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Semper's Cells in the Insect Compound Eye: Insights into Ocular Form and Function

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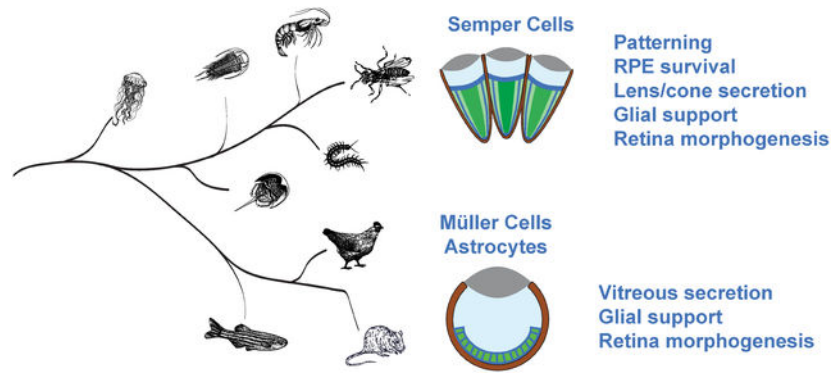
Abstract

The arthropod compound eye represents one of two major eye types in the animal kingdom and has served as an essential experimental paradigm for defining fundamental mechanisms underlying sensory organ formation, function, and maintenance. One of the most distinguishing features of the compound eye is the highly regular array of lens facets that define individual eye (ommatidial) units. These lens facets are produced by a deeply conserved quartet of cuticle-secreting cells, called Semper cells (SCs). Also widely known as cone cells, SCs were originally identified for their secretion of the dioptric system, i.e. the corneal lens and underlying crystalline cones. Additionally, SCs are now known to execute a diversity of patterning and glial functions in compound eye development and maintenance. Here, we present an integrated account of our current knowledge of SC multifunctionality in the *Drosophila* compound eye, highlighting emerging gene regulatory modules that may drive the diverse roles for these cells. Drawing comparisons with other deeply conserved retinal glia in the vertebrate single lens eye, this discussion speaks to glial cell origins and opens new avenues for understanding sensory system support programs.

Graphical Abstract

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Keywords

glia; IRM proteins; Pax2; PaxB; Prospero; Prox1; SoxB; Müller glia; eye evolution; lens; animal vision; crystalline cone

Introduction

Compound eyes are a signature trait and the primary visual sense organ of arthropods, animals unparalleled for their prolific diversification into aquatic, terrestrial, and aerial life environments (Feller et al., 2020; Koenig and Gross, 2020). The defining architecture of compound eyes is the highly organized grid of individual eye units, called ommatidia. Each ommatidium comprises a central light-focusing dioptric structure (a corneal lens facet and crystalline cone) and an underlying light-detecting neural retina (rhabdomeric photoreceptors [PRs]). This light-sensing core is optically separated from neighboring ommatidia by light-insulating pigment cells (interommatidial pigment cells or the retinal pigmented epithelium [RPE]). Ommatidial design is thus not unlike that of the single lens eye in vertebrates, in which a neural retina lies behind a dioptric system, surrounded by an RPE (Fig.1).

Cellular, physiological, and genetic studies of the insect compound eye have led to the discovery of a wide range of deeply conserved neurobiological processes (Bellen et al., 2010). Besides finding similarities with the vertebrate camera eye in retinal neuron development and function, for example, a growing body of research has uncovered common support/glial roles for the RPE on PR health in both vertebrates and invertebrates (Charlton-Perkins and Cook, 2010; Cook et al., 2011; Hartenstein and Reh, 2002; Sparrow et al., 2010; Strauss, 2005; Viets et al., 2016). Studies of the RPE in honeybees, for instance, were foundational for understanding the lactate shuttle of energy support and ion homeostasis between neurons and glia (Coles, 1989; Tsacopoulos and Magistretti, 1996). In *Drosophila*, studies on *white*, the first genetic mutation identified, provided insights into the role of ABC transporters in neuroprotection (Borycz et al., 2008; Ferreira et al., 2018; W. S. Kim et al., 2008; Lee and Montell, 2004; Morgan, 1910). More recent studies have uncovered roles of the fly RPE in the visual cycle, neurotransmitter storage, and lipid metabolism (Chaturvedi et al., 2014; Han et al., 2017; Liu et al., 2017, 2015; Wang et al., 2012, 2010). Thus, glial-like support mechanisms of pigment cells are well-documented in both insect

compound eyes and vertebrate single lens eyes (Bharti et al., 2006; Klettner and Dithmar, 2020; Sparrow et al., 2010; Strauss, 2005).

Here, we focus on a second type of canonical support cell in arthropod ommatidia that is widely recognized for its roles in the formation of the corneal lens and the underlying crystalline cone. We highlight how these cells also contribute to ocular organization, development, and visual system maintenance, which can now be dissected for more general roles in sensory system assembly and support using the power of fly genetics.

Semper's cells: Discovery and phylogenetic origin

The dioptric system of the compound eye captivated some of the very first microscopists and physiologists (Bernhard et al., 1972; Exner, 1989; Nilsson, 1989). Defining the cellular nature of this light-focusing system arose from studies of ommatidial development in a variety of arthropods, eventually published by Edouard Claparède in 1860 (Claparède, 1860). In this work, he credits the German zoologist Carl Semper for sharing his preliminary findings on these cells in both insect and crustacean eyes, hence naming them Semper's cells (SCs) (Claparède, 1860). Claparède and Semper established that, in addition to being the sole source of the prominent vitreous-like compartment called the crystalline cone (Nilsson and Kelber, 2007), the SCs also frequently contribute the major part of the overlying cuticular corneal lens facet (Claparède, 1860). Reflecting their ubiquitous role in crystalline cone production, SCs have also become widely known as cone cells (Cagan and Ready, 1989; Nilsson and Kelber, 2007). However, given their broader functionality and the unfortunate terminological match with the cone PRs of the vertebrate eye, we have returned to their first namesake: SCs (Charlton-Perkins et al., 2017).

The vast number of comparative ultrastructural studies in the second half of the 20th century confirmed that a quartet of SCs is present in the ommatidia of most insect and crustacean species (the arthropod clade Pancrustacea). The presence of four SCs is so characteristic of Pancrustacea compound eyes that the term "Tetraconata" has been introduced as an equivalent name for this group (Dohle, 2001; Richter, 2002; Schwentner et al., 2018). Recent studies of fossil samples revealed crystalline cone structures in the elaborate compound eyes of the extinct trilobites (Schoenemann et al., 2017; Schoenemann and Clarkson, 2020; Scholtz et al., 2019), pointing to an even deeper conserved existence of SCs. SCs have also been described in centipedes (Myriapoda) and horseshoe crabs (an ancient lineage of Chelicerates), suggesting their origin dates minimally back to the dawn of arthropod emergence, i.e. ~500 million years ago (Fahrenbach, 1968; Nilsson, 1989). This positions SCs as originating near the separation of vertebrates and invertebrates, when visual function became more demanding as predator-prey interactions started to emerge (Parker, 2004).

Semper cell specification: A neural fate decision

SC development has been most thoroughly analyzed in the *Drosophila* compound eye (Cagan and Ready, 1989; Kumar, 2012; Morrison et al., 2018; Quan et al., 2012; Tomlinson, 1985; Tomlinson et al., 2011; Tomlinson and Ready, 1987; Treisman, 2013; Tsachaki

and Sprecher, 2012; Voas and Rebay, 2004; Wolff and Ready, 1993). These efforts were propelled by the discovery that one of the first behavioral mutants isolated is caused by misspecification of the UV-sensitive R7 PR to that of a SC (Banerjee et al., 1987; Benzer, 1967; Harris et al., 1976; Tomlinson and Ready, 1986). Today, the choice to be or not to be a SC represents a classic paradigm for understanding cell fate decisions.

Briefly, the events leading up to this decisive step first involve the expansion of *eyeless (ey)*/*Pax6*-positive eye progenitors by cell proliferation through the majority of postembryonic (larval) development (Kumar, 2011). This expansion phase comes to an end when a front of cell differentiation forms just prior to pupation, stopping progenitor proliferation and initiating cell type specification (Wolff and Ready, 1991). The ensuing phase of retinogenesis involves progressive ommatidial cluster formation through two rounds of cell cycle exit. The progenitors that exit first (early progenitors) give rise to 5 PRs (R8–2/5–3/4), while later-exiting progenitors that undergo one more round of cell division (late progenitors) generate the last 3 PRs (R1/6–7) and 4 SCs (Kumar, 2012; Wolff and Ready, 1993) (Fig.2). After pupation, remaining precursors differentiate into three pigment cell populations or are eliminated through apoptosis (Brachmann and Cagan, 2003) (Fig.3).

