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Review

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

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A B S T R A C T

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 a 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.

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 non-apical 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; 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

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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

Table 1
Isl1 in the developing and mature visual system of vertebrates.

Species	Bibliography	Most relevant events described
Fish		
Zebrafish (*Danio rerio*, Hamilton 1822)	Korzh et al., 1993	**Onset of Isl1 immunoreactivity in the retina** - Isl1-immunoreactive neurons appear after 24hpf.
	Link et al., 2000	**Isl1 immunoreactivity in the mature retina** - 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. - The expression progressively spreads to the dorsal and temporal retina. - Isl1 mRNA is expressed in the GCL and in the INL.
	Shkumatava et al., 2004	**Isl1 immunoreactivity in the developing and mature retina** - Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiating and mature retina.
Tench (*Tinca tinca*, Linnaeus 1758)	Bejarano-Escobar et al., 2009	**Isl1 immunoreactivity in the developing and mature retina** - Expressed in the first newborn ganglion cells in the undifferentiated neural retina. - Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiating and mature retina.
Senegalese sole (*Solea senegalensis*, Kaup 1858)	Bejarano-Escobar et al., 2010	**Isl1 immunoreactivity in the developing and mature retina** - Expressed in the first newborn ganglion cells in the undifferentiated neural retina. - Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar, and horizontal cells in the differentiating and mature retina.
Small-spotted catshark (*Scyliorhinus canicula*, Linnaeus 1758)	Bejarano-Escobar et al., 2012	**Isl1 immunoreactivity in the developing and mature retina** - 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 and horizontal cells in the developing and mature retina.
Amphibiams		
South African clawed frog (*Xenopus laevis*, Daudin 1802)	Álvarez-Hernán et al., 2013	**Isl1 immunoreactivity in the developing and mature retina** - 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, and horizontal cells in the differentiating and mature retina.
Reptiles		
Mediterranean turtle (*Mauremys leprosa*, 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 neural retina. - 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		
Chick (*Gallus gallus*, Linnaeus 1758)	Austin et al., 1995	**Retinal determination by Notch selection.** - 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–hatch retina Isl1 is expressed in cholinergic amacrine 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. - Expressed in many differentiated ganglion cells, subsets of amacrine, bipolar, 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 cells in the differentiating and mature retina. - Expressed in the nuclei of a subset of photoreceptors, 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 calretinin.
	Boije et al., 2008	**mRNA expression of different transcription factors in the developing retina** - 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** - Expressed in immature horizontal cells. - The birth of Isl1-positive horizontal cells peaked between E4 and E5. - 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*)

Table 1 (*continued*)

Species	Bibliography	Most relevant events described
	Stanke et al., 2008	**Molecular mechanisms involved in amacrine cell differentiation** - The cholinergic amacrine cells express Isl1 with the onset of differentiation (E6) and into the mature retina.
	Okamoto et al., 2009	**Molecular mechanisms involved in horizontal cell differentiation** - Chronotopographical expression pattern of Isl1 during retinal development. - Fgf19-positive horizontal cells and Isl1-positive cells never overlap.
	Suga et al., 2009	**Molecular mechanisms involved in horizontal cell differentiation** - Isl1 is first detected immunohistochemically at E3.5 in ganglion cells. - Isl1 and Lim1 are required for the subtype-specific morphogenesis of post-migratory horizontal cells at late developmental stages. - Isl1 is expressed in the axonless Type II and Type III horizontal cells. - Overexpression of Isl1 in Type I horizontal cells induces subtype change into Type II horizontal cells, but not differentiation of Type III horizontal cells.
Mammals		
Mouse (*Mus musculus*, Linnaeus 1758)	Elshatory et al., 2007a	**Isl1 immunoreactivity in the developing retina** - 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	**Role in establishing retinal neuronal subtypes** - Controls the differentiation of bipolar cells and cholinergic amacrine cells.
	Li et al., 2014	**Molecular mechanisms involved in retinal ganglion cell development** - Isl1 and Pou4f2 form a complex to regulate essential target genes involved in ganglion cell differentiation. - Isl1 and Pou4f2 interact with other members of POU domain and LIM-homeodomain transcription factors, respectively.
	Mu et al., 2008	**Molecular mechanisms involved in retinal ganglion cell development** - Required for the differentiation and survival 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., 2008	**Molecular mechanisms involved in retinal ganglion cell development** - Involvement of both parallel and cooperative functions of Isl1 and Brn3b in retinal ganglion cell development.
	Whitney et al., 2011	**Genetic modulation of horizontal cell number** - Although Isl1 is not expressed in horizontal cell precursors, it plays a role in regulating horizontal cell numbers.
	Wu et al., 2012	**Molecular 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.
	Whitney et al., 2015	**Role in establishing retinal neuronal subtypes** - Demonstrate the differential expression of the canonical and alternative isoforms of Isl1 amongst retinal cell classes.
	Wu et al., 2015	**Molecular 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., 1991	**Isl1 immunoreactivity in the mature retina** - Expressed in a subset of retinal ganglion cells and a few cells in the INL.
	Galli-Resta et al., 1997	**Early differentiation of a subset of amacrine 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, subsets of amacrine, bipolar, and horizontal cells in the differentiating and mature retina.

