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Ocular forkhead transcription factors: seeing eye to eye

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ABSTRACT Forkhead transcription factors comprise a large family of proteins with diverse functions during development. Recently, there has been accumulating evidence that several members of this family of proteins play an important role in the development of the vertebrate retina. Here, we summarize the cumulative data which demonstrates the integral role that forkhead factors play in cell cycle control of retinal precursors, as well as in cell fate determination, during retinal development. The expression patterns for 14 retinal expressed forkhead transcription factors are presented with an emphasis on comparing the expression profiles across species. The functional data regarding forkhead gene products expressed within the retina are discussed. As presented, these data suggest that forkhead gene products contribute to the complex regulation of proliferation and differentiation of retinal precursors during vertebrate eye development.

KEY WORDS: *forkhead, retina, eye development, progenitor cell*

Introduction

Forkhead factors are an evolutionarily conserved family of proteins whose functions are diverse in developmental processes. The ever-growing family of forkhead proteins are divided into subclasses A to S according to the conservation within their signature winged helix DNA binding domain (Kaestner *et al.*, 2000). They function as transcription factors, modulators of cell cycle machinery function, cell fate determinants, as well as cell survival factors. Recently it has become apparent that several subfamilies of forkhead transcription factors are expressed in developing eye tissue.

Here, we have compiled the accumulating data regarding eye expression of forkhead gene products to iterate the importance of this family in control of retinal precursors during development. We highlight several forkhead proteins that regulate the activity of retinal progenitor cells within the vertebrate eye. We describe the expression patterns of known retinal forkhead genes across vertebrate species. We also discuss the available functional data regarding forkhead proteins in the retina as transcription factors and cell fate determinants.

In this review, we will use species-specific conventions for writing forkhead gene and gene product names: the forkhead box abbreviation (fox), followed by the family designation, followed by the intra-familial individual gene designation with species-specific capitalization. For example, the forkhead box gene A1 will be designated as FOXA1 (human), FoxA1 (frog), Foxa1 (mammals), or foxa1 (zebrafish). The forkhead proteins mentioned in this review, including alternate names and HomoloGene entries, are included in Table 1.

Overview of eye development

Multiple inductive events between a region of competent neural ectoderm and overlying surface ectoderm properly determine eye fields in vertebrates**.** At the end of neurulation, a region of the anterior neural plate evaginates from the ventro-lateral wall of the forebrain to form the optic vesicle. The evaginating vesicle causes the overlying ectoderm to thicken, forming the lens placode, which eventually separates from the surface ectoderm forming the lens vesicle. The cells of the lens vesicle differentiate into primary fiber cells or quiescent secondary fiber cells dependant upon their location in that ectodermal tissue. Simultaneous with the development of the lens vesicle, the optic vesicle invaginates to form a bi-layered structure, the optic cup. The outer layer of the optic cup will give rise to the retinal pigmented epithelium

Abbreviations used in this paper: CMZ, ciliary marginal zone; RGC, retinal ganglion cells; RPC, retinal progenitor cells.

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of the mature eye, while the inner layer of the optic cup consisting of retinal precursors will give rise to the neural retina. Additional anterior structures, including the cornea, iris, ciliary body and sclera, develop as the lens placode or portions of the optic cup induce morphological changes in surrounding tissues. The cornea is induced as the lens placode comes into contact with overlying surface ectoderm. Both the iris and ciliary body form at the apices of the optic cup, as a result of interactions between presumptive neural and pigmented retinal layers. The sclera develops from mesenchymal tissue that is in contact with the prospective pigmented layer surrounding the eye.

Forkhead transcription factors in anterior eye structures

Forkhead transcription factors are known to play critical roles in the development of the anterior eye. Due to the nature of reciprocal interaction of developing neural retina with developing lens and anterior tissue during eye development in vertebrates, these forkhead genes may also have a role in proper retinal development.

Forkhead genes from the C, E and P subclasses are expressed in anterior eye structures. FOXC1 mutations have been linked to Axenfeld-Reiger Anomaly (ARA) characterized by malformations in iris placement, and Type I Iridogonoidysgenesis, an autosomal dominant form of iris hypoplasia. (OMIM:601090). Recently, Tamini *et al.,* demonstrated that foxc1 also directs lens development during zebrafish development (Tamimi *et al*., 2006). Mice heterozygous for either Foxc1 or Foxc2 exhibit anterior segment phenotypes (Smith *et al*., 2000), and a linkage mapping study showed mutations in bovine Foxc2 segregated with ocular dysgenesis phenotypes (Abbasi *et al*., 2006). No human mutation in FOXC2 has been linked to ARA despite screening of 32 patients with ARA (Smith *et al*., 2000). However, mutations in the *FoxC2* locus results in distichisasis, a syndrome in which patients present with two rows of eyelashes (Brooks *et al*., 2000, see OMIM:602402 for additional citations).