At the transcriptional level, both early and late retinal progenitors express the transcription factor-encoding genes *sine oculis*, *eyes absent*, and *glass*, with the late progenitors also expressing the Runt homology protein-encoding gene *lozenge* (Flores et al., 1998; Morrison et al., 2018; Pignoni et al., 1997; Tanaka-Matakatsu and Du, 2008; Yan et al., 2003; Zhang et al., 2006) (Fig. 2). From here, the different ommatidial cell types arise through a combinatorial transcriptional code and synergistic integration with differential Ras and Notch signaling levels (Charlton-Perkins et al., 2011b; Frankfort and Mardon, 2002; Hayashi et al., 2008; Nagaraj and Banerjee, 2003; Tomlinson et al., 2011; Voas and Rebay, 2004; Xu et al., 2000; Yan et al., 2003). The pivotal decision to develop as an R7 (the last retinal neuron to be specified) vs a SC (an accessory/glial fate) is made in a subset of late progenitors, called the R7 equivalence group. This group of 5 cells shares the expression of the proneural transcription factor-encoding gene *prospero (pros)* (Choksi et al., 2006; Doe et al., 1991; Kauffmann et al., 1996; Vaessin et al., 1991). Localized activation of Sevenless/Ras/MAPK signaling promotes R7 fate in a single R7 equivalence group member contacting the R8 PR, while the remaining four members acquire the SC default fate through high Notch and low Ras signaling (Flores et al., 2000; Lai and Rubin, 2001; Raabe, 2000; Simon, 1994; Tomlinson and Ready, 1987; Zipursky and Rubin, 1994) (Fig. 3). Combined, fly retinogenesis follows a developmental theme common to other parts of the fly and vertebrate nervous system where pools of “early” and “late” progenitors give rise to all-neuronal vs neuronal-glial cell types, respectively, with high Notch signaling driving glial fate (Cepko, 1993; Cepko et al., 1996; Dorsky et al., 1995; Flores et al., 2000; Gaiano and Fishell, 2002; Hojo et al., 2000; Lai and Rubin, 2001; MacDonald et al., 2015; Satow et al., 2001; Stiemke and Hollyfield, 1995; Vetter and Moore, 2001; Young, 1985).

Consistent with a glial specification paradigm for SC fate, transcription factors generally known to control glial cell fate are also expressed in early SCs. This includes the fly-specific factors *glial cell missing (gcm)*, *reversed polarity (repo)*, and *tramtrack (ttk)*, as well as more deeply conserved gliogenic factors like *pros/Prox1* and *Pax2* (Badenhorst, 2001; Charlton-

Perkins et al., 2011b, 2017; Choksi et al., 2006; Fu and Noll, 1997; Kato et al., 2015; Mavromatakis and Tomlinson, 2016; Shi and Noll, 2009; Soukkarieh et al., 2007; Wallace et al., 2016). Interestingly, *pros/Prox1* and *Pax2* cooperate in SCs to both control early glial fate decisions as well as later glial functions (Charlton-Perkins et al., 2011b, 2017) (Charlton-Perkins and Cook, in preparation). Given that these factors are each common to other sensory system glia, including the vertebrate retina intrinsically-generated radial Müller glia (MG) (Charlton-Perkins et al., 2011b, 2017; Cid et al., 2010; Freeman and Doe, 2001; Kavalier et al., 1999; Stanke et al., 2010), *pros/Prox1* and *Pax2* may be a part of a conserved genetic module that imposes sensory glial fate.

Semper cell subtypes

Despite the apparent common roles for the full quartet of SCs in the mature eye, early studies of retinal development in *Drosophila* revealed that not all four SCs are created equal. Instead, the “primary” anterior and posterior (A/P) SCs form before the “accessory” equatorial and polar (Eq/Pl) SCs (Tomlinson, 1985; Tomlinson and Ready, 1987) (Fig. 2). At the molecular level, these SC subtypes transiently differ in expression levels of cell fate determinants. *Pax2* and its downstream target *cut* show higher expression in A/P SCs relative to *pros*, while *pros* is more strongly expressed in the Eq/Pl SCs (Charlton-Perkins et al., 2011b). SC subtypes continue to show gene expression differences at least through mid-pupation. For example, A/P SCs consistently express higher levels of Delta (DI), which is a Ras/MAPK-induced Notch ligand. Additionally, reporters for Ras/MAPK signaling exhibit SC subtype-selective gene expression patterns (Parks et al., 1995; Tsuda et al., 2002; Wildonger et al., 2005). Consistent with SCs experiencing different signaling environments, the formation of only two SCs is often observed when the EGFR, Notch or Wingless (Wg)/Wnt signaling pathways are perturbed (Bhattacharya and Baker, 2009; Cordero and Cagan, 2010; Matsuo et al., 1997; Pickup et al., 2009; Rebay and Rubin, 1995; Treier et al., 1995). Intriguing comparative evidence for deeper evolutionary conservation of SC subtypes is provided by the shrimp-like marine crustacean *Meganyctiphanes norvegica* (Hallberg and Nilsson, 1983). In this species, SCs have diversified to the effect that the A/P SCs produce the lens while the Eq/Pl SC maintain contact with the PRs. The complete separation of lens secretion and PR support is intriguing with respect to the possibility that separable genetic and functional modules exist in SCs. Such subfunctionalization is rare, however, suggesting strong developmental constraints for maintaining the A/P and Eq/Pl subfate organization. Indeed, as described next, the SC subfates do play distinct roles in the following phase of ommatidial patterning.

Semper cell-directed patterning of the ommatidial array

Once SC recruitment is complete by early pupation, the differentiating SCs adopt active roles in the patterning of the remainder of the ommatidial unit. First, the apical portions of the SCs migrate over the top of the PRs, covering the surface of the retina (Fig. 2B). At this point, the A/P SCs are in physical contact with each other, pushing the Eq/Pl SC pair to the outside of the cluster (Cagan and Ready, 1989). In this configuration, the A/P SCs recruit the pair of primary pigment cells (PPCs) through DI-driven Notch activation in neighboring progenitors (Nagaraj and Banerjee, 2007; Parks et al., 1995). After PPC recruitment, the

Eq/Pl SCs surfaces migrate above those of the A/P SCs, establish contact with each other, and push the A/P SC pair apart (Cagan and Ready, 1989). From here, the SCs and PPCs join forces to promote the organization and patterning of the interommatidial pigment cells, i.e. the RPE (Bao and Cagan, 2005; Miller and Cagan, 1998) (Fig.3).

SCs drive their own mirror symmetry and steer their concentric arrangement with the PPCs and RPE through differential deployment of two families of cell adhesion proteins: Cadherins and Nephrin/Neph1-related Irre-C Recognition Module (IRM) proteins (Bao et al., 2010; Bao and Cagan, 2005; Fischbach et al., 2009; Grillo-Hill and Wolff, 2009; Grzeschik and Knust, 2005; Hayashi and Carthew, 2004). Both sets of proteins are concentrated at adherens junctions that form near the apical surfaces of cells (Harris and Tepass, 2010; Tepass and Harris, 2007). While all cells in the eye express E-cadherin, N-cadherin is restricted to the SC-SC interfaces during early ommatidial patterning. This selective enrichment in SCs helps to stabilize the stereotypic “soap bubble” organization of the SC quartet (Hayashi and Carthew, 2004). In addition, N-cadherin controls the SC-PPC-RPE concentric organization by driving MyoIIdependent contractility differences across the surface of the eye (Blackie et al., 2020; Chan et al., 2017; Hayashi and Carthew, 2004).

In addition to these Cadherin-mediated functions, Nephrin and Neph1-like IRM-driven adhesion differences are likewise responsible for correct ommatidial patterning (Bao et al., 2010; Bao and Cagan, 2005; Grzeschik and Knust, 2005; Reiter et al., 1996). The Nephrin and Neph1-like subfamilies of adhesion factors show differential distribution in the eye. The Nephrin paralog pair, Hibris and Sticks-N-Stones, is expressed in SCs and PPCs while the Neph1 paralogs Roughest/irregular chiasm (Irre) and Kin of Irre (Kirre) are restricted to the interommatidial cells (IOCs) (Bao et al., 2010; Fischbach et al., 2009). Homophilic interactions between the Nephrin IRMs ensure SC pair switching and PPC wrapping of the SC quartet by dictating maximal contact among SCs and PPCs. This process also effectively separates the apical surfaces of SCs from surrounding interommatidial precursor cells (Bao and Cagan, 2005; Grillo-Hill and Wolff, 2009).

