wing has also called the existence of such shadows into question.

In fact, it may not be necessary to invoke either bucket-brigade or transcytosis to explain the effects of HSPGs on ligand movement; simple diffusion may be sufficient. The predicted effects of HSPGs on ligand diffusion depend in part on whether the HSPG-bound ligand has access to the higher-affinity receptors. Receptor binding can limit the range of ligand movement by lowering the levels of unbound, diffusible ligand and, via endocytosis, clearing ligand from the extracellular space. Binding to HSPGs might protect the ligand from the receptor, giving it a chance to diffuse over a longer range. Similar models have been proposed to explain the positive effects of the Dpp-binding Chordin homolog Short gastrulation on long-range Dpp signaling in the *Drosophila* embryo (for example, see [20]).

All of this serves to remind us how poorly we understand the movement of signaling molecules through tissues. Add a few more wrinkles, such as the signaling-dependent and endocytosis-dependent changes in the levels of receptors, HSPGs, and their modulators, and testing alternative hypotheses becomes a difficult problem for experimentalist and theorist alike.

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DOI: 10.1016/j.cub.2005.01.026

Photoreceptor Evolution: Ancient Siblings Serve Different Tasks

Photoreceptor cells of vertebrate eyes are fundamentally different from those of invertebrate eyes. New work on the brain of a ragworm now suggests that ancestral bilaterians possessed both types of photoreceptor cell.

D-E. Nilsson

Our view of eye evolution has changed several times in the past 30 years. In 1979, Hansjochem Autrum [1] argued that all eyes share an evolutionary connection through the consistent use of membrane-bound rhodopsin as a photopigment. He also noted that, throughout the animal kingdom, photoreceptors are primarily of two different kinds, rhabdomeric and ciliary, coexisting in the major branches of the phylogenetic tree.

The first serious challenge to this view was a survey of photoreceptor cell ultrastructure which claimed independent evolution in 40 to 65 cases in separate phyletic lines [2]. More than a decade later, the discovery of homologous genes controlling eye development in vertebrates, insects and several other animals seemed to suggest that all eyes of recent animals can be traced back to the eyes of a common ancestor [3,4].

The monophyletic eye hypothesis received justified criticism [5–7], because it did not account for the fundamentally different transduction mechanisms in the ciliated photoreceptors of vertebrates and rhabdomeric photoreceptors of invertebrates,

nor did it account for the incompatible embryological origins of vertebrate and invertebrate eyes. The recent discovery by Arendt and co-workers [8] of a ragworm with coexisting ciliary and rhabdomeric receptors now adds a new dimension to the discussion.

The difference between vertebrate rods and cones, on the one hand, and the rhabdomeric receptors of most invertebrate eyes, on the other, involves more than just different membrane extensions — cilia versus microvilli — for housing the photopigment. The transduction cascades are different, employing different enzymes and different second messengers [7], and the receptor cells respond with opposite electric polarity to stimulation. Protein sequences show that the photopigment of ciliary and rhabdomeric photoreceptor cells belong to different and ancient subclasses [9]. Moreover, the G-proteins and a number of other proteins involved in receptor function belong to subclasses that are distinct for ciliary and rhabdomeric receptor cells [9]. Furthermore, developmental genetic networks show small but consistent differences between ciliary and rhabdomeric receptor cells [8].

At every level, it thus seems that ciliary and rhabdomeric receptors are related but still distinctly different. But why are vertebrate eyes based on the ciliary type and most invertebrate eyes based on the rhabdomeric type? The finding by Arendt *et al.* [8] that a ragworm has both systems offers a delightful explanation: the common ancestor to all bilaterian phyla had both types of photoreceptor (Figure 1). The ciliary type may have served entrainment of the biological clock, and the rhabdomeric type may have been for phototaxis [8]. The different photoreceptors in invertebrate and vertebrate eyes would then only mean that most invertebrates employed their rhabdomeric receptors to build eyes whereas vertebrates used their ciliary receptors.

What happened to the photoreceptor systems that did not evolve into proper eyes? In ragworms, we already know that the other system remains as a few cells in the brain, closely associated with the circadian clock system [8]. It is not unlikely that this is a common trait in many invertebrate phyla and some indications to that effect are known from mosquitoes [8,10]. But circadian clock photoreceptors are far less conspicuous than eyes, and the search for ciliary receptors in invertebrate brains is far from finished.