Allelic variants of human *FOXE3* have been linked to congenital eye malformation syndromes in humans (reviewed in Medina-Martinez *et al*., 2005, Medina-Martinez and Jamrich, 2007). A homozygous null mutation causes congenital aphakia, defined as an absence of lens development (Valleix *et al*., 2006). Also, a single nucleotide insertion resulting in a frameshift mutation in the single coding exon of FOXE3 causes anterior segment mesenchymal dysgenesis, in which patients present with abnormalities in anterior eye structures including the lens, and have increased risk of glaucoma and corneal opacity (Semina *et al*., 2001). The mouse dysgenetic lens (*Dyl*) phenotype was shown to be caused by two mutations in the DNA binding domain of Foxe3, thus confirming its role in proper lens development (Blixt *et al*., 2000, Brownell *et al*., 2000). The ability of FoxE family members to contribute to proper lens development is a highly conserved mechanism. Notably, overexpression of xlFoxE3 in the presumptive lens results in a thickening of lens ectoderm (Kenyon *et al*., 1999). Morpholino knockdown of the *Danio rerio* foxe3 orthologue results in morphants with multilayered lens epithelial cells as well as a significant lens fiber cell dysmorphogenic phenotype (Shi *et al*., 2006).

The final forkhead protein to exhibit expression in anterior structures is FoxP1. A recent report describes the expression of the *X. laevis* FoxP orthologues in developing lens tissue. FoxP1 shows lens specific expression in addition to faint expression in the neural retina (see below) (Pohl *et al*., 2005). To date, no ocular phenotype has been identified in association with mutations in genes of the FoxP subclass.

TABLE 1

FORKHEAD GENES EXPRESSED IN EYE STRUCTURES

	Forkhead Gene	Alternate Names	HomoloGene Entry
Anterior Structures	FOXC1	ARA FKHL7 FREAC3 IRID1	20373
	FOXC2	MFH-1	21091
	FOXE3	ASMD *dyl* FKHL-12 FREAC-8	32145
	FOXP1	FKH-1B	13092
Retinal Progenitors	FOXN2	HTLF FKH-19	31078
	FOXN4	whn	17526
	FOXM1	HFH-11 FKHL-16 MPP2 TRIDENT	7318
	FOXP2	SPCH1 TRNC10	33482
Neural Retina	FOXD1	BF-2 FKHL-8 FREAC-4	3290
	FOXF1	FREAC-1 HFH-8 XFD-13	1114
	FOXG1	BF-1 FKH-4 HFH-9	3843
	FOXK1	MNF	82414
	FOXL1	FKH-6 FKHL-11 FREAC-7	48335
	FOXN3	Ches1	3809
	FOXO3	FKHRL-1 FKHR-2	31039
	FOXP1	FKH-1B	13092
	FOXP4	FKHL-A	12536
	FOXS1	FKH-3 FKHL-18 FREAC-10	14239*

Forkhead transcription factors in the developing neural retina

A significant amount of literature describes forkhead proteins in the developing vertebrate retina. We discuss the accumulating expression data for retinal forkhead gene products with a focus on comparison of expression patterns across vertebrate species. This data is also summarized in Table 2.

Two forkhead genes expressed in the developing eye fields include FoxD1 and FoxG1. In lower vertebrates such as *X. laevis*, expression of FoxD1 in the eye fields begins during early tailbud stages and continues in the temporal region of the retina in subsequent stages (Mariani and Harland, 1998). The foxd1 orthologue in zebrafish exhibits a comparable expression pattern (Odenthal and Nusslein-Volhard, 1998). In mammals, Foxd1 is also expressed in the temporal region of the optic cup and retina (Hatini *et al*., 1994)