Whereas Nephrin-associated homophilic interactions drive central ommatidial organization, stronger heterophilic interactions between the Nephrins and Neph1-like molecules maximize PPC-RPE contacts, ultimately leading to the efficient separation of individual ommatidia (Bao et al., 2010; Bao and Cagan, 2005). Importantly, SC-dependent signals are essential for directing this interplay of Nephrin-Neph1 interactions. For instance, the same D1-Notch activation that promotes PPC recruitment also ensures robust Nephrin expression in these cells, leading to the robust accumulation of Neph1 at the PPC-IOC interface (Bao, 2014). In this way, SCs drive an inside-out signaling relay that influences cell adhesion molecule expression two cell diameters away. This process, combined with Myo-II mediated biomechanical forces, pulls individual ommatidia together (Blackie et al., 2020; Chan et al., 2017; Johnson et al., 2011; Larson et al., 2010), bringing the morphology of the differentiating eye one step closer to its mature architecture.

Not much is known regarding the molecular pathways controlling the differential expression of the adhesion molecules needed to drive ommatidial organization. However, it is worth noting that in the radial glia of the zebrafish retina, i.e. the MG, the Nephrin and Neph1

IRM proteins Nphs1 and Kirre1a ensure that the highly ordered tiling of the retina is properly established (Charlton-Perkins et al., 2019). Further notable is that, in both fish and flies, *Pax2* lies upstream of IRM expression to control similar patterning processes (Charlton-Perkins et al., 2019) (Charlton-Perkins and Cook, in preparation). This raises the intriguing possibility that a deeply conserved Pax2-IRM regulatory module controls retinal subunit organization.

Semper cells as RPE survival mediators

Besides regulating the concentric organization and patterning of SCs, PPCs and RPE, SCs further assist in the final shaping of the *Drosophila* eye by influencing programmed cell death. In this context, SCs have been implicated in at least two peaks of apoptosis that unfold during pupal compound eye development (Baker, 2001; Baker and Yu, 2001; Brachmann and Cagan, 2003; Cordero et al., 2004; Lim and Tomlinson, 2006; Lin et al., 2004). First, in the main portion of the eye, SCs provide *EGFR*-dependent survival signals to IOC. These signals allow IOC to avert Notch-dependent pruning during the final stages of RPE patterning, leading to the appropriate separation of individual ommatidia (Miller and Cagan, 1998; Monserrate and Brachmann, 2007; Querenet et al., 2015). Second, at the periphery of the eye, SCs promote survival of the RPE, but in addition, induce death of non-RPE cells (Kumar et al., 2015). This striking dual property is driven by Wg/Wnt signaling from the head capsule tissue surrounding the ocular field. In particular, Wg from the head capsule promotes restricted *wg* expression in SCs located at the periphery of the eye, which in turn leads to the localized activation of Snail transcription factor expression in the SCs (Kumar et al., 2015). These peripheral SCs promote RPE survival, while in parallel, remove remaining ommatidial cells (including the SCs themselves) through apoptosis (Kumar et al., 2015). As a result, incomplete ommatidial units are eliminated at the edge of the eye and the retina becomes optically isolated from the rest of the head by a thick band of RPE cells.

Besides these pupal functions, SCs contribute to IOC progenitor survival in the late larval retina. Here again, studies on *Pax2* provide critical insights, as mutations in this SC fate determinant cause widespread cell death in imaginal discs, producing adult eyes largely lacking an RPE (Fu and Noll, 1997; Siddall et al., 2003). Notably, similar precocious cell death is observed in animals lacking sufficient *EGFR* activation (Baker and Yu, 2001). As *EGFR* contributes to *Pax2* expression, these results raise the possibility that *Pax2* is essential for this signal (Flores et al., 2000). Alternatively, or in addition, because *Pax2* can suppress *Dl* expression (Charlton-Perkins et al., 2011b), young *Pax2*-positive SC progenitors could delay Notch-dependent apoptotic signals by blocking the expression of its ligand. Of note, *Pax2* plays pro-survival roles in other developmental systems, including the vertebrate eye (Bosze et al., 2021; Bouchard et al., 2002; Burton et al., 2004; Park et al., 2006; Viringipurampeer et al., 2012). Therefore, the fly eye provides a valuable model for dissecting a deeply conserved *Pax2*-associated cell survival regulatory module (Park et al., 2006).

Facilitating photoreceptor morphogenesis

The above discussion highlights the role of SCs in patterning the non-neuronal cell types in the fly eye. In addition, SCs help build the retina's neuronal compartment and provide structural support to the PRs. The first SC-dependent role in retinal morphogenesis occurs soon after the start of pupation. At this time, the apical surface of the SCs migrate above the PRs. As the SCs and PRs are attached through zonula adherens (ZAs), this migration leads to the inward rotation of the PRs apical membrane 90 degrees (Longley and Ready 1995). This reorientation of the PR apical surfaces is a critical process that ultimately allows the light-gathering rhabdomeres to extend in the distal-proximal direction to reach from the surface to the base of the retina (Longley and Ready 1995) (Fig. 4). Eventually, the SCs form an electron-dense "rhabdomere cap" that binds the SCs to the PRs via integrin-rich desmosome-like structures (Longley and Ready, 1995) (Fig. 5).

Just as SCs cover the surface of the PRs apically, they also form a plate below the PRs basally. Plate formation proceeds in a pairwise fashion. The A/P SCs initially insert their endfeet into the center of the ommatidial core at ~14% pupation, while the Eq/Pl SCs insert their endfeet at ~37% pupation. Together, the quartet of SC feet form a plate at the base of the retina and connect to the retinal floor through integrins. Once the PRs are oriented and encapsulated at either end, their actin-rich apical membranes begin to expand and grow proximally until reaching the SC-generated floor, where they attach with basal ZAs. The rhabdomeres then continue expanding and deepening through the entire length of the retina in two additional growth spurts at ~55 and 75% pupation (Ready, 2002). While much of rhabdomere growth is likely intrinsic to PRs, evidence suggests SCs also contribute to this process. For example, *Pax2* mutant eyes have abnormally shaped and shortened PR rhabdomeres, suggesting that the SC-PR interface is necessary for proper rhabdomere elongation (Charlton-Perkins et al., 2017; Fu and Noll, 1997).

Stretching to connect the apical cap and the basal plate of the SCs are thin processes, called interretinular fibers. One per SC, these fibers run immediately adjacent to the PRs' zonula adherens (ZA) junctions (Müller et al., 2003; Waddington and Perry, 1963). The presence and positioning of the SC fibers are remarkably conserved across Pancrustacea, highlighting their likely importance in supporting the integrity of the retina (Fischer et al., 2000, 2019; Horridge, 1966; Melzer et al., 2000, 1997; Menzel, 1972). Interestingly, at least in some arthropod eyes, microtubules are present in these SC extensions, raising the possibility that vesicular transport occurs between the distal SC soma to the endfeet (Burton and Stockhammer, 1969; Chen et al., 2019; Horridge and Giddings, 1971; Meyer-Rochow, 1977) (U. Wolfrum, personal communication). In this respect, it is worth noting that, while other cells in the fly eye have their pigment granules distributed through the cell body, the ommochrome pigment granules found in SCs are specifically located in the SC feet but absent in their soma at the top of the eye (Wolff and Ready, 1993). This asymmetric distribution thus allows light to pass through apically, and perhaps prevents light from penetrating into the brain at the base (Tomlinson, 2012; Waddington and Perry, 1963).

Drosophila PRs generate an extracellular matrix filled lumen, called the inter-rhabdomeric space (Husain et al., 2006; Nie et al., 2014; Zelhof et al., 2006). Because the SCs form a

basket around the PR cluster, this lumen is encapsulated by the SCs. Thus, once mature, the SCs contact 3 three separate receptacles: the pseudocone, the inter-rhabdomeric space, and the brain-retina-barrier. The latter has been shown to involve a third important intercellular connection particularly abundant among SCs: septate junctions (SJs) (Banerjee et al., 2008). These junctions form just basal to ZAs in insects and utilize proteins present in junctions associated with barriers and paracellular transport in vertebrates, such as tight junctions (TJs) and the axo-glial nodes of Ranvier (Banerjee et al., 2006; Faivre-Sarrailh, 2020). Support for similar barrier functions in the fly eye comes from genetic analysis of *Neurexin-IV* (*NrxIV*)/*dCaspr*, a deeply conserved factor required for SJ/TJ formation. NrxIV protein is present in the basal feet of the SCs and RPE cells where it controls the fly brain-retina-barrier (Banerjee et al., 2008). Interestingly, while NrxIV is present in both RPE and SCs proximally, it is specifically enriched in SCs distally (Banerjee et al., 2008). Another SJ-associated protein, Fasciclin 3, is likewise enriched distally in SCs (Charlton-Perkins et al., 2017). It thus appears that SC-SC septate junctions are unique, perhaps to form strong selective barriers between the vitreous-like pseudocone, the inter-rhabdomeric space and the brain-retina-barrier (Fig. 5).

