronotopographical expression pattern of 181 during retinal development. Manuals - Signes et al., 2009 - Signes et al., 2009 Manuals - Signes et al., 2007 - Signes et al., 2007 Manuals - Signes et al., 2007 - Signes et al., 2007 Manuals - Signes et al., 2007 - Signes et al., 2007 Manuals - Eshatory et al., 2007a - Eshatory et al., 2007a Manuals - Eshatory et al., 2007a - Eshatory et al., 2007a Manuals - Eshatory et al., 2007b - Espressed in developing retinal Manuals - Eshatory et al., 2007b - Espressed during tertinal ganglion cell sand subtypes of animacrine and bypolar cells, and later maintained in them. Manuals - Eshatory et al., 2007b - Espressed in developing retinal and subtypes of animacrine and bypolar cells, and later maintained in them. Manuals - Eshatory et al., 2007b - Espressed in developing and mature borizonal cells. Mut et al., 2008 - Molecular mechanisms involved in retinal ganglion cell development - Signess et al., 2008 - Not expression in developing and anture borizonal cells. Mut et al., 2008 - Molecular mechanisms involved in retinal ganglion cell development - Signess et al., 2008 - Notecular mechanisms involved in retinal ganglion cell development - Signes et al., 2008		Okamoto et al., 2009	Molecular mechanisms involved in horizontal cell differentiation
Suga et al., 2009 - Fgt19-opsittye horizontal cell sum 181-positive cells fewer overlap. Marmads - Is first detected immunohistochemically at 23.5 im ganglion cells. Marmads - Is first detected immunohistochemically at 23.5 im ganglion cells. Mouse - Is first detected immunohistochemically at 23.5 im ganglion cells. (Mis musculus, Linnaeus 1758) - Espressed diring the matanation of retinal ganglion cells and subtypes of amacrine and bipolar cells. - Overespression of SI in Type I horizontal cells. - Spressed diring the matanation of retinal ganglion cells and subtypes of amacrine and bipolar cells. (Mis musculus, Linnaeus 1758) - Espressed diring the matanation of retinal ganglion cell and subtypes of amacrine and bipolar cells. - U et al., 2007b - Not expressed in developing and mature horizontal cells. - Mu et al., 2007b - Not expressed in developing cella and subtypes of amacrine and bipolar cells. - U et al., 2014 - Molecular mechanisms involved in retinal ganglion cell development - sill and Provad 21 (cma zonnatice). - Sill and Provad 21 (cma zonnatice). - Not expressed in development - sing anglion cell development - sill and Provad 21 (cma zonnatice). - Sill and Provad 21 (cma zonnatice). - Not expressed in retinal ganglion cell development - sill and Provad 21 (cma zonnatice). - Wu et al., 2008 - Wu et al., 2008 - Note expressed in development - sing angglion cell d		· · · · · · · · · · · · · · · · · · ·	- Chronotopographical expression pattern of Isl1 during retinal development.
Mammals Main and Lind Lind Lind Lind Lind Lind Lind Li			- Fgf19-positive horizontal cells and Isl1-positive cells never overlap.
Mammals- Ist Is first detected immunbistochemically at 32.5 in ganglion cells. - Ist I at All unit are required for the subpres-specific morphogenesis of post- migratory horizontal cells at Law Bubby-Sepecific morphogenesis of post- migratory horizontal cells at Law Bubby-Sepecific morphogenesis of post- migratory horizontal cells. Hun troi differentiation of Type II horizontal cells. - Overexpression of Ist II in programs and them. - Post Post Post Post Post Post Post Post		Suga et al., 2009	Molecular mechanisms involved in horizontal cell differentiation
Mammals - Ist1 and Lim1 are required for the subtype-specific morphogenesis of post- migratory horizontal cells at Lei developmental stages. - Ist1 is expressed in the asolites Type II and Type III horizontal cells. Mouse - Ist1 is expressed in the asolites Type II and Type III horizontal cells. - Overexpression of Ist1 in Type II horizontal cells. Mouse - Ist1 is expressed in the asolites Type III and Type III horizontal cells. - Ist1 is expressed in the aveloping refinal expression of Type III horizontal cells. Mouse - Estistatory et al., 2007a Ist1 immunoreactivity in the developing refinal expression of Ist1 in Type III horizontal cells. I et al., 2014 - Expressed durate horizontal cells. - Not expressed in developing and mature horizontal cells. I et al., 2014 - Ist1 and Pould Circma complex to regulate essential target genes involved in gangion cell development - Ist1 and Pould Circma complex to regulate essential target genes involved in gangion cell development - Ist1 and Pould Circma complex to regulate essential target genes involved in gangion cell development - Ist1 and Pould Circma complex to regulate essential target genes involved in treinal gangion cell development - Ist1 and Pould Circma complex to regulate essential target genes involved in retinal gangion cell development - Ist1 and Pould Circma complex to regulate essential target genes involved in retinal gangion cell development - Ist1 and Pould Circma complex to regulate section and UM- homeodonian transcription of the differentiation and UM- homeodonian transcription cell development - Ist1 and Pould Circma complex to regulate sectinal gangion cell development - Ist1 and Pould C			- Isl1 is first detected immunohistochemically at E3.5 in ganglion cells.
MarmolsIsl is expressed in the axonless Type I and Type II horizontal cells. Overexpression of Isl in Type I horizontal cells. 			- Isl1 and Lim1 are required for the subtype-specific morphogenesis of post-
Mammals - Bil is expressed in the cancless Type II and Type III horizontal cells. Mouse - Diverseptication of the internal duces subtype change into Type II horizontal cells hut not differentiation of Type III horizontal cells. Mouse Elshatory et al. 2007a (Mus musculus, Linnaeus 1758) Elshatory et al. 2007b Elshatory et al. 2007b Elshatory et al. 2007b Li et al. 2014 Elshatory et al. 2007b Nu et al. 2008 Nu et al. 2008 Part et al. 2008 For expressed in developing and mature horizontal cells. Molecular mechanism involved in retinal ganglion cell development Elshatory et al. 2008 Nu et al. 2008 For expressed in developing and mature horizontal cells. Molecular mechanism involved in retinal ganglion cell development Elshatory et al. 2008 Vinitney et al. 2008 For expressed in developing et al. 2008 Molecular mechanism involved in retinal ganglion cell development Elshatory et al. 2008 Vinitney et al. 2012 Foreular et al. 2008 Foreular et al. 2008 Wu et al. 2012 Foreular et al. 2008 Foreular et al. 2008 Foreular et al. 2008 Wu et al. 2012 Whitney et al. 2012 Foreular et al. 2008 Foreular et al. 2008 Molecular mechanism involved in retinal gan			migratory horizontal cells at late developmental stages.
Mammais - Overexpression of 181 in Type I horizontal cells induces subtype change into Weise Musculus, Linnaeus 1758) Elshatory et al., 2007a Is1 immunoractivity in the developing retina - Expressed during the maturation of retinal gangion cells and subtypes of amore and bipolar cells, and later maintained in them. - Not expressed in developing and mature horizontal cells. Id is musculus, Linnaeus 1758) Elshatory et al., 2007b Elshatory et al., 2007b Id is a subtype change into amore and bipolar cells, and later maintained in them. - Not expressed in developing and mature horizontal cells. - State in establishing returnal neuronal subtypes Id is a developing and mature horizontal cells. Id is and Pould2 form a complex to regulate sesential target genes involved in gangion cell differentiation. - State and cholinergic amacrine cells. Mu et al., 2008 Mu et al., 2008 Molecular mechanism involved in retinal gangion cell development - State and Dipolar cells. - State and Doublar cells. Mu et al., 2008 Whitney et al., 2011 - Not expressed in development. - State and cooperative functions of retinal gangion cell development. Whitney et al., 2012 Wu et al., 2012 - Molecular mechanism involved in retinal gangion cell methods. - Controls its and starget genes in only its and table pression of 181 and Brab in retinal gangion cell methods. Wu et al., 2015 Wu et al., 2015 - Molecular mechanism involved in retinal gangion cell mevelopment - Pould2 and 181 aret hereins gangion cell			- Isl1 is expressed in the axonless Type II and Type III horizontal cells.
Mammals Type II horizontal cells, but not differentiation of Type III horizontal cells. Mammals Elshatory et al., 2007a Isl immunoractivity in the developing retina (Mus musculus, Linnaeus 1758) Elshatory et al., 2007b - Expressed and ubpolar cells, and later maintained in them. . Not expressed in developing retina end bipolar cells, and there maintained in them. - Not expressed in developing retina . Not expressed in developing and matter horizontal cells. Role in establishing retinal neuronal subtypes . Controls the differentiation. - Expressed in adveloping neuronal subtypes . Controls the differentiation. - Expressed in adveloping retina . Not expressed in adveloping retina - Not expressed in developing retina . Horizontal cells, and Later maintained in them. - Not expressed in developing retina . Individe and the matterination of hipolar cells. Role in establishing retinal neuronal subtypes . Controls the differentiation. - Bill and Poul42 (Birtab) in development . Horizontal cell structure for the differentiation and survival of ancrine and bipolar cells. - Involved in retinal ganglion cell development . Horizontal cell number - Although Is11 is not expressed in horizontal cell number - Horizontal cell number . Horizontal cell number - Although Is11 is not expressed in horizontal cell angagl			- Overexpression of Isl1 in Type I horizontal cells induces subtype change into
Mammads Eishatory et al., 2007a Isil immuoreactivity in the developing etta. Mouse Eishatory et al., 2007a Isil immuoreactivity in the developing etta. (Mus musculus, Linnaeus 1758) Eishatory et al., 2007b - Szpressed during time and topolar cells and cholinergic amacrine cells. Isi i muoreactivity in the developing and mature horizontal cells. - Not expressed in developing and mature horizontal cells. Isi i and Hould2 form a complex to regulate essential targe greenes involved in settial agailon cell development - Isi and Hould2 form a complex to regulate essential targe greenes involved in a gangion cell development Mu et al., 2008 Molecular mechanism involved in retinal agailon cell development No version of the differentiation and survival of retinal agailon cell development - Involved in retinal agailon cell development No version of subpopulations of amacrine and bipolar cells. - Distinct as well as redunation functions between Pould2 (Brabba and Isl) Vinitney et al., 2018 Whitney et al., 2011 Molecular mechanism involved in retinal agailon cell development. Vu et al., 2012 Wu et al., 2015 Molecular mechanism sinvolved in retinal agailon cell development Vinitney et al., 2015 Wu et al., 2015 Molecular mechanism involved in retinal agailon cell development Vu et al., 2015 Wu et al., 2015 Molecular mechanism involved in retinal ag			Type II horizontal cells, but not differentiation of Type III horizontal cells.