Mammalian Foxd1 and Foxg1 are expressed in retinal precursor cells in a distinct, complementary pattern at the optic vesicle stage of development (Hatini *et al*., 1994). Mammalian Foxg1 is expressed in the anterior neural plate and the nasal retina as development proceeds (Huh *et al*., 1999). Expression is also evident in the lens and optic nerve (Pratt *et al*., 2004). It has been suggested that the reciprocal nature of the Foxd1 and Foxg1 expression patterns is related to their function in determining retinal cell fate (see below). The expression of the

FoxG1 homologue in *X. laevis* is observed in the telencephalic region of the developing forebrain (Bourguignon *et al.*, 1998, Dirksen and Jamrich, 1995), and is apparent in the ventral/nasal portion of the retina in *Xenopus* embryos in whole embryos (Bourguignon *et al.*, 1998). We demonstrate a specific pattern for FoxG1 in the retinae of *X. laevis* embryos by section *in situ* hybridization in Figure 1. It is expressed in the ganglion cell layer and ventral CMZ at stage 38 and 41, and is later restricted to the ventral portion of the CMZ.

Three members of the FoxP subclass in *Xenopus laevis* exhibit retinal expression. FoxP1, FoxP2 and FoxP4 are expressed in retinal precursor of *X. laevis* beginning at mid-gastrula stage. FoxP2 appears restricted to the dorsal-most cells within the retinal anlage at this stage; it persists in the eye throughout tailbud stages. Expression of FoxP2 appears highly specific to the ciliary marginal zone (CMZ) during maturation of the neural retina as demonstrated by sections of whole mounted *in situ* hybridization patterns (Schon *et al.*, 2006). Using *in situ* hybridization of sectioned material, FoxP2 expression is observed in the ganglion and inner plexiform layers of the central retina during retinal maturation (Figure 1). This discrepancy may be explained in the use of different techniques. *Danio rerio* foxp2 is expressed in the inner plexiform layer after differentiation of neural retinal subtypes (Bonkowsky and Chien, 2005), demonstrating that FoxP2 expression patterns are not conserved among vertebrate species. Expression of Foxp1 and Foxp2 proteins have been described in developing CNS structures in mice (Ferland *et al.*, 2003, Lu *et al.*, 2002, Shu *et al.*, 2001, Takahashi *et al.*, 2003, Tamura *et al.*, 2003), gut (Pohl *et al.*, 2005, Shu *et al.*, 2001), and lung tissues (Lu *et al.*, 2002, Shu *et al.*, 2001) but neither has been specifically investigated in retinal tissue of mammals. Noteworthy, however, is the high conservation of the FoxP family members across species (86% identical between mouse and human orthologues), and their common expression patterns in other reported tissues such as the cerebellum. A single report describes *Xenopus laevis* FoxP4 being expressed in the retinal anlage at neural tube stages and persists in the neural retina through tailbud and tadpole stages of (Schon *et al.*, 2006).

A single citation regarding *X. laevis* FoxK1 describes its expression in the eye primordia, where it is expressed in a dorsal to ventral gradient (Pohl and Knochel, 2004). Whether FoxK1 is maintained in the CMZ after differentiation was not reported. A search of FoxK1 ESTs does not reveal any derived from eye tissue in other species; this leaves open the question of whether FoxK1 in the developing eye tissue is a species-specific phenomenon.

In zebrafish, foxl1 is expressed in the neural retina (Nakada *et al.*, 2006) after neurulation (33hpf), albeit weakly. Expression patterns of the Foxl1 homologue in mammals does not reveal any similarities (Fukuda *et al.*, 2003, Kaestner *et al.*, 1997). In the case of FoxL proteins, there is little conservation beyond the forkhead domain, requiring more investigation into whether *Danio rerio* foxl1 and mouse Foxl1 are functionally equivalent (Nakada *et al.*, 2006). Even so, the knockdown phenotype (discussed below) reveals a certain involvement for foxl1 in zebrafish eye development.

A recent paper by Pohl *et al.* describes the initiation of FoxO3 expression in the *Xenopus* eye at stage 26, a time in development before retinogenesis occurs (Pohl *et al.*, 2004). FoxO3 expression is specific to the neural retina in *X. laevis*, as the lens is devoid of FoxO3 expression (Pohl *et al.*, 2004). Expression of the mouse homologue of Foxo3 has not been demonstrated in retinal tissue. However, four FoxO family members exist in mammals (Foxo1,3,4 and 6), and Foxo1 is expressed in the photoreceptor layer of P0 mice (Gray *et al.*, 2004). In addition, EST analysis reveals two FoxO3 ESTs derived from mouse eye tissue (AK143198, EL608549). In the future, it will