Secreting the corneal lens

Lens formation and composition:

As all cell specification and patterning events are complete by mid-pupation, the developing eye transitions to terminal differentiation events (Cagan and Ready, 1989; Ready, 2002; Waddington and Perry, 1960). At this point, i.e. by about 50% pupation, the SCs, together with primary and secondary pigment cells, begin to secrete the biconvex corneal lens (Cagan and Ready, 1989). This laminated cuticular structure is largely finalized by 75% of pupal development, although some protein incorporation has been observed in newly eclosed adults (Yoon et al., 1997). Drosocrystallin and Retinin represent the major cuticular constituents of the lens and are expressed by both the SCs and PPCs (Charlton-Perkins et al., 2017; Janssens and Gehring, 1999; E. Kim et al., 2008; Komori et al., 1992; Kryuchkov et al., 2020; Stahl et al., 2017; Xu et al., 2004). There are also two lower abundance cuticular proteins Cpr72Ec and Cpr66D, that are primarily expressed in the interommatidial pigment cells (Kryuchkov et al., 2020; Stahl et al., 2017). Such cell type-specific expression levels presumably set up the differential gradients needed to generate the curved lens structure and achieve appropriate refractive properties.

Corneal lens surface formation:

Another important aspect of the corneal lens is its outer coating, a lawn of tiny protuberances known as corneal nipples. A bioengineering inspiration for surface coatings on solar cells and optic lenses (Brunner et al., 2012; Dewan et al., 2012), these nanostructures are anti-reflective and thus enhance light transmittance. Recent studies revealed that *Drosophila* corneal nipple formation requires *retinin* and the arachidonic acid-specific lysophospholipid acyltransferase-encoding gene *farjavit* (Kryuchkov et al., 2020). Importantly, the failure of corneal nipple formation is considered to be the cause of the glossy or glassy eye phenotypes seen in a variety of *Drosophila* mutants (Bernhard et al., 1963; Kryuchkov et al., 2011). This includes the eye-specific allele of *Pax2*, *spa^{pol}*

(named for its sparkling, polished eye appearance), thus tying *Pax2* to corneal lens surface formation.

Conservation of Pax-Sox mediated crystallin production:

As the most abundant corneal lens protein in *Drosophila*, *Drosocrystallin* has been most thoroughly studied (Komori et al., 1992; Stahl et al., 2017). Like other crystallins in animal lenses, *Drosocrystallin* is of critical functional importance outside of the lens, including in the peritrophic membrane of the gut, revealing broader requirements for this structural protein (Charlton-Perkins et al., 2011a; Dziejczak et al., 2009; Janssens and Gehring, 1999; Kozmik et al., 2003; Kuraishi et al., 2011; Piatigorsky et al., 1988; Vopalensky and Kozmik, 2009). Molecularly, an enhancer that recapitulates *Drosocrystallin*'s expression in the eye is activated by *Pax2*, further exemplifying the pervasive role of this factor in SC biology (Dziejczak et al., 2009; Janssens and Gehring, 1999). Remarkably, *Pax2* not only activates a fly crystallin gene enhancer, but can also substitute for another *Pax* gene, *Pax6*, to activate an enhancer of the chicken gamma-crystallin gene *DC5*, when the latter is introduced into the fly (Blanco et al., 2005; Kamachi et al., 2001; Kozmik, 2005). Furthermore, just as *Pax6* cooperates with *Sox2* to activate the DC5 enhancer in their authentic host, i.e. the chicken, *Pax2* cooperates with *Drosophila SoxN* to regulate the enhancer in flies (Blanco et al., 2005; Kamachi et al., 2001; Kozmik, 2005). These findings raise the possibility of a deeply conserved Pax-Sox regulatory module in charge of lens production.

The interchangeability of *SoxN* and *Sox2* is consistent with them both being members of the *SoxB1* subgroup of the SRY-related HMG-box transcription factor gene family (Guth and Wegner, 2008). Similarly, the participation of *Pax6* and *Pax2* in bilaterian crystallin gene regulation is explained by shared ancestry and functional conservation. Both factors are phylogenetically related to the *PaxB* factors in the Cnidaria (Suga et al. 2010; Kozmik et al. 2003), an ancient metazoan phylum that diversified in parallel to the emergence of the Bilateria. In this ancient group, lens-forming eyes originated multiple times (Picciani et al., 2018). Functional homology of cnidarian PaxB with fly *Pax2* has been demonstrated by studies which revealed that the *PaxB* homologs of two distantly related cnidarian species, the box jellyfish *Tripedalia cystophora* (Cubozoa) and the hydrozoan *Cladonema radiatum* rescue the eye-specific *Pax2 spa^{pol}* mutant phenotype (Kozmik et al., 2003; Suga et al., 2010). Remarkably, with respect to *crystallin* regulation, *T. cystophora PaxB* was found to activate the promoters of three *crystallin* genes of the same species (Kozmik et al., 2003). Thus, the transcriptional control of *crystallin* genes by PaxB factors appears to constitute a deeply conserved aspect of animal eye development. The intriguing prediction that SoxB is likewise involved in cnidarian *crystallin* gene regulation remains to be tested.

Secreting the pseudocone

Following lens secretion, the SCs switch to secreting the pseudocone, the extracellular vitreous-like substance that represents the dipteran-type of crystalline cone. In *Drosophila*, this secretory switch happens at 75% pupation. As the pseudocone gains in volume, the SCs are pushed away from the hard cuticular lens, with the major portion of their cell bodies being pressed onto the PRs' tops, and their nuclei being forced aside, thus minimizing light

interference (Ready, 2002). While crystalline cone formation is the most characteristic role for SCs, very little is known about its content, even in the well-studied *Drosophila* model. The same holds for how the correct focal distance between the corneal lens and the PRs is achieved to establish what is known as emmetropia. Recent work in a range of arthropod eyes revealed that, unlike the single lens eye types in vertebrates and squids, arthropods do not seem to require visual input to reach emmetropia, suggesting that an intrinsic system is in place for this process (Owens et al., 2020; Sivak and Sivak, 2019). As for the pseudocone contents, the only known protein marker identified thus far is an 85 kDa glycoprotein recognized by the now unavailable monoclonal antibody 3G6 (Edwards and Meyer, 1990). Originally isolated for its specificity for neuropil glia in crickets, the epitope recognized by this 3G6 is concentrated in crystalline cones in insects, crustacea, and even myriapods (Edwards and Meyer, 1990; Meyer et al., 1987). While preliminary, these data indicate the existence of a deeply conserved molecular component produced by both nervous system glia and SCs.

More recently, the amino acid B-alanine was also shown to be enriched in the *Drosophila* pseudocone (Borycz et al., 2012; Han et al., 2017; Xu et al., 2015). B-alanine is a substrate for both energy production and the recycling of the fly PR neurotransmitter histamine. Knockdown of the B-alanine synthesis enzyme *pyd3* in SCs resulted in weaker neuronal activity in neighboring PRs, but showed no changes in neurotransmission (Charlton-Perkins et al., 2017). These observations hint at the possibility that the pseudocone not only contributes to the focusing of the eye, but also stores metabolic substrates, not unlike other fluid-filled tissues in the vertebrate nervous system (e.g., ventricles, vitreous).

Semper cell-mediated homeostatic support in the adult retina

Until recently, our understanding of SC function was confined to their role in supporting ommatidial development and structure. However, SC-targeted transcriptomic and genetic approaches have uncovered an additional glial support role for these cells in the adult retina via deeply conserved effector genes (Charlton-Perkins et al., 2017). Glia maintain nervous system function by providing structural and physiological support. Structurally, the SCs radially encapsulate the rhabdomeres and provide a *Pax2*-dependent scaffold for rhabdomere elongation as alluded to above (Charlton-Perkins et al., 2017). As with many radial-like glia, including retinal MG, the mechanics of this glial structural support requires further exploration (MacDonald et al., 2015).