Mouse Eishatory et al., 2007a Isil immuoreactivity in the developing retina (Mus musculus, Linnaeus 1758) - Expressed and during the maturation of retinal gangion cells and subtypes of amacrine and bipolar cells, and later maintained in them. . Not expressed in developing and mature horizontal cells. - Expressed and developing and mature horizontal cells. . Not expressed in developing and mature horizontal cells. - Controls the differentiation of bipolar cells and choinergic amacrine cells. . Not expressed in adveloping retina - Controls the differentiation. - Bill and Poul42 (orm a complex to regulate essential target genes involved in gangion cell development . Isil and Poul42 (orm a complex to regulate essential target genes involved in gangion cell development - Bill and Poul42 (orm a complex to regulate essential target genes involved in gangion cell development . Bill and Poul42 (orm a complex to regulate essential target genes involved in retinal gangion cell development - Bill and Poul42 (Birlab) in development . Horize et al., 2008 - Molecular mechanisms involved in retinal gangion cell development . Involve et al., 2014 - Nonevenent of botip parelle development . Involve et al., 2015 - Nonevenent of botip parelle development . Not expressed in horizontal cell number - Athough IsH is not expressed in horizontal cell number . Involve et al., 2015 - Nonevenant cell number - Athough IsH	Mammals		Type in nonzontal tens, out not amerentation of Type in nonzontal tens,
(Mus musculus, Linnaeus 1758) - Expressed during the maturation of retinal ganglion cells and subtypes of amacrine and bipolar cells, and later maintained in them. - Not expressed in developing and mature horizontal cells. Elshatory et al., 2007b - Not expressed in moveloping and mature horizontal cells. Li et al., 2014 - Not expressed in moveloping and mature more horizontal cells. Mu et al., 2008 - Not expressed in developing and mature mature in the initial specification of bipolar cells and cholinergic amacrine cells. Mu et al., 2008 - Not expressed in any eveloping and mature mature specific speci	Mouse	Elshatory et al 2007a	Isl1 immunoreactivity in the developing retina
(number index ind	(Mus musculus Linnaeus 1758)	Elshatory et al., 2007a	- Expressed during the maturation of retinal ganglion cells and subtypes of
Not expressed in developing and mature horizontal cells. Elshatory et al., 2007b Li et al., 2014 Not expressed in developing and mature horizontal cells. Not expressed in developing and mature horizontal cells. Li et al., 2014 Notecular mechanisms involved in retinal ganglion cell development - Isit and Pou42; Iteract with other members of POU domain and LIM-homeodomain transcription factors, respectively. Mu et al., 2008 Mue et al., 2008 Whitney et al., 2011 Nu wet al., 2012 Molecular mechanisms involved in retinal ganglion cell development. Molecular mechanisms involved in retinal ganglion cell development. Mue et al., 2012 Wu et al., 2012 Mue et al., 2014 Mue et al., 2015 Mue e	(mus musculus, Emilieus 1756)		amacrine and bipolar cells and later maintained in them
Elshatory et al., 2007b Folde of elstabilishing returnal neuronal subtypes - Controls the differentiation of bipolar cells and cholinergic amacrine cells. Li et al., 2014 Foldecular mechanisms involved in returnal ganglion cell development - Isl1 and PoulaZ interact with other members of POU domain and LIM-homedomain transcription factors, respectively. Mu et al., 2008 Molecular mechanisms involved in retinal ganglion cell development - Bill and PoulaZ interact with other members of POU domain and LIM-homedomain transcription factors, respectively. Mu et al., 2008 Molecular mechanisms involved in retinal ganglion cell development - Required for the differentiation and survival of retinal ganglion cell face. - Involved in tretinal ganglion cell development - Nulceular mechanisms involved in retinal ganglion cell development. Molecular mechanisms involved in retinal ganglion cell development - Required for the differentiation and survival of retinal ganglion cell development. Molecular mechanisms involved in retinal ganglion cell development - Whitney et al., 2011 Cenetic modulation of horizontal cell number - Wu et al., 2012 - Molecular mechanisms involved in retinal ganglion cell development - Required for the differential expression of the canonical and alternative isoforms of Isl1 and Banglion cell advelopment - Retar and prove and prove and prove and prove and prove and prove anon pretinal cell prove and prove and prove anone prov			- Not expressed in developing and mature horizontal cells
Instituty (t the 2007)Instituty (t the 2007)Instituty (t the 2007)Instituty (t the 2007)Instituty (t the 2007)Controls the differentiation of bipolar cells and cholinergic amacrine cells.Instituty (t the 2007)Controls the differentiation of bipolar cells and cholinergic amacrine cells.Instituty (t the 2007)Controls the differentiation of bipolar cells and cholinergic amacrine cells.Instituty (t the 2007)Nu et al., 2008Mu et al., 2008Molecular mechanisms involved in retinal ganglion cell development- Required for the differentiation of subpolutions of amacrine and bipolar cells.Pan et al., 2008Molecular mechanisms involved in retinal ganglion cell development.Pan et al., 2008Whitney et al., 2011Whitney et al., 2011Molecular mechanisms involved in retinal ganglion cell development.Mu et al., 2012Nu et al., 2012Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development- Involved in the contrast cell number- Introlyte the contrast cell number- Multiney et al., 2015Molecular mechanisms involved in retinal ganglion cell development- Nu et al., 2015Wu et al., 2015Wu et al., 2015Molecular mechanisms involved in retinal ganglion cell development- Nu et al., 2015Nu et al., 2015RatThor et al., 1991(Ratus norvegicus, Berkenhout 1769)Gali-Resta et al., 1997Gali-Resta et al., 1997- Supressed in a subset of amacrine, cells in the NL.Expressed in a subset of amacrine, bipolar, cells un thoridifice and enverues mechanic- Unv		Elshatory et al. 2007b	Pole in establishing retinal neuronal subtypes
Li et al., 2014 Li et al., 2014 Li et al., 2014 Li et al., 2014 Molecular mechanisms involved in retinal ganglion cell development - Isl and Pou422 form a complex to regulate essential target genes involved in ganglion cell differentiation - Isl and Pou422 form a complex to regulate essential target genes involved in ganglion cell differentiation - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Isl and Pou422 form a complex to regulate essential target genes involved in - Involvement of both parallel and cooperative functions of Isl 1 and Brn3b in regulating horizontal cell numbers. - Involvement of both parallel and cooperative functions of Isl 1 and Brn3b in regulating horizontal cell numbers. - Nou422 and Isl 1 are the earliest ganglion cell development - Pou422 and Isl 1 are the earliest ganglion cell development - Pou422 and Isl 1 are the earliest ganglion cell aganglion cell fate. - Demostrate the differential expression of the cranonical and alternative isoforms of Isl 1 and the regulatory core for the ganglion cell fate in the retinal - Pou422 and Isl 1 entore retinal ganglion cells and few cells in the INL Early differential on a subset of fanal ganglion cells and few cells in the INL Early differential in the retinal - Expressed in a su		Lishatory et al., 2007b	- Controls the differentiation of binolar cells and cholinergic amacrine cells
 Hist dam Red training Jackborn der Gereicher Gereicher, 2014 Hist dam Pould2 form a complete to regulate essential target genes involved in gangion cell differentiation. Hist and Pould2 form a complete to regulate essential target genes involved in gangion cell differentiation. Hist and Pould2 form a complete to regulate essential target genes involved in gangion cell development. Required for the differentiation and survival of retinal gangion cell development. Required for the differentiation and survival of retinal gangion cells but not for the initial specification of retinal gangion cells but not for the initial specification of retinal gangion cells. Distinct as well as redundant functions between Pould2 (Brn3b) and Isl1 during retinal gangion cell development. Nu et al., 2008 Whitney et al., 2011 Whitney et al., 2012 Wu et al., 2012 Wu et al., 2012 Wu et al., 2013 Vu et al., 2015 Whitney et al., 2015 Wu et al., 2015 Wu et al., 2015 Nu et al., 2015 Nu et al., 2015 Nu et al., 2015 Molecular mechanisms involved in retinal gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development Poud72 and Isl1 are the earliest gangion cell development		Lietal 2014	Molecular mechanisms involved in retinal ganglion cell development
Rat (Ratus norvegicus, Berkenhout 1769) Rat Rat (Ratus norvegicus, Berkenhout 1769) Calip-Resta et al., 1997 Calip-Resta et al., 2009 Calip-Resta et al., 2009 Calip-R		El et uli, 2011	- Isl1 and Pou4f2 form a complex to regulate essential target genes involved in
Nu et al., 2008Au et al., 2008Isil and Pou42 interact with other members of POU domain and LIM-homeodomain transcription factors, respectively.Mu et al., 2008Molecular mechanisms involved in retinal gangion cell developmentPan et al., 2008Pan et al., 2008Whitney et al., 2011Molecular mechanisms involved in retinal gangion cell development.Whitney et al., 2012Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2012Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2012Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2012Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2012Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2015Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2015Molecular mechanisms involved in retinal gangion cell development.Wu et al., 2015Kole in a pathway independent of Math5, Pou412, and Is11Canado Car and Pozi transcription factors regulate the formation of retinal gangion cell development.RatThor et al., 1991(Ratus norvegicus, Berkenhout 1769)Galli-Resta et al., 1997Canine apig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuine apig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009			ganglion cell differentiation
Nu et al., 2008Nu et al., 2008Nu et al., 2008Pan et al., 2008Pan et al., 2008Nolecular mechanisms involved in retinal ganglion cell developmentPan et al., 2008Pan et al., 2008Nolecular mechanisms involved in retinal ganglion cell fate. • Distinct as well as redundant functions between Pou412 (Brn3b) and Isl1 during retinal ganglion cell development. • Distinct as well as redundant functions between Pou412 (Brn3b) and Isl1 during retinal ganglion cell development. • Nolveed in the formation of subpopulations of amacrine and bipolar cells. • Distinct as well as redundant functions between Pou412 (Brn3b) and Isl1 during retinal ganglion cell development. • Nuolveement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell development. • Nuolveement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell markers, and initiation of their explanation cell development. • Nuolveement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell markers, and initiation of their explanation of horizontal cell numbers. • Nuolveement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell markers, and initiation of their explanation of horizontal cell numbers. • Oud2 and Isl1 are the caller strest and isl1. Bro4d Can dIsl1 are the caller strest and isl1. Bro4d Can dIsl1 are the caller strest and isl1.Rat (Ratus norvegicus, Berkenhout 1769)Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell development • Pou422 and Isl1. Bro4d Isl1 and Isl1 compose a minimally sufficient regulatory core for tagangion cell fate in the retinal. Isl immunoreactivity in the mature retina • Expressed in a subset of retinal ganglion cells in the INL. Early differenti			- Isl1 and Pou/f2 interact with other members of POIL domain and LIM-