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

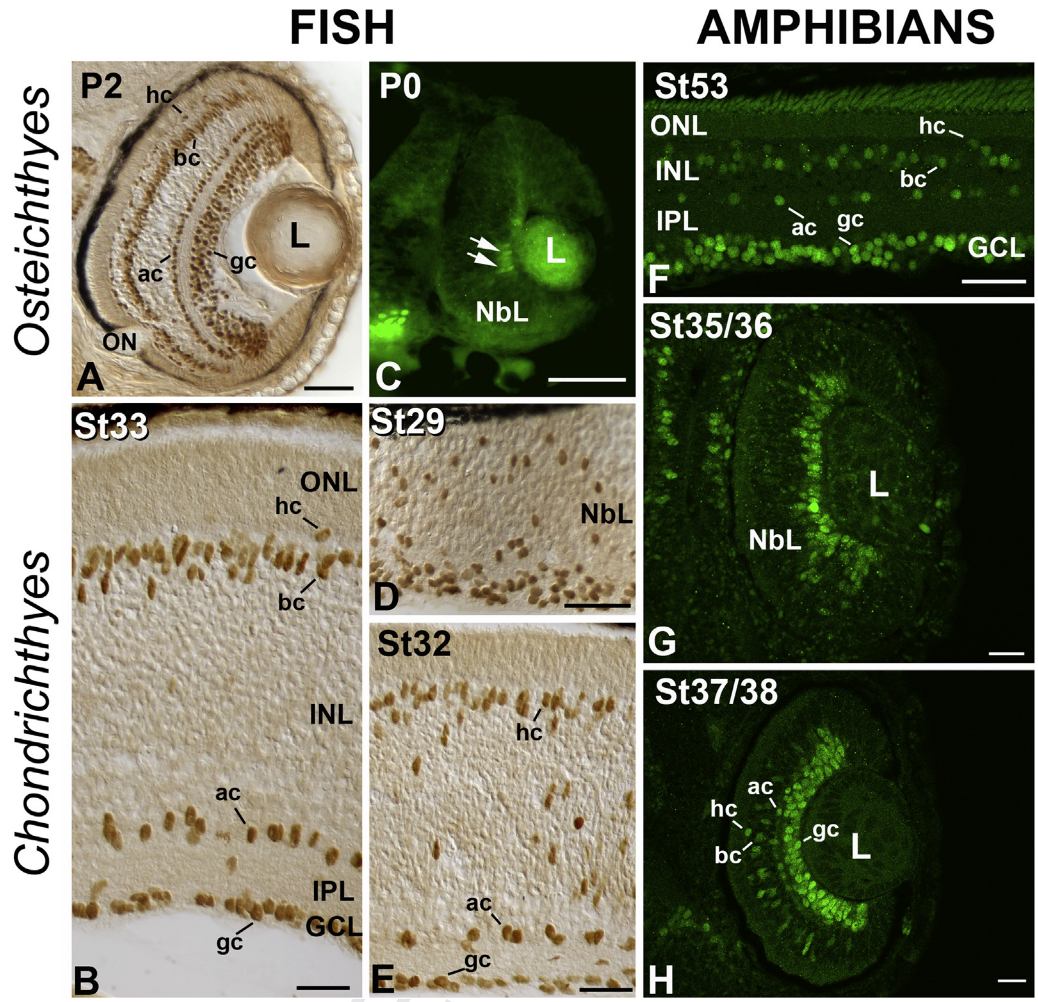

Fig. 1. Spatial and temporal expression of the transcription factor Isl1 in the mature and developing retina of anamniotes. Isl1 is expressed in the nuclei of subpopulations of ganglion, amacrine, bipolar, and horizontal cells in the differentiated retina of the tench (A), small spotted catshark (B), and South African clawed frog (C). During early stages of development, Isl1 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, Isl1 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; *gc*, ganglion 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 fate-determining 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 co-expression 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 (Isl1α) and alternative (Isl1β) 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