Physiologically, SCs participate in at least two glial support roles: energy maintenance and ion homeostasis. In highly active areas of the nervous system like the retina, the exceptional energy demand is met by neuron-glia metabolic coupling (Bittern et al., 2020; Country, 2017; Magistretti, 2004). In the most simplistic model of this interaction, glia maintain glycolysis utilizing glycogen or glucose reserves to generate citric acid cycle substrates (Tsacopoulos et al., 1994; Tsacopoulos and Magistretti, 1996; Volkenhoff et al., 2015). These resources in turn are transported or diffuse to neighboring neurons for mitochondrial ATP production (Rittschof and Schirmeier, 2018). Consistent with similar coupling in other insect eyes, ultrastructural studies of the honeybee retina uncovered an abundance of glycogen reserves in SCs (Perrelet 1970). SCs also appear to use similar metabolic

effectors as vertebrate glia for providing nutrients to their intimately linked PRs (Hurley et al., 2015; Reichenbach and Bringmann, 2013; Rittschof and Schirmeier, 2018; Vohra and Kolko, 2018). This is suggested by findings in genetic studies that *Drosophila* SCs require the glucose transporter *Glut1* and *lactate dehydrogenase, dLdh*, to help sustain neighboring PR function (Charlton-Perkins et al., 2017).

Another interesting function of SCs is glutamate recycling. Glutamate is the primary neurotransmitter in the vertebrate retina, while the fly retina uses histamine (Hardie, 1987; Sarthy, 1991). However, highly active neurons release glutamate and ammonium as metabolic byproducts that are recycled by neighboring glia to either alanine (for reuse) or glutamine (as storage for future energy demands) (Rittschof and Schirmeier, 2018; Tsacopoulos et al., 1997, 1994). The glutamate-sodium symporters *EAAT1* and *EAAT2* as well as the glutamate-ammonia ligase *glutamine synthase (GS2)* are strongly expressed in SCs and, in the case of *EAAT1*, similarly help to sustain PR function (Charlton-Perkins et al., 2017). In light of this, SCs have become an attractive model to study glutamate recycling in the context of glial energy production rather than neurotransmission (Chaturvedi et al., 2016; Han et al., 2017; Xu et al., 2015).

Potassium ion homeostasis is another essential support function for glia to maintain the membrane potentials of highly active neurons (Beckner, 2020). Throughout the nervous system, including the retina, this support relies on a complex potassium-ion buffering system consisting of glia-expressed inward rectifying potassium (Irk, or Kir) channels and an interconnected glial Connexin network of gap junctions (Beckner, 2020; Reichenbach and Bringmann, 2013). Potassium ions that are released during neuronal activity have an immediate impact on membrane potential; however, uptake of these by interconnected glia through Irk channels offsets this change, thereby stabilizing neural activity (Beckner, 2020). While the *Drosophila* SCs express two Irks (*Irk1* and *Irk2*), knockdown experiments indicate that *Irk2* is specifically critical in SC-mediated support of PR activity (Charlton-Perkins et al., 2017). SCs are also uniquely enriched with the Connexin-related *innexin* gene family member *innexin 6* (Stebbins et al., 2002), raising the possibility that SCs may use a similar gap junction network for maintaining ion homeostasis in the compound eye.

The SCs' ability to provide metabolic and homeostatic glial support is a salient finding that invites further studies to identify additional functions they might perform. For instance, SCs are enriched with the single Na/K-ATPase alpha subunit (*Atpα*) and two of its beta subunits (*Nrv2* and *Nrv3*), each of which are required for PR activity (Charlton-Perkins et al., 2017). Na/KATPases (Na/K pumps) are broadly expressed in animal cells, executing a diverse set of functions ranging from transport of water, ions, neurotransmitters, amino acids, to that of metabolites. Moreover, Na/K pumps are a critical component of several cellular junctions (Clausen et al., 2017; Genova and Fehon, 2003; Rajasekaran et al., 2001; Vagin et al., 2006). We therefore expect further metabolic and structural roles of SCs to emerge from future studies.

A cooperative Pax2-Prox module for retinal gliogenic potential

The above discussion highlights a number of deeply conserved elements that ensure the proper organization (e.g. Nephrens) and maintenance (e.g. *Glut1*, Kir channels, and *EAAT1*) of retinas in the two major animal eye types. This raises the question as to whether evolutionarily more deeply seated factors contribute to retinal glia support roles. Candidates for these are the transcriptional regulators *pros* and *Pax2*, which not only cooperate during early SC specification, as mentioned earlier, but also in later functions. For example, *Pax2* provides photoreceptor structural support, whereas *pros* provides homeostatic support (Charlton-Perkins et al., 2017).

A closer look reveals some parallels of *Pax2* functions between fly and vertebrate eyes. In flies, *Pax2* ensures the restriction of retinal neurons to the retina, participates in ommatidial organization, and drives glial fate (Charlton-Perkins et al., 2011b, 2017; Siddall et al., 2003). In vertebrates, *Pax2* is expressed in the optic stalk where it works to close around the axons of the optic nerve, form the boundary between the neural retina and glial optic stalk, and promote glial fate in the optic stalk (Bosze et al., 2021; Schwarz et al., 2000; Soukkaieh et al., 2007; Torres et al., 1996). Thus, in both cases, *Pax2* controls the organization of the ocular structure and glial formation. While most genetic studies on vertebrate *Pax2* have focused on its role in optic nerve glia, *Pax2* is also expressed in other retinal glia. In animals lacking intra-retinal vasculature (e.g. fish and chick), *Pax2* is expressed in MG, whereas in vascularized retinas (e.g. mammals), *Pax2* expression is instead expressed in the intra-retinal astrocytes (Stanke et al., 2010). While the cause for this apparent switch has not specifically been addressed, it is notable that this change in *Pax2* expression correlates with the glia most involved in the blood-retina-barrier. Given *Pax2*'s association with other neural tissue barriers (Bosze et al., 2021; Rhinn and Brand, 2001), it seems promising to further explore the role of *Pax2* in its boundary-forming processes using the fly eye as a model. In addition, it is worth noting that the other vertebrate *Pax2*-related factors, *Pax5* and *Pax8*, are transcriptomically enriched in mammalian MG, raising the possibility that radial glia-enriched expression has subfunctionalized to other PaxB orthologs during evolution (Hoang et al., 2020; Nelson et al., 2011; Roesch et al., 2008; Uhlén et al., 2015) (<https://www.proteinatlas.org/ENSG00000196092-PAX5/celltype>; <https://www.proteinatlas.org/ENSG00000125618-PAX8/celltype>). We predict that comparative transcriptomics for PaxB-related targets in various model systems will unearth deeply conserved *Pax*-mediated gene regulatory modules.

The possible conservation of *pros* functions in retinal gliogenesis is less clear. In *Drosophila*, *pros* is initially weakly expressed in a subpopulation of retinal precursors with neuro-glial potential. *Pros* then accumulates and maintains strong expression in the last neuron to form, i.e., R7, where it controls later terminal differentiation events for this UV-sensitive PR (Cook et al., 2003; Kauffmann et al., 1996; Morey et al., 2008). Weaker, more dynamic expression is observed in the SCs, where its presence is likewise important for terminal differentiation events (Cook et al., 2003; Kauffmann et al., 1996). For example, the knockdown of *pros* in SCs leads to reduced PR activity and premature retinal degeneration in adult flies (Charlton-Perkins et al., 2017). This gliogenic role is in line with studies of *pros* in the developing *Drosophila* nervous system where, in addition to its well-established role in

neural progenitor cell cycle exit, *pros* initiates the expression of several glia-associated gene products and aids astrocyte differentiation (Choksi et al., 2006; Peco et al., 2016).

In mice, *Prox1* is mostly known for its role in neural progenitor cell cycle exit and neuronal differentiation. For example, in the mouse retina, *Prox1* affects early progenitor cell cycle exit, participates in horizontal cell fate decisions, and later in bipolar cell differentiation (Dyer et al., 2003). However, *Prox1* expression is also detected in subsets of vertebrate glial cells, including radial glia, astrocytes, and oligodendrocytes (Bunk et al., 2016; Kato et al., 2015; Lavado and Oliver, 2007). In addition, weak expression of *Prox1* has been reported in both fish and mammalian MG (Charlton-Perkins et al., 2019; Cid et al., 2010), raising the possibility that *Prox1* plays later glial roles not yet tested in the vertebrate eye. Remarkably, the *pros* homolog in the nematode *Caenorhabditis elegans* also directs glial function, revealing the importance of *pros* for gliogenesis even in a highly reduced sensory system (Wallace et al., 2016).

As a whole, these findings suggest that *pros/Prox1* may represent an ancient player in providing a “neural” environment during early development, and homeostatic glial function in more mature cell types, while *Pax2* plays important roles in promoting glial fate and providing structural support for the developing retina.