Mu et al., 2008Molecular mechanisms involved in retinal ganglion cell developmentPan et al., 2008Pan et al., 2008Pan et al., 2008Pan et al., 2008Pan et al., 2008Whitney et al., 2011Whitney et al., 2011Molecular mechanisms involved in retinal ganglion cell development.Wole et al., 2012Molecular mechanisms involved in retinal ganglion cell development.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development.Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell developmentWu et al., 2015Nolecular mechanisms involved in retinal ganglion cell development.Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell developmentNolecular mechanisms involved in retinal ganglion cell fate NouPerement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell acelopment.Cenetic modulation of horizontal cell numbers Although Isl is not expressed in horizontal cell number NouPerement in the artifer ganglion cell fate NouPerement fator sequelate the formation of retinal ganglion cell fate Pou422 and Isl are the earliest ganglion cell fate Pou422 and Isl are the earliest ganglion cell fate NouPerement in the differential expression of the canonical and alternative isoforms of Isl anotyper- Demonstrate the differential expression of the canonical and alternative isoforms of Isl anotyper etinal ganglion cell fate.RatThor et al., 1991- Sapressed in a subset of retinal ganglion cells in the INL. <td></td> <td>homeodomain transcription factors respectively</td>			homeodomain transcription factors respectively
Nu ct al., 2000- Required for the differentiation and survival of retinal ganglion cells but not for the initial specification of retinal ganglion cells but not for the initial specification of retinal ganglion cell fate. - Involved in the formation of subpopulations of amacrine and bipolar cells. - Distinct as well as redundant functions between Pou4f2 (Brn3b) and Isl1 during retinal ganglion cell development.Pan et al., 2008Molecular mechanisms involved in retinal ganglion cell development. - Involvement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell development.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development. - Although Isl1 is not expressed in horizontal cell precursors, it plays a role in regulating horizontal cell numbers.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development. - Out42 and Isl1 are the earliest ganglion cell developmentWu et al., 2015Molecular mechanisms involved in retinal ganglion cell development - Pou4f2 and Isl1 are the earliest ganglion cell developmentRat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991 Galli-Resta et al., 1997Sil1 immunoreactivity in the mature retina - Subset of retinal ganglion cells and few cells in the INL. Expressed in a subset of retinal ganglion cells - Devid2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cells and few cells in the INL. Expressed in a subset of retinal ganglion cells - Devid2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cells and a few cells in the INL. Expressed in a subset of retinal ganglion cells and - Expressed in a subset of retinal ganglion cells - Larky differentiation of a subset of macrine cells - Identification of		Mu et al. 2008	Molecular mechanisms involved in retinal ganglion cell development
Rat (Ratus norvegicus, Berkenhout 1769)Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell development - Although Isl1 is not expressed in horizontal cell number - Although Isl1 is not expressed in horizontal cell mamber - Pou4f2 and Isl1 are the earliest ganglion cell developmentRat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Sil and Der et al., 2005Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Sil and Der et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Sil and Der et al., 2009Carbon Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Sil and procellus, Linnaeus 1758)Carbon Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Sil and procellus, Linnaeus 1758)Carbon Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Sil and procellus to the differential expression of Isl in the developing retinal - Expressed in anay ganglion cells of anacrine, bipolar, and horizontal cells to the differential expression of Isl in the developing retina - Expressed in a subset of retinal ganglion cells of anacrine, bipolar, and horizontal - Expressed in anay ganglion cells of anacrine, bipolar, and horizontal - Expressed in many ganglion cells of anacrine, bipolar, and horizontal - Expressed in anay ganglion cells of anacrine, bipolar, and horizontal - Expressed in anay ganglion cell developing retina - Expressed in anay ganglion cells of anacrine, bipolar, and horizontal - Expressed in anay ganglion cell and procenting - Liter and the differential expression of Isl in the developing retina - Expressed in anay ganglion cells of anacrine, bipolar, and horizontal - Call and the differential celloping retina		Witi et al., 2008	Required for the differentiation and survival of retinal ganglion cells but not
Pan et al., 2008Pan et al., 2008Distinct as well as redundant functions between Pou4f2 (Brn3b) and Isl1 during retinal ganglion cell development.Whitney et al., 2011Whitney et al., 2011Molecular mechanisms involved in retinal ganglion cell development.Wu et al., 2012Wu et al., 2012Cenetic modulation of horizontal cell numbers.Wu et al., 2013Nolecular mechanisms involved in retinal ganglion cell development.Wu et al., 2014Cenetic modulation of horizontal cell number.Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell developmentWu et al., 2015Nolecular mechanisms involved in retinal ganglion cell development.Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell developmentRat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Galli-Resta et al., 1997Siduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Giduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Giduric-Fuchs et al., 2009			for the initial specification of retinal ganglion cell fate
Pan et al., 2008Molecular mechanisms involved in retinal ganglion cell development.Whitney et al., 2011Genetic modulation of an population of and population of an population of and population of anapopulation of an			- Involved in the formation of subpopulations of amacrine and bipolar cells
Pan et al., 2008Molecular mechanisms involved in retinal ganglion cell development.Whitney et al., 2011Kolecular mechanisms involved in retinal ganglion cell development.Whitney et al., 2012Cenetic modulation of horizontal cell numberWu et al., 2012Autough Isl 1 is not expressed in horizontal cell numbers.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development.Wu et al., 2012Cenetic modulation of horizontal cell number.Although Isl 1 is not expressed in horizontal cell numbers.Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development.Pou4f2 and Isl 1 are the earliest ganglion cell meters, and initiation of their expression is concurrent with the specification of the retinal ganglion cell face.Oc1 and Oc2 transcription factors regulate the formation of retinal ganglion cell faces in a pathway independent of MathS, Pou4f2, and Isl 1.RatThor et al., 2015RatThor et al., 1991Galli-Resta et al., 1997Galli-Resta et al., 1997Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009			- involved in the formation of subpopulations of amacrine and bipolar cens.
Pan et al., 2008Wolceular mechanisms involved in retinal ganglion cell development.Whitney et al., 2011Galli-Resta et al., 1997Kat (Ratus norvegicus, Berkenhout 1769)Galli-Resta et al., 1997Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Bart al., 2009Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Gudu			- Distinct as well as redunidant functions between rou412 (DIIDD) and ISIT
Whitney et al., 2003Notecular inclusions involved in retinal gangitor cell development.Whitney et al., 2011- Involvement of both parallel and cooperative functions of Isl1 and Bra3b in retinal gangiton cell development.Wu et al., 2012- Involvement of both parallel and cooperative functions of Isl1 and Bra3b in retinal gangiton cell development.Wu et al., 2012- Although Isl1 is not expressed in horizontal cell numberWu et al., 2015- Molecular mechanisms involved in retinal gangiton cell developmentPou4f2 and Isl1 are the earliest gangiton cell meters, and initiation of their expression is concurrent with the specification of the retinal gangiton cell fate. - Oct and Oc2 transcription factors regulate the formation of retinal gangiton cell fate. - Deuf2 and Isl1 are the earliest gangiton cell developmentWu et al., 2015Role in establishing retinal neuronal subtypes - Demonstrate the differential cell classes.Wu et al., 2015Molecular mechanisms involved in retinal gangiton cell development - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the gangiton cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Galli-Resta et al., 1997Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009		Pap of al 2008	Molocular mochanisms involved in retinal ganglion cell development
Whitney et al., 2011Genetic modulation of horizontal cell numberWu et al., 2012Sector modulation of horizontal cell numbers.Wu et al., 2012Wu et al., 2012Wu et al., 2013Molecular mechanisms involved in retinal ganglion cell developmentPou4f2 and Is11 are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of the retinal ganglion cell are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of the retinal ganglion cell are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of the retinal ganglion cell are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of the retinal ganglion cell are the earliest ganglion cell developmentVu et al., 2015Whitney et al., 2015Wu et al., 2015Role in establishing retinal expression of the canonical and alternative isoforms of Is11 amongst retinal ganglion cell developmentPou4f2 and Is11 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Galli-Resta et al., 1991Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009		Fall et al., 2008	Involvement of both parallel and cooperative functions of Isl1 and Prn2h in
Whitney et al., 2011Genetic modulation of horizontal cell number - Although Isl1 is not expressed in horizontal cell number - Although Isl1 is not expressed in horizontal cell number - Although Isl1 is not expressed in horizontal cell number - Although Isl1 is not expressed in horizontal cell number - Pou422 and Isl1 are the earliest ganglion cell development - Pou422 and Isl1 are the earliest ganglion cell development - Pou422 and Isl1 are the earliest ganglion cell formation of tretinal ganglion cells in a pathway independent of MathS, Pou42, and Isl1.Whitney et al., 2015Whitney et al., 2015Wu et al., 2015Kole in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal cell classes.Wu et al., 2015Molecular mechanisms involved in retinal ganglion cell development - Pou422 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retinal - Expressed in a subset of amacrine cells - Identification of a subset of amacrine cells - Identification of Isl1 in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009			retinal ganglion cell development
Wintery et al., 2011Center Centre ConstraintsWu et al., 2012- Although IsI1 is not expressed in horizontal cell precursors, it plays a role in regulating horizontal cell numbers.Wu et al., 2012- Oct and Oc2 transcription factors regulate the formation of tertinal ganglion cell face. - Oct and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Pou4f2, and IsI1.Wu et al., 2015Wu et al., 2015Nolecular mechanisms involved in retinal ganglion cell development - Deumstrate the differential expression of the canonical and alternative isoforms of IsI1 amongst retinal cell classes.Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Galli-Resta et al., 1997Galli-Resta et al., 1997Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Cuinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009		Whitney at al. 2011	Constic modulation of horizontal call number
Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell developmentPoud42 and Isl1 are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of netinal ganglion cell fate. - Oct and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Pou4f2, and Isl1.Whitney et al., 2015Wu et al., 2015Wu et al., 2015Role in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal ganglion cell development - Pou4f2 and Isl1 amongst retinal ganglion cell development - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal ganglion cell development - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Galli-Resta et al., 1997Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009		Willing et al., 2011	Although Isl1 is not expressed in horizontal cell procursors it plays a role in
Wu et al., 2012Molecular mechanisms involved in retinal ganglion cell development - Pou4f2 and Isl1 are the earliest ganglion cell markers, and initiation of their expression is concurrent with the specification of the retinal ganglion cell fate. - Oc1 and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Pou4f2, and Isl1. - Oc1 and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Pou4f2, and Isl1.Whitney et al., 2015Whitney et al., 2015Wu et al., 2015Role in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal cell classes.Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Galli-Resta et al., 1997Isl1 immunoreactivity in the mature retina - Expressed in a subset of retinal ganglion cells and a few cells in the INL. Early differentiation of a subset of amacrine cells - Identification of isl1 in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia dorcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009			 Annough isn'ts not expressed in nonzonial cen precursors, it plays a role in regulating horizontal cell numbers.
Will et al., 2012Will et al., 2012Will et al., 2012Will et al., 2012Will et al., 2012Pou4f2 and Isl1 are the earliest ganglion cell areters, and initiation of their expression is concurrent with the specification of the retinal ganglion cell fate. - Oc1 and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Pou4f2, and Isl1.Whitney et al., 2015Wu et al., 2015Molecular mechanisms involved in retinal ganglion cell development 		W/u at al. 2012	regulating nonzontal ten numbers.
 Fourier 2 and is if are the earliest gangion cell indices, and infinitely, and is if are the earliest gangion (earliest, and infinitely, and is if are the earliest gangion (earliest, and infinitely, and is if are the expression is concurrent with the specification of the retinal gangion cells in a pathway independent of Math5, Pou4f2, and Is1. Oc1 and Oc2 transcription factors regulate the formation of retinal gangion cells in a pathway independent of Math5, Pou4f2, and Is1. Role in establishing retinal neuronal subtypes Demonstrate the differential expression of the canonical and alternative isoforms of Is1 amongst retinal cell classes. Wu et al., 2015 Wu et al., 2015 Wu et al., 2015 Molecular mechanisms involved in retinal ganglion cell development Pou4f2 and Is1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina. Is11 immunoreactivity in the mature retina Expressed in a subset of retinal ganglion cells and a few cells in the INL. Early differentiation of a subset of amacrine cells Identification of is11 in the developing retina. Is11 immunoreactivity in the developing retina. Is11 immunoreactivity in the developing retina. Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the other and mature retine and mature retine. 		Wu et al., 2012	Bou462 and Iol1 are the earliest ganglion cell markers and initiation of their
Whitney et al., 2015Whitney et al., 2015Col and Oc2 transcription factors regulate the formation of retinal ganglion cells in a pathway independent of Math5, Poudf2, and Isl1.Rat (Ratus norvegicus, Berkenhout 1769)Wu et al., 2015Kole in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal ganglion cell development - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Isl1 immunoreactivity in the mature retina - Expressed in a subset of retinal ganglion cells and a few cells in the INL.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina. - Isl1 immunoreactivity in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina. - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal colls in the differentiation end mature retina - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal colls in the differentiation end mature retina - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal colls in the differentiation retina			- Fourier and Isi' are the earliest gangion cen markers, and miniation of their
Whitney et al., 2015We et al., 2015Role in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal cell classes.Wu et al., 2015Wu et al., 2015Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal ganglion cell development - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Isl1 immunoreactivity in the mature retina - Expressed in a subset of retinal ganglion cells and a few cells in the INL.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina. - Isl1 immunoreactivity in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells by their early expression of Isl1 in the developing retina			~ 0.01 and 0.02 transcription factors regulate the formation of retinal gaugiton
Whitney et al., 2015Role in establishing retinal neuronal subtypes - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal cell classes.Wu et al., 2015Wu et al., 2015Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Galli-Resta et al., 1997Isl1 immunoreactivity in the mature retina - Expressed in a subset of retinal ganglion cells and a few cells in the INL.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009			cells in a nathway independent of Math5 Dou/f2 and Isl
Witting et al., 2015Kore in establishing return incurrent and studypesWu et al., 2015- Demonstrate the differential expression of the canonical and alternative isoforms of Is1 amongst retinal cell classes.Wu et al., 2015Wu et al., 2015Rat (<i>Ratus norvegicus</i> , Berkenhout 1769)Thor et al., 1991Galli-Resta et al., 1997Is1 immunoreactivity in the mature retina - Expressed in a subset of amacrine cells - Identification of a subset of amacrine cells - Identification of Is11 in the developing retina.Guinea pig (<i>Cavia porcellus</i> , Linnaeus 1758)Guduric-Fuchs et al., 2009Guinea pig (<i>Cavia porcellus</i> , Linnaeus 1758)Guduric-Fuchs et al., 2009		Whitney et al. 2015	Cons in a pailiway independent of Mains, rou412, and isll.
Wu et al., 2015Wu et al., 2015Molecular mechanisms involved in retinal ganglion cell development - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991Isl1 immunoreactivity in the mature retina - Expressed in a subset of retinal ganglion cells and a few cells in the INL.Galli-Resta et al., 1997Galli-Resta et al., 2009Isl1 immunoreactivity in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiation of and ganglion cells.		winning et al., 2015	- Demonstrate the differential expression of the canonical and alternative
Wu et al., 2015 Wu et al., 2015 Rat (Ratus norvegicus, Berkenhout 1769) Thor et al., 1991 Galli-Resta et al., 1997 Isl1 immunoreactivity in the mature retinal (Ratus porcellus, Linnaeus 1758) Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009			isoforms of left amongst ratinal call classes
Rat (Ratus norvegicus, Berkenhout 1769)Thor et al., 1991International subset of retinal ganglion cell acvetophient - Pou4f2 and Isl1 compose a minimally sufficient regulatory core for the ganglion cell fate in the retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina.Guinea pig (Cavia porcellus, Linnaeus 1758)Guduric-Fuchs et al., 2009Isl1 immunoreactivity in the developing retina.		Wu et al. 2015	Molecular mechanisms involved in retinal ganglion cell development
Rat Thor et al., 1991 Immunoreactivity in the mature retina (Ratus norvegicus, Berkenhout 1769) Galli-Resta et al., 1997 Immunoreactivity in the mature retina Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 Immunoreactivity in the developing retina. Isl1 immunoreactivity in the developing retina. Isl1 immunoreactivity in the developing retina. Isl1 immunoreactivity in the developing retina. Isl1 immunoreactivity in the developing retina.		WU CL dl., 2013	- Pould? and Isl1 compose a minimally sufficient regulatory core for the
Rat Thor et al., 1991 Isl1 immunoreactivity in the mature retinal. (Ratus norvegicus, Berkenhout 1769) Galli-Resta et al., 1997 Isl1 immunoreactivity in the mature retinal ganglion cells and a few cells in the INL. Early differentiation of a subset of retinal ganglion cells - Expressed in a subset of retinal ganglion cells and a few cells in the INL. Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 - Identification of immature choline acetyl-transferase expressing amacrine cells by their early expression of Isl1 in the developing retina. Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiation or and mature retinal.			ganglion cell fate in the retina
(Ratus norvegicus, Berkenhout 1769) Galli-Resta et al., 1997 Financial cells in a subset of retinal ganglion cells and a few cells in the INL. Early differentiation of a subset of macrine cells - Identification of immature choline acetyl-transferase expressing amacrine cells by their early expression of Isl1 in the developing retina. Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 Isl1 immunoreactivity in the developing retina - Expressed in many ganglion cells, subset of amacrine, bipolar, and horizontal cells in the differentiation of intervention of the cells of the cell	Pat	Thor et al. 1991	Eansion contact in the nature ration
Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009	(Ratus norvagicus Rerkonhout 1760)	1101 Ct dl., 1331	- Expressed in a subset of ratinal ganglion calls and a faw calls in the INI
Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 Guduric-Fuchs et al., 2009 Identification of a subset of affacting cells by their early expression of Isl1 in the developing retina. Isl1 immunoreactivity in the developing retina - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiation of a subset of affacting and matrixe retination of a subset of affacting cells in the differentiation of a subset of affacting cells affacting cells in the differentiation of a subset of affacting cells in the differenting cells in the differentiation of a subset	(Natus norvegicus, berkennout 1709)	Calli Posta et al. 1007	- Expressed in a subset of reunal galigilon tens and a few tens in the link.
Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009 Guinea pig (Cavia porcellus, Linnaeus 1758) Guduric-Fuchs et al., 2009		Galli-Resta et al., 1997	Early unterentiation of immeture, choling, acetul transforace, everyosing, emerging
Guinea pig (<i>Cavia porcellus</i> , Linnaeus 1758) Guduric-Fuchs et al., 2009 Guduric-Fuchs et al., 2009 - Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiating and mature retires.			- inclution of initiature choine decivi-transferase expressing anacrifte
- Expressed in many ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the developing retina	Guinea pig (<i>Cavia porcellus</i> , Linnaeus 1758)	Cuduric Fuchs et al. 2000	In the developing retination of the developin
- Expressed in many garginor cens, subsets or amachine, bipolar, and nonzontal colles in the differentiating and matter region.		Guudi IC-FUCIIS Et al., 2009	- Expressed in many ganglion cells, subsets of amacring, bindlar, and berigental
			 Expressed in many gaugnon cens, subsets of anactine, pipolal, and nonzonidal colls in the differentiating and mature ratina.