TABLE 2

FORKHEAD GENE EXPRESSION IN THE RETINA

GENE	CMZ				NEURAL RETINA							
Retinal Progenitors	PE	Zone 1	Zone 2	Zone 3	Zone 4	GCL	IPL	INL	OPL	ONL	PL	AS	REFERENCES
FOXG1	+	+	+	+	+	+							Tao et al., 1992; Hatini et al., 1994; Dirksen et al., 1995; Picker et al., 2005
FOXN2	+		+	+	+	+		+				+	Schuff et al. 2006, Figure 1
FOXN4	+		+	+	+								Gouge et al., 2004;,Danilova et al., 2004; Schuff et al., 2006; Kelly et al., 2007; Figure 1
FOXM1	+	+	+	+	+								Pohl et al., 2003 Figure 1
FOXP2	+					+		+					Bonkowsky et al., 2004; Schon et al., 2006; Figure 1
Neural Retina													
FOXD1	+												Hatini et al., 1994; Mariani et al., 1998; Odenthal et al., 1998
FOXF1										+			Kalinichenko et al., 2003
FOXK1	+												Pohl et al., 2004
FOXL1													Adult eye tissue, Nakada et al., 2006
FOXN3	+					+						+	Schuff et al. 2006
FOXO3	+												Pohl et al., 2004; Figure 2
FOXP1	+									+			Pohl et al., 2005; Schon et al., 2006
FOXP4	+					+							Schon et al., 2006
FOXS1						+				+			Heglind et al., 2005

be interesting to compare the expression patterns of these ESTs with the established pattern in *X. laevis*.

Forkhead transcription factors in differentiated retinal cell types

Neural retinal precursors of the optic cup differentiate to produce seven neural retinal cell types (6 neuronal and one glial). The differentiation of the neural retinal precursors occurs in a conserved stereotypical manner to produce proper retinal layering. The differentiation of these cell types is dependant upon proper expression of transcription factors to determine proper cycling of the cells as well as cell fate.

Only two forkhead gene products are known to be expressed exclusively in the fully mature neural retina. A single citation for Foxs1 describes its expression in the outer nuclear layer of the adult mammalian retina, as well as in a subset of ganglion cells at P14 by analysis of a β-galactosidase reporter gene knock-in mouse at the Foxs1 locus (Heglind *et al.*, 2005). However, eye expression has not been described for either endogenous mouse Foxs1 (Kaestner *et al.*, 1993) or the *X. laevis* orthologue, FoxD2 (Pohl and Knochel, 2002).

The Foxf1 β-galactosidase reporter mouse also demonstrates staining in a subset of the cells within the outer nuclear layer of the retina (Kalinichenko *et al.*, 2003). The *X. laevis* homologue of the predominantly mesodermally expressed Foxf1 has not been detected in the eye, although two reports describe complete expression patterns (Koster *et al.*, 1999, Tseng *et al.*, 2004). A single EST described as moderately similar to Foxf1 was isolated from a *Danio rerio* retinal library (Dr.91954), although the expression pattern has not been reported. Species-specific differences may account for the discrepancies between these reports.

Forkhead transcription factors in retinal progenitor cells

Several vertebrate species have a pool of retinal progenitor cells that remain active as slowly dividing precursor cells for all retinal cell types, even after complete differentiation of the retinal cell layers. In zebrafish and *X. laevis*, these cells reside in a compartment that is termed the ciliary marginal zone (CMZ) (Johns, 1977, Straznicky and Gaze, 1971). A spatial gradient along the peripheral to central axis of the CMZ further defines the level of stem cell potential: peripheral cells remain undifferentiated and are slowly dividing (Zone 1), followed by a zone of proliferating neuroblast cells (Zone 2), a region of actively differentiating precursors (Zone 3), and, finally, post-mitotic neurons (Zone 4). In addition, cells residing in the inner nuclear layer of fish retina normally contribute to the rod photoreceptor lineage (Johns, 1982, Julian *et al.*, 1998). In retinal injury models, these cells have clearly been shown to exhibit multipotency, defining them as a second population of stem cells within the teleost retina (Del Rio-Tsonis and Tsonis, 2003, Hitchcock and Raymond, 1992, Otteson *et al.*, 2001, Otteson and Hitchcock, 2003). In rodents, potential retinal stem cells reside within the pigmented ciliary epithelium (Ahmad *et al.*, 2000, Perron and Harris, 2000, Reh and Fischer, 2001, Tribioli *et al.*, 2002, Tropepe *et al.*, 2000). The expression of a given factor in the retinal stem cell population suggests a potential involvement in the developmental processes of cell-cycle control and differentiation. The gene expression profiles of the subdivisions of the CMZ in *Xenopus* correspond to sequential expression of transcription factors during retinoblast development during embryogenesis (Dorsky *et al.*, 1995, Perron *et al.*, 1998). Thus, knowledge of the spatial expression patterns in lower vertebrates contributes to the understanding of embryonic retinoblast differentiation in mammals. For this reason, we highlight forkhead transcription factors that are expressed in the retinal progenitor population.