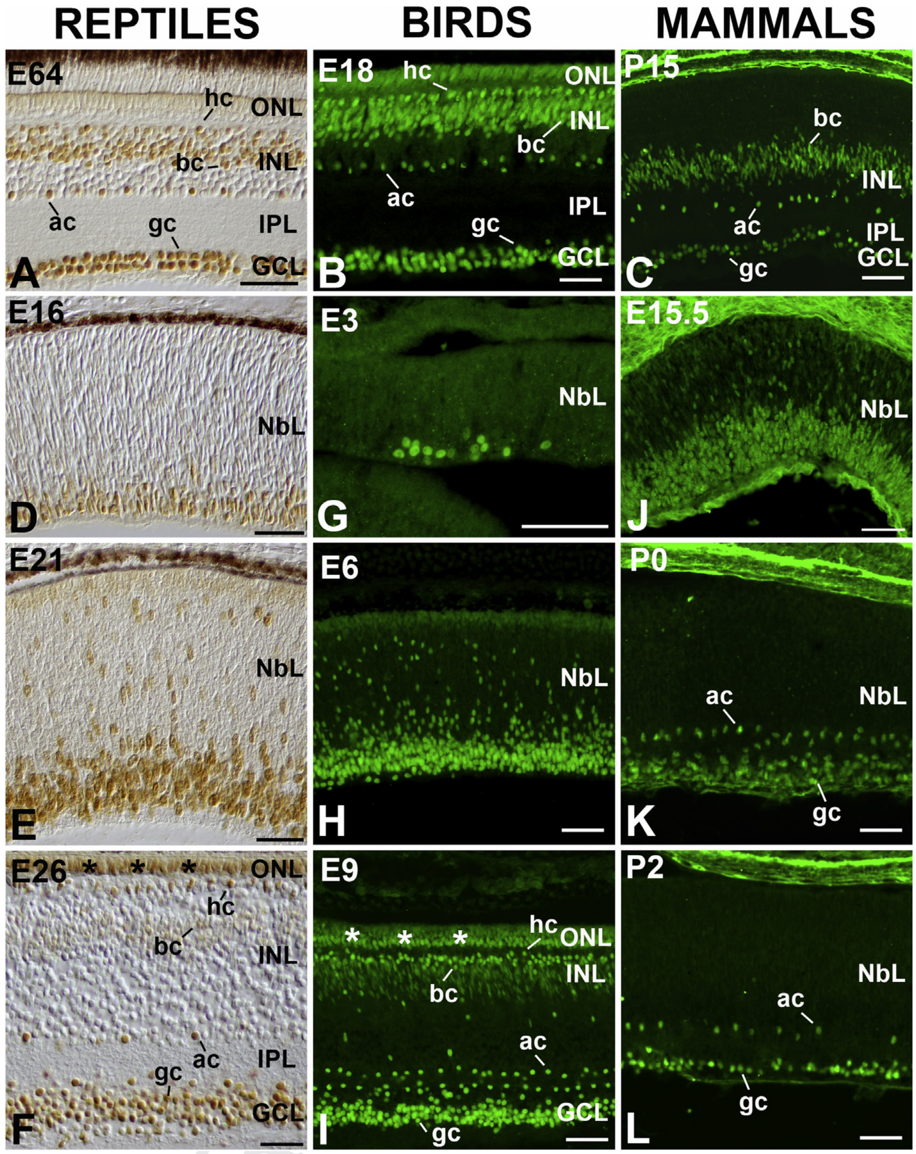

Fig. 2. Spatial and temporal expression of the transcription factor Isl1 in the mature and developing retina of amniotes. Isl1 is expressed in the nuclei of subpopulations of ganglion, amacrine, and bipolar cells in the differentiated retina of the Mediterranean turtle (A), chick (B), and mouse (C). 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; *gc*, ganglion 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 co-localized 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-