of Isl1 in the outer nuclear layer (ONL) during retinal development in the turtle (Francisco-Morcillo et al., 2006) and in the chick (Edqvist et al., 2006; Fischer et al., 2008).

4.1. Isl1 and ganglion cell differentiation

Anti-Isl1 antibodies have been used for many years as markers of ganglion cell identity in the mature retina (Figs. 1A, B, F and 2A–C) (Austin et al., 1995; Galli-Resta et al., 1997; Francisco-Morcillo et al., 2006; Elshatory et al., 2007a; Bejarano-Escobar et al., 2009, 2010; 2012; Guduric-Fuchs et al., 2009; Álvarez-Hernán et al., 2013). Many Isl1-immunoreactive ganglion cells also express calretinin (CR), a typical marker of a subpopulation of ganglion cells in the vertebrate retina (Fig. 3A–C). During development, in most of the species studied, the first appearance of Isl1 immunoreactivity coincides with the onset of ganglion cell neurogenesis, the first cell type that differentiates in the vertebrate retina, and is detected in nuclei located near the vitreal surface of the retina (Figs. 1D, G and 2D, G, J) and in sparse ovoid nuclei dispersed throughout the neuroblastic layer (NbL) with the major axis oriented vitreo-sclerally (Figs. 1E, G and 2E, H, J) (Edqvist et al., 2006; Francisco-Morcillo et al., 2006; Elshatory et al., 2007a; Pan et al., 2008; Bejarano-Escobar et al., 2009, 2010; 2012; Álvarez-Hernán et al., 2013). Therefore, Isl1 seems to be one of the molecules that regulate retinal ganglion cell development. Functional studies have shown that three transcription factors, Math5/Atoh7, Brn3b/Pou4f2, and Isl1 occupy key nodes in the gene regulatory network that controls retinal ganglion cell development (Yang

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

R. Bejarano-Escobar et al. / Experimental Eye Research xxx (2015) 1-10



Fig. 1. Spatial and temporal expression of the transcription factor IsI1 in the mature and developing retina of anamniotes. IsI1 is expressed in the nuclei of subpopulations of ganglion, amacrine, bipolar, and horizontal cells in the differentiated retina of the tench (A), small spotted catshark (B), and South African clawed frog (C). During early stages of development, IsI1 expression is mainly detected in the nuclei of differentiating ganglion cells located near the inner surface of the retina (D, E, G), but also in the nuclei of migratory neuroblasts dispersed throughout the retinal tissue (E, G). In more advanced stages of development, IsI1 labeling patterns resemble those observed in differentiated retinas (F, H). Developmental stages are referred to as: P. postnatal day; St, developmental stages in *Scyliorhinus canicula* (Ballard et al., 1993) and in *Xenopus laevis* (Nieuwkoop and Faber, 1967). Scale bars denote 25 µm. *ac*, amacrine cell; *bc*, bipolar cell; *GCL*, ganglion cell layer; *hc*, horizontal cell; *INL*, inner nuclear layer; *IPL*, inner plexiform layer; *L*, lens; *NbL*, neuroblastic layer; *ON*, optic nerve; *ONL*, outer nuclear layer.

et al., 2003; Mu et al., 2005, 2008; Yao et al., 2007; Pan et al., 2008; Sapkota et al., 2011; Li et al., 2014). Thus, Atoh7 determines retinal ganglion cell competence (Yang et al., 2003; Mu et al., 2005; Sapkota et al., 2011) and is essential for the activation of a network of transcription factors in developing retinal ganglion cells, including Isl1 and Brn3b. In the mouse retina, Isl1-positive nascent retinal ganglion cell neuroblasts also express Brn3b (Elshatory et al., 2007a; Pan et al., 2008). Thus, retina-specific mouse knockouts of Isl1 and Brn3b show similar phenotypes. The eyes of mutant mice are smaller than those of wild type, and the optic nerves are significantly thinner. Moreover, the majority of their ganglion cells are defective in axon growth and pathfinding, and are lost at later stages of development (Elshatory et al., 2007b; Mu et al., 2008; Pan et al., 2008). These data suggest that Isl1 and Brn3b are not required for the specification of this cell type, but play a key role in their differentiation and survival (Mu et al., 2008; Pan et al., 2008; Sapkota et al., 2011; Li et al., 2014). However, it has recently been shown that ectopic expression of Isl1 and Brn3b in the Atoh7-null retina is sufficient for the specification of the retinal ganglion cell fate (Wu et al., 2015), suggesting that these transcription factors compose a minimally sufficient regulatory core for the retinal ganglion cell fate. These authors suggest that ectopic Isl1 and Brn3b can activate the native Isl1 and Brn3b genes, determining the retinal ganglion cell fate. Therefore, the function of Atoh7 is to activate the core of retinal ganglion cell fatedetermining transcription factor genes including Isl1 and Brn3b. These transcription factors sustain their own expression and no longer rely on the activator Atoh7. Then, Isl1 and Brn3b activate the gene expression program required for RGC differentiation (Wu et al., 2015). Brn3b binds to Isl1 within the C-terminal region forming a complex to regulate target genes in developing retinal ganglion cells (Li et al., 2014). This collaboration of Isl1 and Brn3b is very similar to that of Isl1 and Brn3a, another class of IV POU domain transcription factor, in the developing root ganglia and trigeminal ganglia (Dykes et al., 2011). Isl1 and Brn3 factors coexpression in all sensory neurons has suggested that they form a combinatorial code for sensory development. Finally, a recent study describes the differential expression of the canonical (Isl1 α) and alternative (Isl1^β) isoforms amongst retinal ganglion cell classes in the mouse retinal tissue during development (Whitney et al., 2015). As Isl1 participates in the differentiation of multiple cell types within the retinal tissue, the results of this study support a role for





Fig. 2. Spatial and temporal expression of the transcription factor Isl1 in the mature and developing retina of amniotes. Isl1 is expressed in the nuclei of subpopulations of ganglion, amacrine, and bipolar cells in the differentiated retina of the Mediterranean turtle (A), chick (B), and mouse (C). Horizontal immunoreactive cells are also detected in the retina of reptiles and birds, but not in the mouse (A–C). During early stages of development, Isl1 expression is mainly detected in the nuclei of differentiating ganglion cells located near the inner surface of the retina (D, E, G, H, J, K), but also in the nuclei of migratory neuroblasts dispersed throughout the retinal tissue (J, E, H). In more advanced stages of development, the labeling patterns of Isl1 resemble those observed in differentiated retinas (F, I). In the retina of mammals, Isl1 expression in bipolar cells is detected later in development than in ganglion and amacrine cells (C, J–L). Notice the transient expression of Isl1 detected in the ONL during retinal differentiation in reptiles (asterisks in F) and birds (asterisks in I). Scale bars denote 25 µm. Developmental stages referred to as: E, day of embryonic development; *P*, postnatal day. *ac*, amacrine cell; *bc*, bipolar cell; *GCL*, ganglion cell layer; *hc*, horizontal cell; *INL*, inner nuclear layer; *IPL*, inner plexiform layer; *NbL*, neuroblastic layer; *ONL*, outer nuclear layer.

alternative splicing in the establishment of ganglion cell diversity in the developing mouse retina.

4.2. Isl1 and amacrine cell differentiation

Two populations of Isl1-positive amacrine cells are found commonly spaced in an orderly manner in the inner region of the inner nuclear layer (INL) and in the outer region of the ganglion cell layer (GCL) (Galli-Resta et al., 1997; Francisco-Morcillo et al., 2006; Elshatory et al., 2007a). In both subpopulations, Isl1 always colocalized with choline acetyltransferase (ChAT), a marker of cholinergic amacrine cells (Galli-Resta et al., 1997; Haverkamp et al., 2003; Elshatory et al., 2007a; Stanke et al., 2008), and occasionally with CR, expressed by subpopulations of amacrine and displaced amacrine cells (Fig. 3D–F). Moreover, during retinal development, the cholinergic amacrine cell neuroblasts can be characterized immunohistochemically by using antibodies against Isl1, Pax6, and NeuroD (Elshatory et al., 2007a; Stanke et al., 2008). The expression of Isl1 in cholinergic amacrine neuroblasts precedes ChAT immunoreactivity in the developing rat retina (Mitrofanis et al., 1988; Galli-Resta et al., 1997). Disruption of *Isl1* in the mouse retina abolishes all cholinergic amacrine cells (Elshatory et al., 2007b).