Evolution and conservation of retinal support cells

As this review underscores, SCs control a wide range of functions: patterning, cell survival, lens and pseudocone secretion, retinal morphogenesis, and PR-directed glial support. Of note, the recently reported expression of a specialized opsin in both SCs and pigment cells of butterfly compound eyes gives reason to expect even further roles yet to be uncovered (Macias-Muñoz et al., 2019). Besides cementing the broad significance of SCs for retinal development and function, all of this begs the question of how this multifunctional cell type originated. As highlighted throughout the review, comparative genetic data indicate four potentially deeply conserved candidate modules representing defined SC functions: a *PaxB-SoxB1* module related to crystallin gene expression, a *Pax2-pros* module controlling gliogenesis and glial support functions, a *Pax2-IRM* module directing cellular patterning events and a separate *Pax2* module regulating cell survival (Fig. 6). The strikingly pervasive involvement of *Pax2* in these modules is consistent with its deep associations with sensory system formation (Fritzsch et al., 2005; Vopalensky and Kozmik, 2009).

Compelling support for the modular nature of SC functions at the genetic level is provided by the earlier mentioned crustacean *M. norvegica*, in which only the A/P SCs are lens-secreting, while only the Eq/PI SCs reach fibres to the retinal floor (Hallberg and Nilsson, 1983). In this case, it is tempting to speculate that the putative *PaxB-SoxB1* lens production module has become A/P SC-specific, while the *Pax2-pros* PR support module may be partitioned into the Eq/PI SCs. While such a possibility is intriguing, the existence of these candidate modules requires further scrutiny, by necessity in a broader sample of species. Their possible existence, however, speaks to a scenario in which SCs originated by co-option of conserved kernel-like gene regulatory modules that drive distinct cellular functions (Arendt et al., 2016). The same scenario, of course, may apply to MG, a vertebrate

counterpart to arthropod SCs with respect to retinal homeostatic and structural support. While both cell types can be traced back over hundreds of millions of years to the early evolution of Bilateria (Fig. 6), pinpointing the existence and nature of SC/MG-like precursor cells represents a greater challenge. Recent morphological and immunohistochemical studies in a variety of protostomes provided evidence for a secretory radial glial cell type in simpler sensory systems, raising the possibility that such a cell type did emerge at the beginning of bilaterian evolution (Hartline, 2011; Helm et al., 2017; Losada-Perez, 2018; Rey et al., 2020). The shared genetic modules of SCs and MG could thus be explained through inheritance from a common visual system-specific primordial radial glia.

Concluding remarks

The important question of the existence of primordial radial glia should be addressed by a new generation of studies of glial support sources in animal visual organs. While mammalian camera lens eyes and arthropod compound eyes represent key reference points, similarities in the structures, functions, and genetic programs of different eye types in the animal tree of life highlight the potential for expanding cellular and molecular studies of deeply conserved gliogenic programs. This includes species with no apparent accessory cells except pigment cells, as the latter are part of the PR support system in both vertebrates and invertebrates. The most critical information on the origin of SC/MG can be expected to emerge from the camera eyes of squids (Cephalopoda) (Fig. 6). The retinas of these sophisticated visual organs are populated by pigmented radial glial-like support cells that extend proximo-distal fibres (Koenig et al., 2016; Saibil, 1990; Tomarev et al., 1997). The time seems ripe to elucidate the transcriptomic cell signatures in this third type of high resolution animal eye (Nilsson, 2013), given the success of temporal cross-species developmental transcriptomic studies. Such studies have already started to provide new insights into the existence of conserved regulatory modules responsible for cell type-specific development, structure, and function in the retina (Charlton-Perkins et al., 2019, 2017; Hoang et al., 2020). Thus, cultivating this area of retinal biology will give rise to new and exciting discoveries that will likely elucidate conserved accessory/glial cell type fates and functions in animal vision.

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Abbreviations:

SC	Semper cells
PR	Photoreceptors
MG	Müller glia

PPC	Primary pigment cell
IOC	Interommatidial cell
RPE	Retinal pigment epithelium
IRM	Irre-C Recognition Module
pros	prospero
DI	Delta
ZA	zonula adherens

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Highlights

Drosophila Semper cells, also known as cone cells, are highly multifunctional

Semper cells direct the differentiation of all three tissue types in the compound eye

Semper cells serve homeostatic support roles in the adult compound eye

Semper cells share many characteristics with vertebrate retinal Muller glia

Conserved gene regulatory modules are associated with specific Semper cell functions

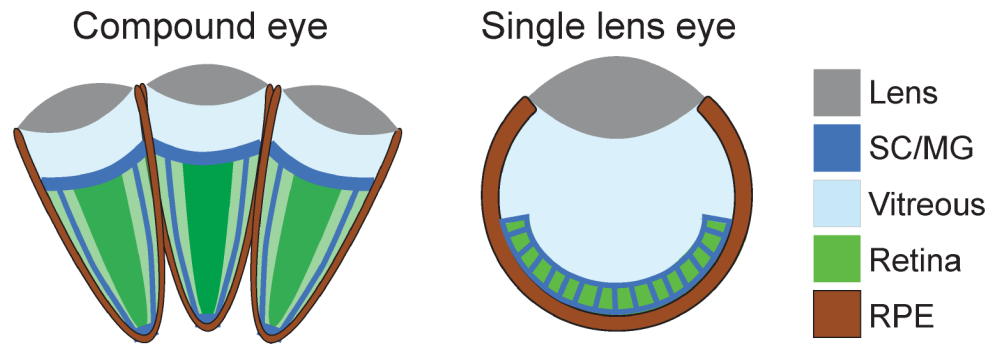


Figure 1: Structural comparison of arthropod compound eye and vertebrate single lens eye. SC/MG represents radial glia-like support cells, Semper cells (SCs) in arthropod eyes and Müller glia (MG) in vertebrate eyes. RPE = retinal pigment epithelium.

Late Larval Imaginal Disc

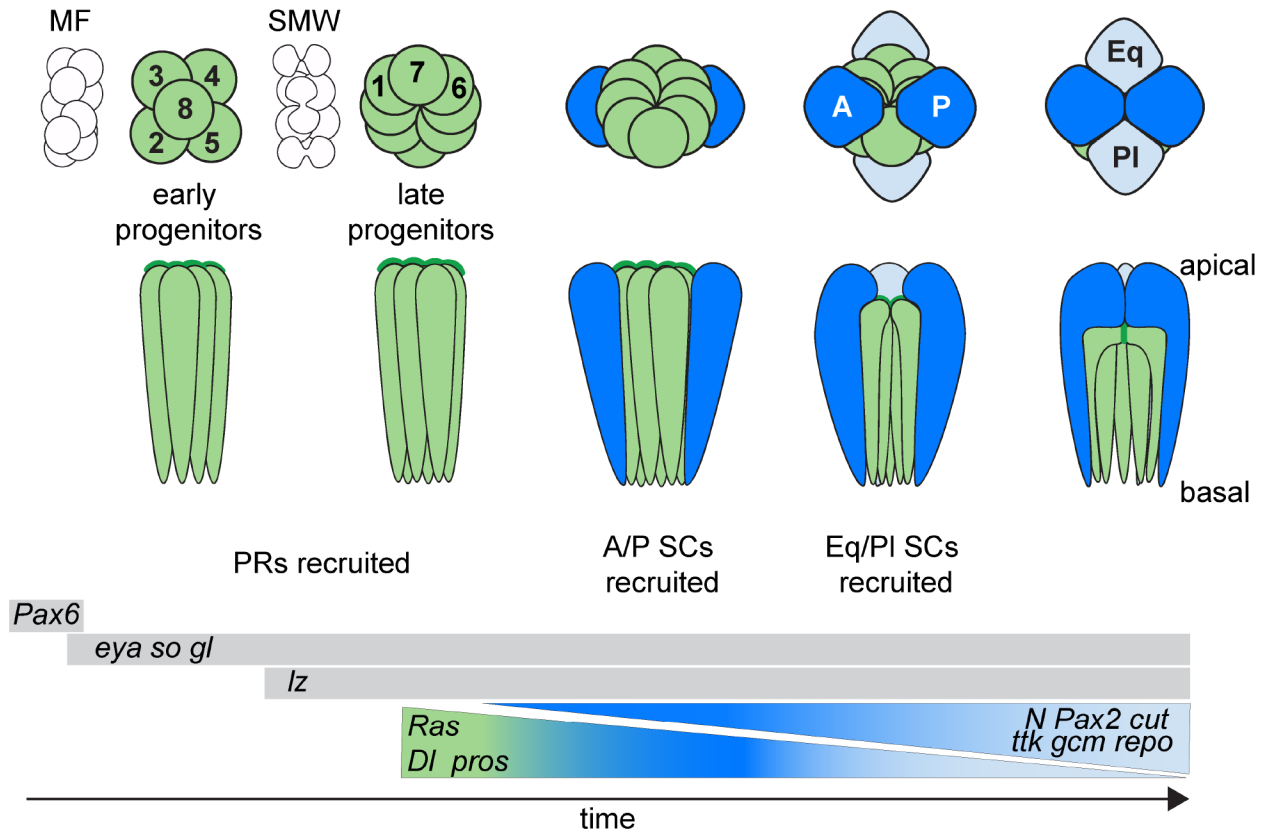


Figure 2: Cellular events during *Drosophila* late larval eye development.