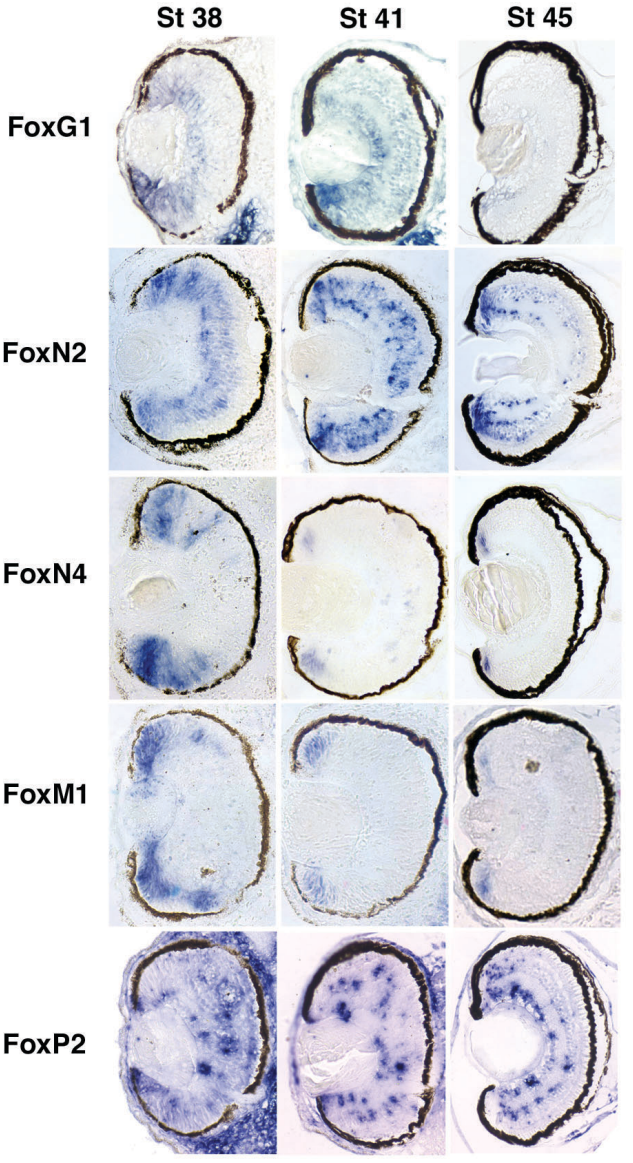

Fig. 1. Expression of retinal *forkhead* genes in the ciliary marginal zone of the maturing neural retina. In situ *hybridization on sections of paraffin-embedded* X.laevis *embryos at stages 38, 41, and 45 using antisense riboprobes specific for FoxG1, FoxN2, FoxN4, FoxM1 and FoxP2.*

The FoxN subclass demonstrates distinct patterns of eye specificity. Mouse Foxn2 is first detected at E10.5 in the optic cup (Tribioli *et al.*, 2002). Expression is less robust in the eye field at 11.5, and is restricted to the nasal ventral region within the eye.

FoxN2 is first detected in the early eye field of *X. laevis* embryos and persists through tailbud stages in the differentiating retina (Schuff *et al.*, 2006). In the mature retina, FoxN2 is expressed throughout the CMZ, and in a subset of cells in the ganglion, inner plexiform, and outer plexiform layers at the periphery of the retina (Figure 1).

FoxN3 is robustly expressed in the prospective eye fields at the time of neurulation in *X. laevis* embryos. Expression becomes limited to cells of the inner nuclear layer of the central retina at stage 38. Later, minimal expression can be seen in a subset of cells of both the ganglion cell layer and the inner nuclear layer (Figure 1). Expression is also visible in the lens at stages 38 and 41, appearing in the region of proliferating lens cells. A mouse orthologue of Foxn3 has been identified (Schorpp *et al.*, 1997), although its expression pattern has yet to be published.