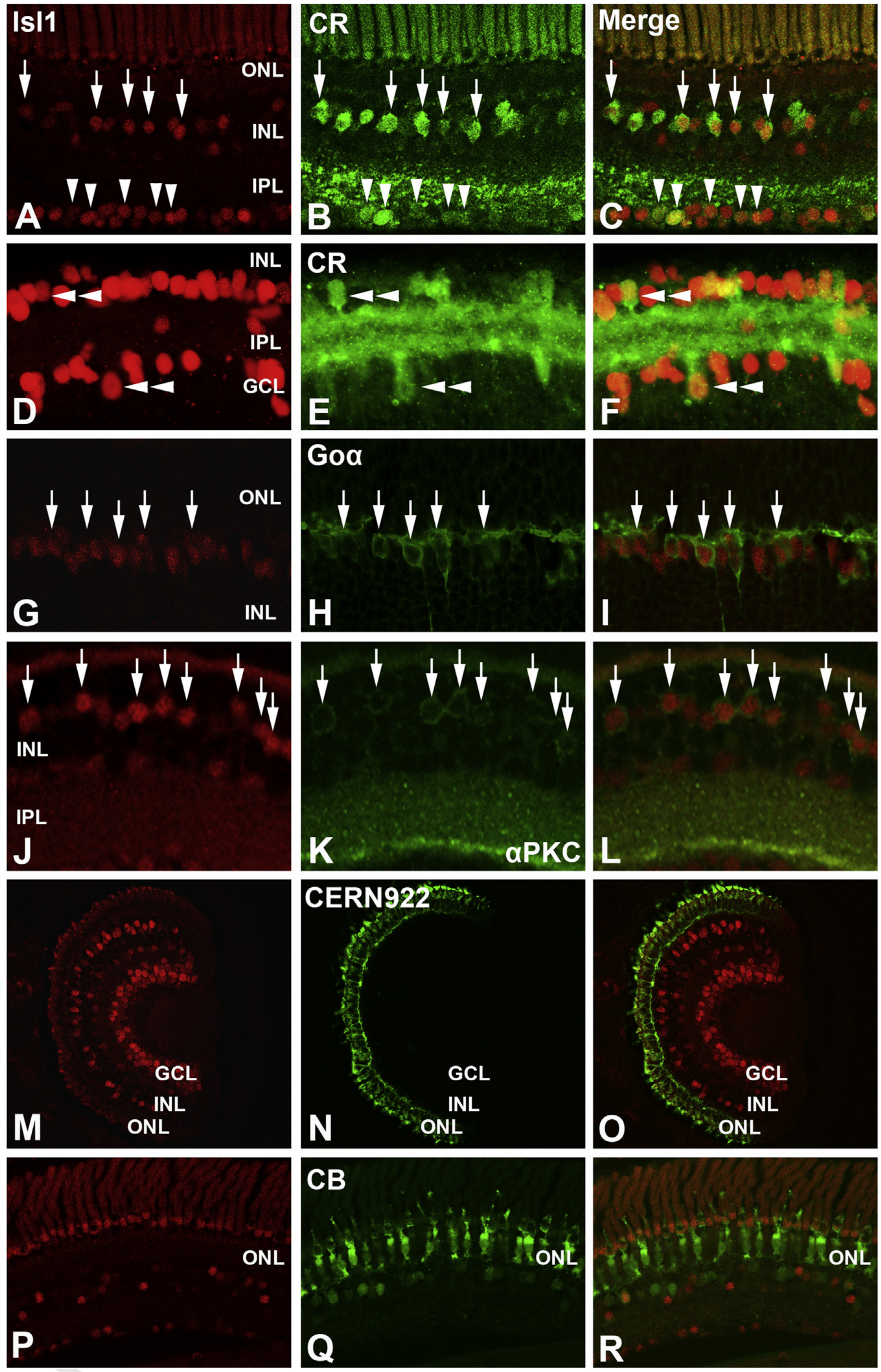

Fig. 3. Photomicrographs of the South African clawed frog (A–C, M–R), small-spotted catshark (D–I), and Senegalese sole (J–L) differentiated retinas showing the double immunolabeling of Is1 (red) and different retinal markers (green): CR (A–F), Goα (G–I), αPKC (J–L), CERN922 (M–O), and CB (P–R). Isl1 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 Isl1 (double arrowheads in D–F). Isl1 co-localizes with typical bipolar cell markers (arrows in A–C, G–L). Isl1 never co-expressed with typical rod (M–O) and cone (P–R) markers. Scale bars denote 25 µm. *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 nucleotide-binding protein Go (Goα) (Fig. 3G–I), the α-isoform of protein kinase C (αPKC) (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).