Green = retinal neurons (photoreceptors), dark blue = anterior (A) and posterior (P) Semper cells (SCs), light blue = equatorial (Eq) and Polar (PI) SCs. MF = morphogenetic furrow, a moving front that stops progenitor cell proliferation in G1 and initiates a first wave of neurogenesis of 5 neurons/ommatidia (PRs R8, 2/5 and 3/4). An additional round of proliferation at the second mitotic wave (SMW) provides sufficient progenitors for building the remainder of the eye. Key transcription factors are listed as markers for proliferating ocular progenitors (*eyeless [ey]*), early retinal progenitors (*eyes absent [eya]*, *sine oculis [so]* and *glass [gl]*), and with additional *lozenge [Lz]* expression in late progenitors. *Pax2*, *tramtrack (ttk)*, *cut*, *glial cells missing (gcm)* and *reversed polarity (repo)* are pro-glial in SCs. *prospero (pros)* marks the last PR (R7) and the SC progenitors. R7 fate is promoted by a *pros/Ras* positive feedback loop, whereas SC fate is promoted by a *Pax2/Notch* positive feedback loop. Anterior to the left.

Early pupation

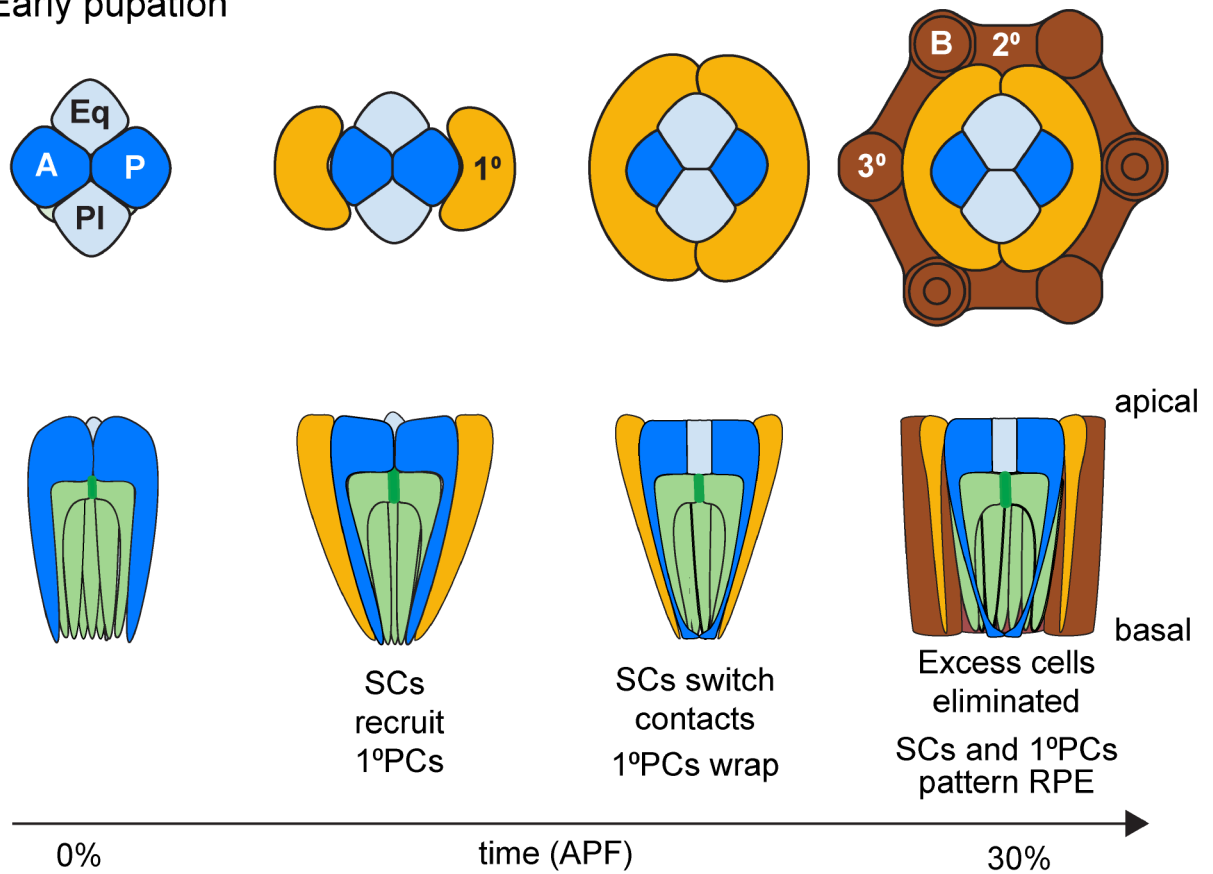


Figure 3: Cellular events during early pupal stages of *Drosophila* eye development.

Color code as in Figure 1 for retina (green) and Semper cells (blue). Light orange = primary pigment cells (PPCs), dark brown = interommatidial cells (IOCs). IOCs include the highly pigmented elongated secondary (2°) and hexagonal tertiary (3°) cells (= i, RPE). Interommatidial bristles indicated with circles.

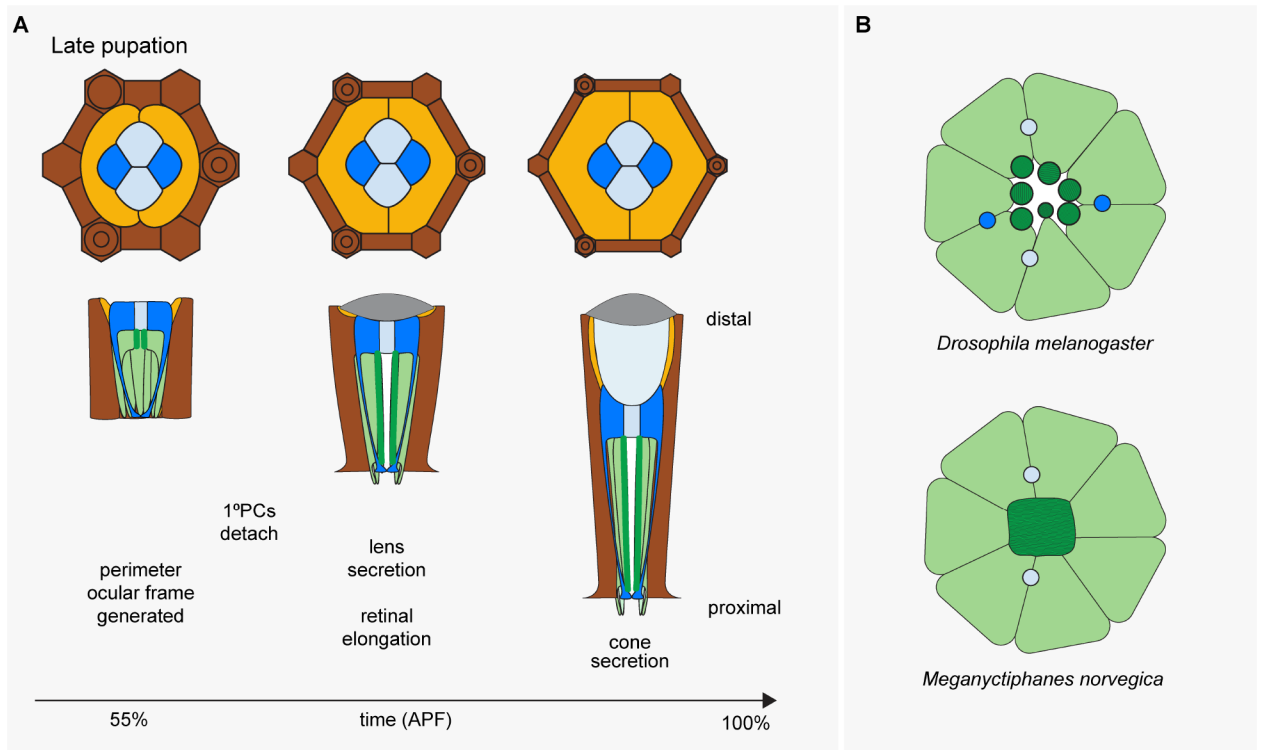


Figure 4: Final stages of *Drosophila* eye development.