4.3. Isl1 and bipolar cell differentiation

Isl1 expression in the bipolar cell layer (Figs. 1A, B, F and 2A–C) is restricted to ON-bipolar cells (Elshatory et al., 2007a). Thus, double-

ARTICLE IN PRESS

R. Bejarano-Escobar et al. / Experimental Eye Research xxx (2015) 1-10



Fig. 3. Photomicrographs of the South African clawed frog (A–C, M–R), small-spotted catshark (D–I), and Senegalese sole (J–L) differentiated retinas showing the double immunolabeling of Is1 (red) and different retinal markers (green): CR (A–F), Go α (G–I), α PKC (J–L), CERN922 (M–O), and CB (P–R). Is11 is expressed by CR-immunoreactive ganglion cells (arrowheads in A–C). CR-expressing amacrine cells located in the GCL and in the INL are also immunoreactive for Is11 (double arrowheads in D–F). Is11 co-localizes with typical bipolar cell markers (arrows in A–C, G–L). Is11 never co-expressed with typical rod (M–O) and cone (P–R) markers. Scale bars denote 25 μ m. *GCL*, ganglion cell layer; *INL*, inner nuclear layer; *IPL*, inner plexiform layer; *ONL*, outer nuclear layer. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

labeling experiments reveal that Isl1 co-localizes with typical bipolar cell markers, such as the α -subunit of the guanine nucleotidebinding protein Go (Go α) (Fig. 3G–I), the α -isoform of protein kinase C (α PKC) (Fig. 3J–L), and CR (Fig. 3A–C). Bipolar cell specification is dependent on the combined action of different homeodomain and bHLH transcription factors (Hatakeyama et al., 2001). During retinal development, Isl1 expression is also detected in differentiating bipolar cells (Elshatory et al., 2007a). The deletion of *Isl1* in the mouse retina does not affect bipolar cell generation, but causes loss of multiple bipolar subtypes and greatly reduced expression of other genes that are required for differentiation of different bipolar cell subpopulations (Elshatory et al., 2007b).

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

4.4. Isl1 and horizontal cell differentiation

In the retina of vertebrates, many of the Isl1-positive cells located in the outermost portion of the INL correspond to horizontal cells (Figs. 1A, B, F and 2A, B). The horizontal cell population in the chick retina is composed of three cell subtypes (H1, H2, and H3) that can be distinguished morphologically (Génis-Gálvez et al., 1981). Thus, the H1, or "brush-shaped" horizontal cell, is axonbearing and constitute 50% of all horizontal cells, whereas the H2 "stellate" and H3 "candelabrum-shaped" horizontal cells are axonless. The chick horizontal cell populations can also be distinguished molecularly by the expression of Prox1, Lim1, Isl1, TrkA, and GABA (Fischer et al., 2007; Edqvist et al., 2008). Isl1 is expressed by H2 and H3 horizontal cells (Fischer et al., 2007; Edqvist et al., 2008; Poche and Reese, 2009; Suga et al., 2009). In the developing chick retina, Lim1-positive H1 horizontal cells are generated one day before the Isl1 immunoreactive horizontal cells. It has recently been reported that Isl1 drives the differentiation of H2 cells (Suga et al., 2009). Thus, these authors have shown that the overexpression of Isl1 in developing chick retinas represses endogenous Lim1 expression in H1 cells, and a larger proportion of the H2 subtype is observed at the expense of H1 cells.

Isl1 is detected in the horizontal cell layer of different mammals (Haverkamp et al., 2003; Guduric-Fuchs et al., 2009). However, it has been described that the axon-bearing horizontal cell (H1

horizontal cells in the chick) is the only type present in the mouse retina (Peichl and González-Soriano, 1994). Therefore, Isl1 is not detected in horizontal cells in the developing and mature mouse retina (Fig. 2C, J–L) (Elshatory et al., 2007a; Poche et al., 2007). Surprisingly, Whitney et al. (2011), using conditional knockout mice, demonstrate that *Isl1* plays a key role in regulating horizontal cell numbers. In particular, there is a substantial increase in horizontal cells in the knockout retina with drastically reduced numbers of ganglion, cholinergic amacrine, and bipolar cells. However, exactly how the modulation of Isl1 expression affects horizontal cell numbers in the developing mouse retina remains to be determined.

4.5. Isl1 expression in the photoreceptor cell layer

Isl1 mRNA is never detected in the photoreceptor layer (Elshatory et al., 2007a; Boije et al., 2008). Inmunohistochemical studies have shown that it usually fails to co-localize with typical markers of rods (Fig. 3M–O) or cones (Fig. 3P–R). However, some workers have described Isl1 immunoreactivity in the ONL of the embryonic retina of several vertebrates (Fig. 2F and I) (Edqvist et al., 2006; Francisco-Morcillo et al., 2006; Fischer et al., 2008). Isl2 is known to be expressed in developing photoreceptors (Tsuchida et al., 1994; Fischer et al., 2008). In many cases, commercial Isl1 antibodies also recognize Isl2. Therefore, the Isl1 immunostaining



Fig. 4. Schematic summary of Isl1 expression (red nuclei) in the developing and mature vertebrate retina. Isl1 is involved in specification and differentiation of ganglion, amacrine, bipolar, and horizontal cells. Brn3b and Isl1 are synergistically required for retinal ganglion cell differentiation and survival. Among other transcription factors that specify distinct subtypes of amacrine cells, Isl1 is also implicated in cholinergic amacrine cell differentiation. Isl1 regulates bipolar cell differentiation, and its expression is restricted to ON-bipolar cells in the mature retina. Lim1 and Isl1 begin to be expressed in a distinct subset of undifferentiated horizontal cells, resulting in complementary expression of these genes in horizontal cells of type I and type II/III, respectively, in mature chick retinas. Isl1 expression is not detected in the developing and mature mouse retina. *AC*, amacrine cell; *BC*, bipolar cell; *dAC*, displaced amacrine cell; *GC*, ganglion cell; *GL*, ganglion cell layer; *HC*, horizontal cell; *INL*, inner nuclear layer; *IPL*, inner plexiform layer; *ONL*, outer nuclear layer; *OPL*, outer plexiform layer; *RCP*, retinal progenitor cell. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in the ONL is likely a result of antibody cross-reactivity with Isl2 (Boije et al., 2008; Fischer et al., 2008).

5. Concluding remarks

In conclusion, comparative analyses demonstrate that the LIM homeodomain transcription factor Isl1 shows similar but not identical patterns of expression throughout vertebrate phylogeny. It seems to play a highly conserved role in cell specification, differentiation, and maintenance of phenotypes of the ganglion, cholinergic amacrine, ON-bipolar, and horizontal cells in the retina from fish to mammals (Fig. 4). Thus, the absence of Isl1 during retinal development results in variations in the number of ganglion, amacrine, bipolar, and horizontal cells (Elshatory et al., 2007b; Whitney et al., 2011). It has been shown that retinal cell fate determination and differentiation are controlled by intrinsic cues, such as transcription factors, and extrinsic signals, such as neurotrophic factors. An understanding of the factors that generate cellular diversity in the mammalian retina can be exploited to reprogram retinal stems cells to generate desired cell types. Stem cell based therapies provide new hope for treating optic neuropathies. Transplanting stem cells into the retina of mammals could replace degenerated neurons in order to restore visual function. The majority the research on retinal cell transplantation has concentrated on pathologies involving photoreceptor degeneration. Photoreceptor regeneration efforts for diseases like retinitis pigmentosa or age related macular degeneration need complementary strategies to promote proper connectivity of rods and cones to existing or newly generated bipolar cells. This requires a firm understanding of the factors involved in proper development and connectivity of bipolar cells. Moreover, retinal ganglion cell degeneration is involved in several retinal diseases such as glaucoma and optic ischemia, which often lead to vision loss and even blindness. Much effort has been undertaken to produce retinal ganglion cells for cell-based therapies directly in vitro from various stem cells. Recent studies showing that transcription factors, including Isl1, and specific gene regulatory pathways can determine the retinal ganglion cell fate and promote their genesis, will provide guidance for those efforts. Therefore, with deeper understanding of the cellular and molecular basis of retinal neurogenesis, the true potential of stem cell-based therapy in retinal repair will be realized, and with time and careful consideration, transitioned into the clinic.

Acknowledgments

We express our gratitude to María Salud Holguín Arévalo for her excellent technical assistance. We thank María Victoria Alarcón, "Centro de Investigación Finca la Orden", Junta de Extremadura, for assistance with confocal microscopy. R.B.E. was a recipient of a PhD studentship from the *Junta de Extremadura*. This work was supported by Grants from the Spanish Ministerio de Ciencia y Tecnología (BFU2007-67540; BFU2012-31687), Junta de Extremadura (PRI06A195; GR10152).

References

- Ahlgren, U., Pfaff, S.L., Jessell, T.M., Edlund, T., Edlund, H., 1997. Independent requirement for ISL1 in formation of pancreatic mesenchyme and islet cells. Nature 385, 257–260.
- Álvarez-Hernán, G., Bejarano-Escobar, R., Morona, R., González, A., Martín-Partido, G., Francisco-Morcillo, J., 2013. Islet-1 immunoreactivity in the developing retina of Xenopus laevis. Sci. World J. 2013, 740420.
- Austin, C.P., Feldman, D.E., Ida Jr., J.A., Cepko, C.L., 1995. Vertebrate retinal ganglion cells are selected from competent progenitors by the action of Notch. Development 121, 3637–3650.
- Bach, I., 2000. The LIM domain: regulation by association. Mech. Dev. 91, 5-17.