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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 axon-bearing 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

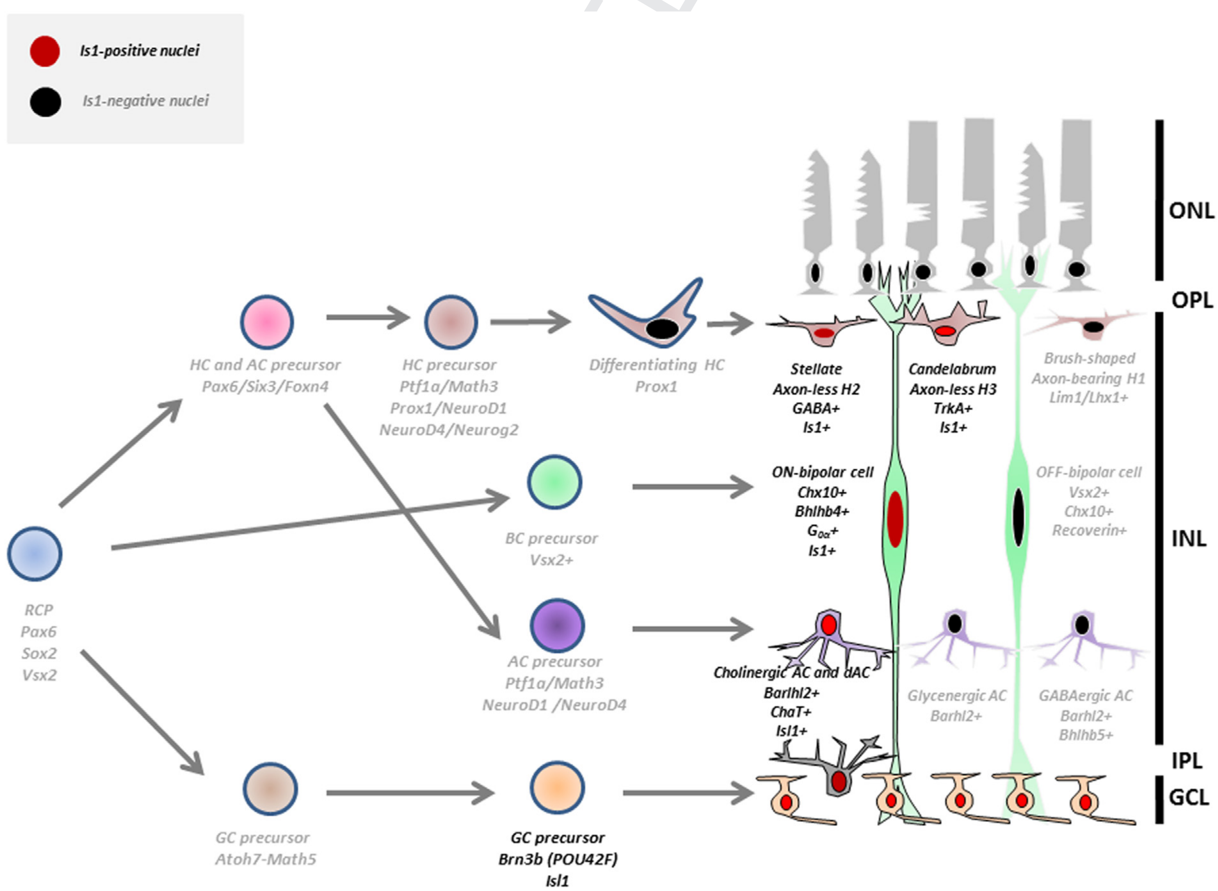

Fig. 4. Schematic summary of Isl1 expression (red nuclei) in the developing and mature vertebrate retina. Isl1 is involved in specification and differentiation of ganglion, amacrine, bipolar, and horizontal cells. Brn3b and Isl1 are synergistically required for retinal ganglion cell differentiation and 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; *GCL*, 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.

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