(A) Same color code as Figure 3. (B) SC-based interretinular fiber locations in the adult eyes of *Drosophila melanogaster* (open rhabdomeres) and *Meganyctiphanes norvegica* (fused rhabdome). Rhabdomeres are indicated in dark green, while photoreceptor cell bodies are in light green.

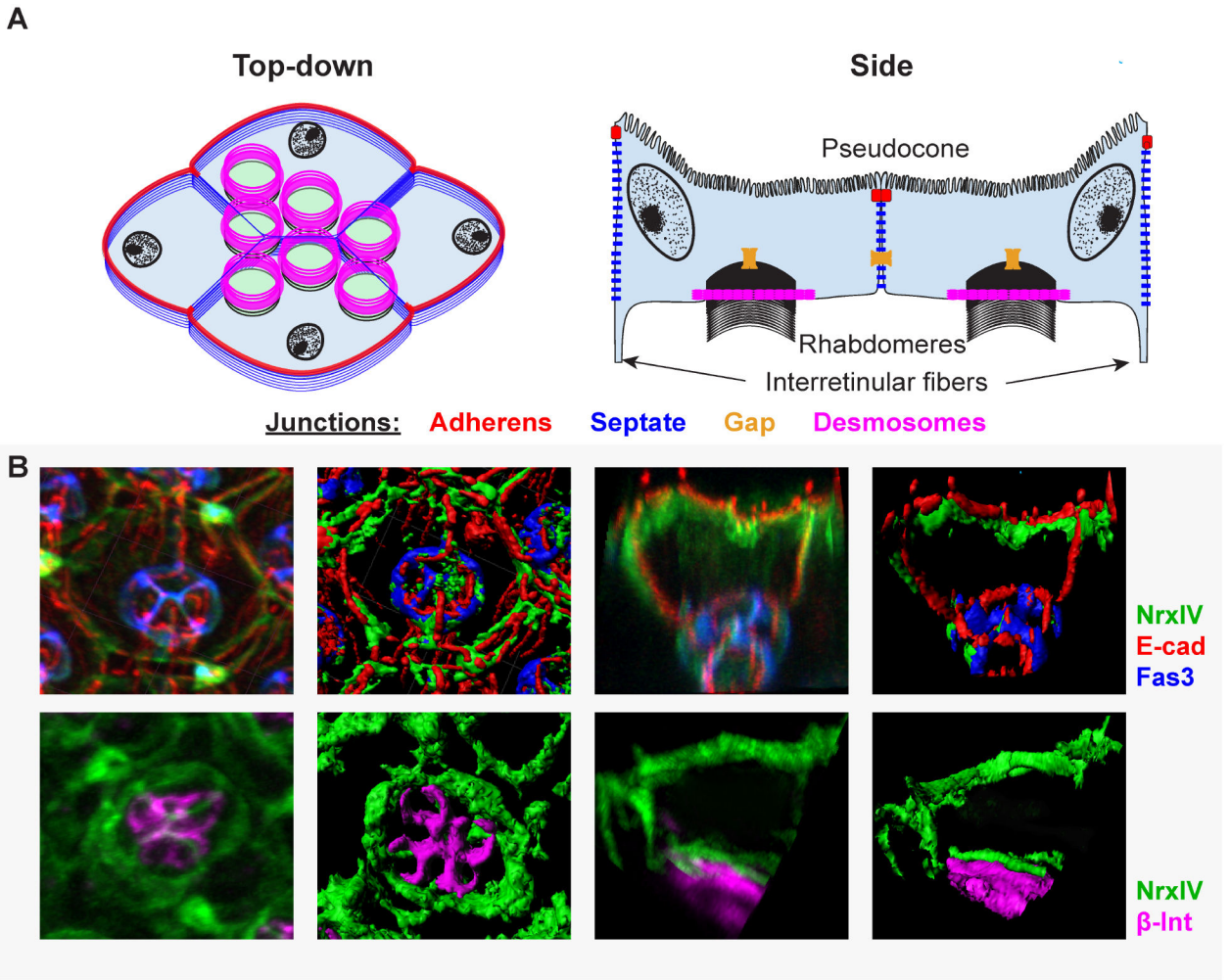


Figure 5: Junctions present in mature Semper cells.

(A) Top down and side view representations of different junctional complexes found in SCs. These include adherens junctions (zonula adherens, red), septate junctions (ladder-like junctions found beneath zonula adherens, blue), and gap junctions (yellow). Confocal images represent individual ommatidia stained for: the septate junction markers Neurexin IV (NrxCIV, green) and Fasciclin 3 (Fas3, blue) and the adherens junction marker E-cadherin (E-cad, red) (top) or NrxCIV (green) and hemi-desmosome marker β -integrin (β -int, magenta) (bottom).

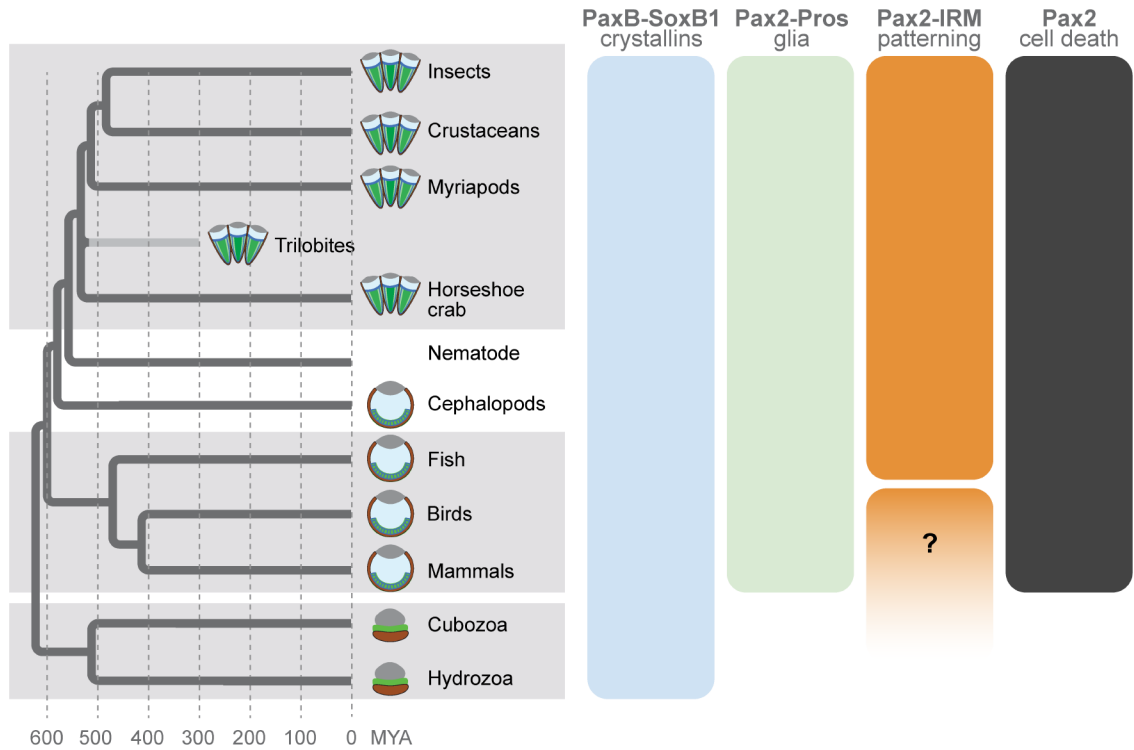


Figure 6: Hypothesized gene regulatory modules utilized by retinal support cells.

Phylogenetic tree depicts the relationships between taxa and species explored in the review with arthropods represented by five major lineages: insects, crustaceans, myriapods, the extinct trilobites, and chelicerates. The latter are represented by its only member with a compound eye, the horseshoe crab *Limulus polyphemus*. Schematics at branch tips depict generalized versions of the major eye types, ranging from compound eyes (arthropods) to independently evolved camera eyes of squids (cephalopods) and vertebrates (e.g. fish, birds, and mammals), as well as the independently derived eye types in the cnidarian species like *Tripedalia cystophora* (Cubozoa) and *Cladonema radiatum* (Hydrozoa). Bars to the right depict hypothesized ancient gene regulatory modules utilized in diverse visual organs as discussed in the text.