Foxn4 expression is predominantly eye-specific in mammals (Gouge *et al.*, 2001). Homologues in both *X. laevis* and *Danio rerio* also exhibit this highly specific pattern of expression (Danilova *et al.*, 2004, Kelly *et al.*, 2007, Schuff *et al.*, 2006). In each species, the expression of FoxN4 begins in the eye field before the time an eye is morphologically evident. Expression is maintained in the neural retina during development, but is downregulated as differentiation occurs. In the mouse, this is evident as Foxn4 is expressed in cells of the ventricular zone, encompassing the entire central retina at E12.5. By P2, Foxn4 is downregulated in both differentiated ganglion and photoreceptor cells layers, but maintained in the ventricular zone. The expression of FoxN4 is similar in zebrafish and *X. laevis*: high expression in the primordial eye fields and downregulated in differentiated retina, although maintained in the CMZ of the respective species (Danilova *et al.*, 2004, Pohl *et al.*, 2005, Schuff *et al.*, 2006). We have determined that FoxN4 is expressed in all but the most peripheral of the CMZ compartments in the maturing retina, and in CMZ zone 2 of the fully differentiated retina (Figure 1).

FoxM1 is expressed in eye fields of *X. laevis* embryos from neurulation through tailbud stage, and also evident in CMZ (Pohl *et al.*, 2005). Additionally, FoxM1 is not expressed in the most peripheral region of the CMZ adjacent to the lens (Figure 1), suggesting it may not be critical to maintain these cells in a true stem cell state. This is consistent with reports regarding Foxm1 function in mammals; Foxm1 was initially published as a factor present in all proliferating mammalian cells, although downregulated in terminally differentiated cells (Korver *et al.*, 1997a, Korver *et al.*, 1997b, Yao *et al.*, 1997, Ye *et al.*, 1997). There has been no report to date of the Foxm1 expression specifically within the developing retina within mammals. A zebrafish entry for foxm1-like clone exists (BC054560), however no expression pattern or functional data has been published. We report for the first time that FoxM1 is expressed in entire CMZ of the developing *Xenopus* retina; expression is maintained in zone 2,3 and 4 of the fully mature retina (Figure 1).

Retinal forkhead function in eye development

The forkhead family of proteins is defined by the conserved forkhead DNA binding domain. These factors function to regulate expression of target genes through their ability to activate or repress transcription in a sequence-specific manner. The following section summarizes the published data regarding transcriptional regulation by forkhead proteins that are expressed in the retina. Discussion of targets is limited to those most pertinent to eye development, and does not represent a comprehensive view of known targets of forkhead proteins.

FoxD1 was shown to be a transcriptional repressor during neurulation events (Mariani and Harland, 1998). Fusion proteins comprising FoxD1 and the engrailed transcriptional repression domain exhibit the same biological activity as the wild type protein, suggesting that FoxD1 normally functions as a transcriptional repressor. Foxd1 activity is not required for the proper specification of neural retinal precursors, since Foxd1 deficient mice develop grossly normal eyes (Hatini *et al.*, 1994; Herrara *et al.*, 2004). However, inactivation of the Foxd1 gene results in an abnormality in optic chiasm formation, as well as anomalies in kidney, forebrain and adrenal gland development (Hatini *et al.*, 1994, Herrera *et al.*, 2004). Mouse Foxd1 is expressed in retinal ganglion cells (RGCs) of the temporal retina, and this expression is required for maintaining the proper number of RGCs as well as for normal RGC axon projections into the optic tract. Although this phenotype allows the retinae of Foxd1 deficient embryos to appear grossly normal, the Foxd1 phenotype has a profound impact on the development of binocular vision by affecting the development of the optic chiasm. In these animals, the Foxg1 expression domain is expanded ventral-temporally. Foxg1 and Foxd1 have been proposed to regulate downstream targets within the optic cup to determine regional specificity of axon projections (Yuasa *et al.*, 1996).