- Balasubramanian, R., Bui, A., Ding, Q., Gan, L., 2014. Expression of LIMhomeodomain transcription factors in the developing and mature mouse retina. Gene Expr. Patterns 14, 1–8.
- Ballard, W.W., Mellinger, J., Lechenault, H., 1993. A series of normal stages for development of Scyliorhinus canicula, the lesser spotted dogfish (Chondrichthyes: Scyliorhinidae). J. Exp. Zool. 267, 318–336.
- Bejarano-Escobar, R., Blasco, M., DeGrip, W.J., Martín-Partido, G., Francisco-Morcillo, J., 2009. Cell differentiation in the retina of an epibenthonic teleost, the Tench (Tinca tinca, Linneo 1758). Exp. Eye Res. 89, 398–415.
- Bejarano-Escobar, R., Blasco, M., DeGrip, W.J., Oyola-Velasco, J.A., Martín-Partido, G., Francisco-Morcillo, J., 2010. Eye development and retinal differentiation in an altricial fish species, the senegalese sole (Solea senegalensis, Kaup 1858). J. Exp. Zool. B Mol. Dev. Evol. 314, 580–605.
- Bejarano-Escobar, R., Blasco, M., Durán, A.C., Rodríguez, C., Martín-Partido, G., Francisco-Morcillo, J., 2012. Retinal histogenesis and cell differentiation in an elasmobranch species, the small-spotted catshark Scyliorhinus canicula. J. Anat. 220, 318–335.
- Bejarano-Escobar, R., Blasco, M., Martín-Partido, G., Francisco-Morcillo, J., 2014. Molecular characterization of cell types in the developing, mature, and regenerating fish retina. Rev. Fish. Biol. Fish. 24, 127–158.
- Bhati, M., Lee, C., Nancarrow, A.L., Lee, M., Craig, V.J., Bach, I., Guss, J.M., Mackay, J.P., Matthews, J.M., 2008. Implementing the LIM code: the structural basis for cell type-specific assembly of LIM-homeodomain complexes. EMBO J. 27, 2018–2029.
- Boije, H., Edqvist, P.H., Hallböök, F., 2008. Temporal and spatial expression of transcription factors FoxN4, Ptf1a, Prox1, Isl1 and Lim1 mRNA in the developing chick retina. Gene Expr. Patterns 8, 117–123.
- Boije, H., Edqvist, P.H., Hallböök, F., 2009. Horizontal cell progenitors arrest in G2phase and undergo terminal mitosis on the vitreal side of the chick retina. Dev. Biol. 330, 105–113.
- Cai, C.L., Liang, X., Shi, Y., Chu, P.H., Pfaff, S.L., Chen, J., Evans, S., 2003. Isl1 identifies a cardiac progenitor population that proliferates prior to differentiation and contributes a majority of cells to the heart. Dev. Cell. 5, 877–889.
- Cepko, C.L., Austin, C.P., Yang, X., Alexiades, M., Ezzeddine, D., 1996. Cell fate determination in the vertebrate retina. Proc. Natl. Acad. Sci. U. S. A. 93, 589–595.
- Chow, R.L., Lang, R.A., 2001. Early eye development in vertebrates. Ann. Rev. Cell. Dev. Biol. 17, 255–296.
- Deng, M., Yang, H., Xie, X., Liang, G., Gan, L., 2014. Comparative expression analysis of POU4F1, POU4F2 and ISL1 in developing mouse cochleovestibular ganglion neurons. Gene Expr. Patterns 15, 31–37.
- Dykes, I.M., Tempest, L., Lee, S.I., Turner, E.E., 2011. Brn3a and Islet1 act epistatically to regulate the gene expression program of sensory differentiation. J. Neurosci. 31 (27), 9789–9799.
- Edqvist, P.H., Hallböök, F., 2004. Newborn horizontal cells migrate bi-directionally across the neuroepithelium during retinal development. Development 131, 1343–1351.
- Edqvist, P.H., Lek, M., Boije, H., Lindback, S.M., Hallböök, F., 2008. Axon-bearing and axon-less horizontal cell subtypes are generated consecutively during chick retinal development from progenitors that are sensitive to follistatin. BMC Dev. Biol. 8, 46.
- Edqvist, P.H., Myers, S.M., Hallböök, F., 2006. Early identification of retinal subtypes in the developing, pre-laminated chick retina using the transcription factors Prox1, Lim1, Ap2alpha, Pax6, Isl1, Isl2, Lim3 and Chx10. Eur. J. Histochem. 50, 147–154.
- Elshatory, Y., Deng, M., Xie, X., Gan, L., 2007a. Expression of the LIM-homeodomain protein lsl1 in the developing and mature mouse retina. J. Comp. Neurol. 503, 182–197.
- Elshatory, Y., Everhart, D., Deng, M., Xie, X., Barlow, R.B., Gan, L., 2007b. Islet-1 controls the differentiation of retinal bipolar and cholinergic amacrine cells. J. Neurosci. 27, 12707–12720.
- Elshatory, Y., Gan, L., 2008. The LIM-homeobox gene Islet-1 is required for the development of restricted forebrain cholinergic neurons. J. Neurosci. 28, 3291–3297.
- Ericson, J., Thor, S., Edlund, T., Jessell, T.M., Yamada, T., 1992. Early stages of motor neuron differentiation revealed by expression of homeobox gene Islet-1. Science 256, 1555–1560.
- Fischer, A.J., Dierks, B.D., Reh, T.A., 2002. Exogenous growth factors induce the production of ganglion cells at the retinal margin. Development 129, 2283–2291.
- Fischer, A.J., Foster, S., Scott, M.A., Sherwood, P., 2008. Transient expression of LIMdomain transcription factors is coincident with delayed maturation of photoreceptors in the chicken retina. J. Comp. Neurol. 506, 584–603.
- Fischer, A.J., Stanke, J.J., Aloisio, G., Hoy, H., Stell, W.K., 2007. Heterogeneity of horizontal cells in the chicken retina. J. Comp. Neurol. 500, 1154–1171.
- Francisco-Morcillo, J., Hidalgo-Sánchez, M., Martín-Partido, G., 2006. Spatial and temporal patterns of proliferation and differentiation in the developing turtle eye. Brain Res. 1103, 32–48.
- Francisco-Morcillo, J., Sánchez-Calderón, H., Kawakami, Y., Izpisúa Belmonte, J.C., Hidalgo-Sánchez, M., Martín-Partido, G., 2005. Expression of Fgf19 in the developing chick eye. Brain Res. Dev. Brain Res. 156, 104–109.
- Galli-Resta, L., Resta, G., Tan, S.S., Reese, B.E., 1997. Mosaics of islet-1-expressing amacrine cells assembled by short-range cellular interactions. J. Neurosci. 17, 7831–7838.
- Génis-Gálvez, J.M., García-Lomas, V., Prada, F., Armengol, J.A., 1981. Developmental

Please cite this article in press as: Bejarano-Escobar, R., et al., Expression and function of the LIM-homeodomain transcription factor Islet-1 in the developing and mature vertebrate retina, Experimental Eye Research (2015), http://dx.doi.org/10.1016/j.exer.2015.06.021

66

67

68

69

70

71

72

73

74

75

76

77

78

79

80

81

82

83

84

85

86

87

88

89

90

91

92

93

94

95

96

97

98

99

100

101

102

103

104

105

106

107

108

109

110

111

112

113

114

115

116

117

118

119

120

121

122

123

124

125

126

127

128

129

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30

31

32

33

34

35

36

37

38

39

40

41

42

43

44

45

46

47

48

49

50

51

52

53

54

55

56

57

58

59

60

61

62 63

64

65

study of axon formation in the horizontal neurons of the retina of the chick embryo. Anat. Embryol. Berl. 161, 319-327.

- Godinho, L., Williams, P.R., Claassen, Y., Provost, E., Leach, S.D., Kamermans, M., Wong, R.O., 2007. Nonapical symmetric divisions underlie horizontal cell layer formation in the developing retina in vivo. Neuron 56, 597–603. Guduric-Fuchs, J., Ringland, L.J., Gu, P., Dellett, M., Archer, D.B., Cogliati, T., 2009.
- Immunohistochemical study of pig retinal development. Mol. Vis. 15, 1915-1928.
- Hatakeyama, J., Tomita, K., Inoue, T., Kageyama, R., 2001. Roles of homeobox and bHLH genes in specification of a retinal cell type. Development 128, 1313–1322.
- Haverkamp, S., Haeseleer, F., Hendrickson, A., 2003, A comparison of immunocytochemical markers to identify bipolar cell types in human and monkey retina. Vis. Neurosci. 20. 589-600.
- Hobert, O., Westphal, H., 2000. Functions of LIM-homeobox genes. Trends Genet. 16, 75-83.
- Kaku, Y., Ohmori, T., Kudo, K., Fujimura, S., Suzuki, K., Evans, S.M., Kawakami, Y., Nishinakamura, R., 2013. Islet1 deletion causes kidney agenesis and hydro-ureter resembling CAKUT. J. Am. Soc. Nephrol. 24, 1242–1249.
- Karlsson, O., Thor, S., Norberg, T., Ohlsson, H., Edlund, T., 1990. Insulin gene enhancer binding protein Isl-1 is a member of a novel class of proteins containing both a homeo- and a Cys-His domain. Nature 344, 879–882. Kim, D.S., Matsuda, T., Cepko, C.L., 2008. A core paired-type and POU
- homeodomain-containing transcription factor program drives retinal bipolar cell gene expression. J. Neurosci. 28, 7748-7764.
- Kobayashi, A., Shawlot, W., Kania, A., Behringer, R.R., 2004. Requirement of Lim1 for female reproductive tract development. Development 131, 539-549.
- Korzh, V., Edlund, T., Thor, S., 1993. Zebrafish primary neurons initiate expression of the LIM homeodomain protein Isl-1 at the end of gastrulation. Development 118 417-425
- Lamb, T.D., Collin, S.P., Pugh Jr., E.N., 2007. Evolution of the vertebrate eye: opsins, photoreceptors, retina and eye cup. Nat. Rev. Neurosci. 8, 960-976.
- R., Wu, F., Ruonala, R., Sapkota, D., Hu, Z., Mu, X., 2014. Isl1 and Pou4f2 form a complex to regulate target genes in developing retinal ganglion cells. PLoS One 9, e92105
- Liang, X., Song, M.R., Xu, Z., Lanuza, G.M., Liu, Y., Zhuang, T., Chen, Y., Pfaff, S.L. Evans, S.M., Sun, Y., 2011. Isl1 is required for multiple aspects of motor neuron development. Mol. Cell. Neurosci. 47, 215-222.
- Link, B.A., Fadool, J.M., Malicki, J., Dowling, J.E., 2000. The zebrafish young mutation acts non-cell-autonomously to uncouple differentiation from specification for all retinal cells. Development 127, 2177-2188.
- Liu, W., Wang, J.H., Xiang, M., 2000. Specific expression of the LIM/homeodomain protein Lim-1 in horizontal cells during retinogenesis. Dev. Dyn. 217, 320-325
- López-Bendito, G., Cautinat, A., Sánchez, J.A., Bielle, F., Flames, N., Garratt, A.N., Talmage, D.A., Role, L.W., Charnay, P., Marín, O., Garel, S., 2006. Tangential neuronal migration controls axon guidance: a role for neuregulin-1 in thalamocortical axon navigation. Cell 125, 127-142.
- Masai, I., Stemple, D.L., Okamoto, H., Wilson, S.W., 2000. Midline signals regulate retinal neurogenesis in zebrafish. Neuron 27, 251-263.
- Mitrofanis, J., Maslim, J., Stone, J., 1988. Catecholaminergic and cholinergic neurons in the developing retina of the rat. J. Comp. Neurol. 276, 343-359.
- Moreno, N., Domínguez, L., Retaux, S., González, A., 2008a. Islet1 as a marker of subdivisions and cell types in the developing forebrain of Xenopus. Neuroscience 154, 1423-1439.
- Moreno, N., González, A., Retaux, S., 2008b. Evidences for tangential migrations in Xenopus telencephalon: developmental patterns and cell tracking experiments. Dev. Neurobiol. 68, 504-520.
- Moreno, N., Morona, R., López, J.M., Domínguez, L., Joven, A., Bandín, S., González, A., 2012. Characterization of the bed nucleus of the stria terminalis in the forebrain of anuran amphibians. J. Comp. Neurol. 520, 330-363.
- Moreno, N., Morona, R., López, J.M., González, A., 2010. Subdivisions of the turtle Pseudemys scripta subpallium based on the expression of regulatory genes and neuronal markers. J. Comp. Neurol. 518, 4877-4902.
- Moreno, N., Retaux, S., González, A., 2008c. Spatio-temporal expression of Pax6 in Xenopus forebrain. Brain Res. 1239, 92-99.
- Moretti, A., Lam, J., Evans, S.M., Laugwitz, K.L., 2007. Biology of Isl1+ cardiac progenitor cells in development and disease. Cell. Mol. Life Sci. 64, 674-682.
- Mu, X., Fu, X., Sun, H., Beremand, P.D., Thomas, T.L., Klein, W.H., 2005. A gene network downstream of transcription factor Math5 regulates retinal progenitor cell competence and ganglion cell fate. Dev. Biol. 280, 467-481.
- Mu, X., Fu, X., Beremand, P.D., Thomas, T.L., Klein, W.H., 2008. Gene regulation logic in retinal ganglion cell development: Isl1 defines a critical branch distinct from but overlapping with Pou4f2. Proc. Natl. Acad. Sci. U. S. A. 105, 6942-6947.
- Mullen, R.D., Colvin, S.C., Hunter, C.S., Savage, J.J., Walvoord, E.C., Bhangoo, A.P., Ten, S., Weigel, J., Pfaffle, R.W., Rhodes, S.J., 2007. Roles of the LHX3 and LHX4 LIM-homeodomain factors in pituitary development. Mol. Cell. Endocrinol. 265-266, 190-195.
- Narkis, G., Tzchori, I., Cohen, T., Holtz, A., Wier, E., Westphal, H., 2012. Isl1 and Ldb co-regulators of transcription are essential early determinants of mouse limb development. Dev. Dyn. 241, 787-791.
- Nieuwkoop, P.D., Faber, J., 1967. Normal table of Xenopus laevis (Daudin). North Holland, Amsterdam.