FoxG1 had been hypothesized to have both activating and repressive functions (Ahlgren *et al.*, 2003, Bourguignon *et al.*, 1998, Li *et al.*, 1996, Yao *et al.*, 2001). Overexpression of fusion constructs of FoxG1 containing a strong activation domain or a strong repressor domains fail to recapitulate the full phenotype of wild type FoxG1 (Bourguignon *et al.*, 1998). The dual role in transcriptional activity is supported by sequence data. A conserved portion of the N-terminus of FoxG1 is highly similar to the transactivation domain of FoxA2 (Pani *et al.*, 1992) and the C-terminal region was specifically shown to have repressive function in the chick homologue, *qin (Li et al., 1995)*. It remains unclear what allows FoxG1 to change between the activating and repressing function.

Several data suggest retinal expressed targets of FoxG1. FoxG1 induces the expression of Ephrin A family members (Takahashi *et al.*, 2003). When FoxG1 is misexpressed in the temporal retina, it represses EphA3, a tyrosine kinase receptor expressed in the retina, as well as FoxD1. In *X. laevis*, p27XIC1, the homologue of the cdk inhibitor p27Kip1, has been shown to be a direct downstream target of FoxG1 (Ahlgren *et al.*, 2003, Hardcastle and Papalopulu, 2000). The activation of Ephrin family members may indirectly result from regulation of p27XIC1 by FoxG1. The repression of p27Kip1 removes a growth-inhibitory signal, allowing activation of Ephrin A family members (Ahlgren *et al.*, 2003, Pohl and Knochel, 2005). The repressive function of FoxG1 is mediated by interaction with groucho and Hes transcriptional corepressors in telencephalic progenitors (Marcal *et al.*, 2005, Yao *et al.*, 2001). It will be interesting to test the possibility that this mechanism is conserved in retinal progenitors with retinal expressed groucho family members, such as Grg4 or Grg5 (Zhu *et al.*, 2002). The previous data demonstrate that FoxG1 contributes to the control of neuroectoderm proliferation in the develop-

ing retina.

FoxG1 loss of function studies demonstrate the importance of FoxG1 in proper eye development. Foxg1 mutant mice never develop an optic stalk, the most ventral of structures to be derived from the optic vesicle during eye development (Huh *et al.*, 1999, Xuan *et al.*, 1995). Instead, optic stalk tissue is replaced by neural retina. In these mutants, Pax6 and Pax2 expression, normally distributed along a dorsal-ventral gradient, is perturbed, suggesting that Foxg1 acts to control a dorsal-ventral gene expression program within the neuroepithelium during eye development. A specific loss of sonic hedgehog (shh) expression in the ventral telencephalic region of neuroepithelium precedes the phenotypic changes in the eye in the Foxg1$^{-/-}$ mice. This raises the possibility that Foxg1 acts upstream of shh and that the Foxg1 phenotype is caused by this local loss of shh signaling (Huh *et al.*, 1999, Xuan *et al.*, 1995). In addition to the morphological phenotypes seen in Foxg1$^{-/-}$ eyes, RGC axon navigation is perturbed. RGC axons extend along the optic nerve to the ventral surface of the hypothalamus. Most RGCs subsequently cross the midline at the optic chiasm and join the contralateral optic tract, while those that do not reside in the ipsilateral optic tract. In Foxg1$^{-/-}$ eyes, the proportion of RGCs that contribute to the ipsilateral optic tract is significantly increased compared to wild type RGCs (Pratt *et al.*, 2004). The authors contend that loss of Foxg1 affects the ability of RGCs to respond to attractive or repulsive cues at the optic chiasm to correctly navigate along optic tracts. These data suggest a dual role for Foxg1 in eye development: initially, in the control of eye morphogenesis by control of gene expression in the retinal epithelium and subsequently in axon guidance of RGCs.

Recently, *Xenopus* knockdown has demonstrated a critical role for FoxN3 in proper eye formation (Schuff *et al.*, 2007). Embryos injected with antisense morpholino oligonucleotides exhibited small eyes with normally laminated retinae. The mechanism of FoxN3 action during eye development appears to be linked to apoptosis, and not cell cycle progression, since injected embryos have higher rates of apoptosis while cell proliferation rates are not affected.

FoxN3 interacts with Sin3 and RPD3, components of the histone deacetylase complex in *Xenopus* (Schuff *et al.*, 2007). Sin3 is thought to act as a co-repressor of histone deacetylases (HDACs) (Laduron *et al.*, 2004). Thus, FoxN3 may act as a transcriptional repressor by recruiting HDACs to target DNA during eye development. Inhibition of HDACs has been linked to an increase in apoptosis (Peart *et al.*, 2003, Sonnemann *et al.*, 2006), revealing why knockdown of FoxN3 increases apoptosis. The interactions of FoxN3 homologues with components of the HDAC complex are conserved across species; it will be interesting to investigate whether the role of FoxN3 in eye development is also conserved.

Another FoxN family member, Foxn4, is involved in retinal cell fate specification. Knocking out the Foxn4 gene in mice results in animals with a reduced number of amacrine and horizontal cells in the differentiated retina (Li *et al.*, 2004). This data suggests that Foxn4 is necessary to enable RPCs to produce amacrine and horizontal cells during retinogenesis, but is not critical for the production/specification of progenitor cells. In this same report, Li *et al.* show that overexpression of Foxn4 results in an abundance of amacrine cells with no alteration in the horizontal cell subtype. These data indicate that Foxn4 is sufficient for the commitment to the amacrine cell fate, but not for the production of horizontal cells.

Ocular retardation (or) mutant mice give another clue to the complete function of Foxn4. *Or* mice have retinal progenitors that divide at a slower rate than that of wt mice. In *or* mice, Foxn4 expression is limited to a few cells of the central retina at a time point when Foxn4 is normally expressed throughout the proliferating ventricular zone (Gouge *et al.*, 2001). This is intriguing data that suggests that Chx10, the gene mutated in *or* mice, is upstream of Foxn4, and may suggest that Foxn4 is involved in the early proliferation of RPCs.

Downstream targets of Foxn4 include Math3, NeuroD, and Prox1 (Li *et al.*, 2004), although these have not been demonstrated to be direct targets. Collectively, the data suggest that Foxn4 is expressed in proliferating progenitor cells, and plays a role in the commitment to amacrine and horizontal cell fates.

Foxl1 involvement in eye development is demonstrated by the phenotype of foxl1 morphants, which have small eyes as well as degenerated brains (Nakada *et al.*, 2006). In addition to aberrations in eye size, morpholino-injected eyes do not display proper retinal layer formation. An increase in the number of apoptotic cells was observed in the morpholino-injected embryos, contributing to the microophthalmic phenotype. The layering defect suggests that foxl1 may play a role in proper migration of differentiating retinal progenitor cells. Interestingly, overexpression of the same gene results in a similar, yet more severe, phenotype; very small or no eyes are observed in injected embryos (Nakada *et al.*, 2006). Additionally expression of pax6a is absent in tissue where foxl1 is overexpressed, placing foxl1 upstream of the zebrafish pax6 gene. The zebrafish pax6a gene is a downstream effector *shh* signaling. Using both *in vivo* and *in vitro* techniques, the authors showed that foxl1 was able to repress transcription through the *shh* promoter. This implicates foxl1 as a negative regulator of the *shh* pathway in zebrafish. Also, expression of a zebrafish foxl1 protein fusion with the engrailed repression domain gives a similar phenotype to that induced by overexpression of foxl1 (Nakada *et al.*, 2006). Together, these data suggests that foxl1is a transcriptional repressor involved in retinal development by negatively regulating the shh pathway.

In summary, accumulating data demonstrates that a number of forkhead transcription factors are present in developing retinal tissue in vertebrates. The expression pattern data reveal forkhead transcription factors from multiple subfamilies are present in different subtypes of retinal cells. In addition, the animal model phenotypes exhibit various roles for forkhead proteins during eye development. They collectively demonstrate that several forkheads are important determinants of retinal cell fate. The data and results presented here underscore the enormous potential forkhead transcription factors holds for our understanding of the development and biology of retinal progenitor cells, certainly only the tip of the forkhead iceberg.

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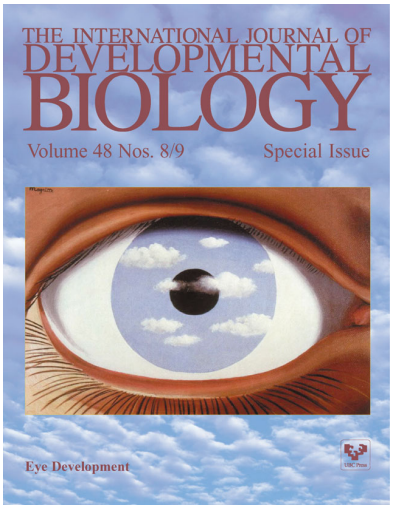

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