- Ohsawa, R., Kageyama, R., 2008. Regulation of retinal cell fate specification by multiple transcription factors. Brain Res. 1192, 90-98.
- Okamoto, M., Bito, T., Noji, S., Ohuchi, H., 2009. Subtype-specific expression of Fgf19 during horizontal cell development of the chicken retina. Gene Expr. Patterns 9, 306-313.
- Pak, W., Hindges, R., Lim, Y.S., Pfaff, S.L., O'Leary, D.D., 2004. Magnitude of binocular vision controlled by islet-2 repression of a genetic program that specifies laterality of retinal axon pathfinding. Cell 119, 567–578.
- Pan, L., Deng, M., Xie, X., Gan, L., 2008. ISL1 and BRN3B co-regulate the differentiation of murine retinal ganglion cells. Development 135, 1981-1990.
- Pandur, P., Sirbu, I.O., Kuhl, S.J., Philipp, M., Kuhl, M., 2013. Islet1-expressing cardiac progenitor cells: a comparison across species. Dev. Genes. Evol. 223, 117-129.
- Peichl, L., González-Soriano, J., 1994. Morphological types of horizontal cell in rodent retinae: a comparison of rat, mouse, gerbil, and guinea pig. Vis. Neurosci. 11. 501-517.
- Pfaff, S.L., Mendelsohn, M., Stewart, C.L., Edlund, T., Jessell, T.M., 1996, Requirement for LIM homeobox gene Isl1 in motor neuron generation reveals a motor neuron-dependent step in interneuron differentiation. Cell 84, 309–320.
- Poche, R.A., Kwan, K.M., Raven, M.A., Furuta, Y., Reese, B.E., Behringer, R.R., 2007. Lim1 is essential for the correct laminar positioning of retinal horizontal cells. J. Neurosci. 27, 14099–14107.
- Poche, R.A., Reese, B.E., 2009. Retinal horizontal cells: challenging paradigms of neural development and cancer biology. Development 136, 2141-2151.
- Porter, F.D., Drago, J., Xu, Y., Cheema, S.S., Wassif, C., 1997. Lhx2, a LIM homeobox gene, is required for eye, forebrain, and definitive erythrocyte development. Development 124, 2935–2944.
- Rapaport, D.H., Wong, L.L., Wood, E.D., Yasumura, D., LaVail, M.M., 2004. Timing and topography of cell genesis in the rat retina. J. Comp. Neurol. 474, 304-324.
- Roy, A., de Melo, J., Chaturvedi, D., Thein, T., Cabrera-Socorro, A., Houart, C., Meyer, G., Blackshaw, S., Tole, S., 2013. LHX2 is necessary for the maintenance of optic identity and for the progression of optic morphogenesis. J. Neurosci. 33, 6877-6884.
- Sapkota, D., Wu, F., Mu, X., 2011. Focus on molecules: Math5 and retinal ganglion cells. Exp. Eye Res. 93, 796-797.
- Shirazi Fard, S., Jarrin, M., Boije, H., Fillon, V., All-Eriksson, C., Hallböök, F., 2013. Heterogenic final cell cycle by chicken retinal Lim1 horizontal progenitor cells leads to heteroploid cells with a remaining replicated genome. PLoS One 8, e59133
- Shkumatava, A., Fischer, S., Muller, F., Strahle, U., Neumann, C.J., 2004. Sonic hedgehog, secreted by amacrine cells, acts as a short-range signal to direct differentiation and lamination in the zebrafish retina. Development 131, 3849 - 3858
- Shkumatava, A., Neumann, C.J., 2005. Shh directs cell-cycle exit by activating p57Kip2 in the zebrafish retina. EMBO Rep. 6, 563-569.
- Stanke, J.J., Lehman, B., Fischer, A.J., 2008. Muscarinic signaling influences the patterning and phenotype of cholinergic amacrine cells in the developing chick retina. BMC Dev. Biol. 8, 13.
- Suga, A., Taira, M., Nakagawa, S., 2009. LIM family transcription factors regulate the subtype-specific morphogenesis of retinal horizontal cells at post-migratory stages. Dev. Biol. 330, 318-328.
- Thor, S., Ericson, J., Brannstrom, T., Edlund, T., 1991. The homeodomain LIM protein Isl-1 is expressed in subsets of neurons and endocrine cells in the adult rat. Neuron 7, 881–889.
- Tsuchida, T., Ensini, M., Morton, S.B., Baldassare, M., Edlund, T., Jessell, T.M., Pfaff, S.L., 1994. Topographic organization of embryonic motor neurons defined by expression of LIM homeobox genes. Cell 79, 957-970.

Wang, H.F., Liu, F.C., 2001. Developmental restriction of the LIM homeodomain transcription factor Islet-1 expression to cholinergic neurons in the rat striatum. Neuroscience 103, 999-1016.

- Whitney, I.E., Raven, M.A., Ciobanu, D.C., Poche, R.A., Ding, Q., Elshatory, Y., Gan, L., Williams, R.W., Reese, B.E., 2011. Genetic modulation of horizontal cell number in the mouse retina. Proc. Natl. Acad. Sci. U. S. A. 108, 9697-9702.
- Whitney, I.E., Kautzman, A.G., Reese, B.E., 2015. Alternative splicing of the LIMhomeodomain transcription factor Isl1 in the mouse retina. Mol. Cell. Neurosci. 65. 102-113.
- Wu, F., Sapkota, D., Li, R., Mu, X., 2012. Onecut 1 and Onecut 2 are potential regulators of mouse retinal development. J. Comp. Neurol. 520, 952-969.

Wu, F., Kaczynski, T.J., Sethuramanujam, S., Li, R., Jain, V., Slaughter, M., Mu, X., 2015. Two transcription factors, Pou4f2 and Isl1, are sufficient to specify the retinal ganglion cell fate. Proc. Natl. Acad. Sci. U. S. A. 112 (13), 1159-1168

- Xiang, M., 2013. Intrinsic control of mammalian retinogenesis. Cell. Mol. Life Sci. 70, 2519-2532.
- Yang, Z., Ding, K., Pan, L., Deng, M., Gan, L., 2003. Math5 determines the competence state of retinal ganglion cell progenitors. Dev. Biol. 264, 240-254.
- Yao, J., Sun, X., Wang, Y., Xu, G., Qian, J., 2007. Math5 promotes retinal ganglion cell expression patterns in retinal progenitor cells. Mol. Vis. 13, 1066-1072.
- Young, R.W., 1985. Cell differentiation in the retina of the mouse. Anat. Rec. 212, 199-205 Yun, S., Saijoh, Y., Hirokawa, K.E., Kopinke, D., Murtaugh, L.C., Monuki, E.S.,
- Levine, E.M., 2009. Lhx2 links the intrinsic and extrinsic factors that control optic cup formation. Development 136, 3895-3906.

66

67

68

69

70

71

72

73