Given the range of available molecular markers, we may not have to wait very long before the fate of the two photoreceptor systems is mapped out in the different animal phyla. This mapping may, however, result in difficulties of interpretation. Vertebrates do indeed express a rhabdomeric type of rhodopsin in skin melanophores and retinal ganglion cells [11]. But it could well be that these cells secondarily have co-opted parts of a cell specification scheme to become light sensitive [7]. Nevertheless, the existence of rhabdomeric photopigments in vertebrates provides strong support for the existence of two parallel and ancient systems for light detection in animals.

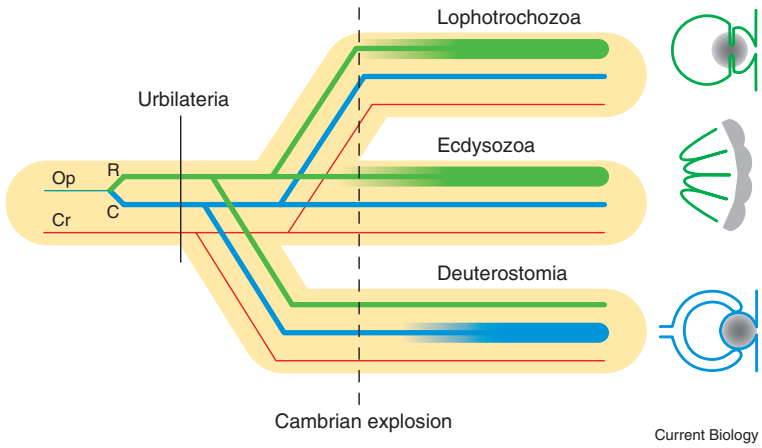

Figure 1. A phylogenetic tree of photoreceptive systems in the main branches of Bilateria.

The opsin based systems (Op) exists in two versions, rhabdomeric (R, green) and ciliary (C, blue). Another ancient system is based on cryptochrome (Cr, red). The level of development of the systems is indicated by line width: thin line, receptor cells without membrane specialisations or amplification cascade; medium line, receptor cells with membrane specialisations and amplification cascade; fat line, eyes with spatial resolution. Epithelial folds of some modern eyes from each branch are drawn to the right; from the top: cephalopod camera-eye, arthropod compound eye, vertebrate camera-type eye.

Eyes in arthropods, molluscs and annelids could very well date back to simple rhabdomeric pit eyes on the lateral head ectoderm, and from there they might have evolved independently by multiplication into arthropod compound eyes, and by elaboration into the camera type eyes of molluscs. But vertebrate eyes are clearly derived from the ciliary photoreceptive system. We can only speculate on the reasons for this peculiarity. It is quite possible that early deuterostomes had lateral rhabdomeric photoreceptors for phototaxis, and brain photoreceptors for other purposes. Perhaps the pre-vertebrate deuterostomes went through an evolutionary phase of sedentary life in which lateral rhabdomeric eyes were lost, after which new eyes evolved from their ciliary brain photoreceptors in response to a readoption of a mobile life-style. Such a scenario leaves room for understanding the unique embryological origin of the vertebrate eye [12].

We can now safely put the monophyletic eye hypothesis to rest. Eye evolution is not that simple. Even if photopigments evolved only once, photoreceptor cells with membrane specialisations have evolved at

least twice, and proper eyes have evolved many times. The majority of the 40–65 photoreceptor cell types identified ultrastructurally are likely to display molecular markers for either rhabdomeric or ciliary types. But it may turn out that some do not. The photoreceptors of mantle eyes in clams [13] is one example that may prove impossible to accommodate in either system. It would also be interesting to learn about the molecular identity of photoreceptor cells outside the Bilateria. Jellyfish have ciliary photoreceptors [14], but their transduction mechanism is as yet unknown. Larval photoreceptors of jellyfish are even more interesting because they are not neurons and their structure is intermediate between ciliary and rhabdomeric [15].

There is of course a possibility that the common bilaterian ancestor had more than two sibling systems for photoreception. Modern animals generally have many such systems in addition to lateral imaging eyes [2,16]. A third photoreceptive system is in fact already known: the cryptochrome system (Figure 1), which is not rhodopsin based, has no molecular amplification cascade, and is not associated with membrane specialisations [17]. This system is implicated for circadian function in both *Drosophila* and vertebrates [17,18] and it controls the iris muscle in birds [19]. It seems that this system too must have been present in the common bilaterian ancestor.

Ironically, the new scenario for eye evolution comes close to the view that prevailed 30 years ago. But we are not just back to square one. Molecular markers for effector genes and developmental genes have provided a new window to the evolutionary history of photoreceptors and eyes. There is great potential here, because the fate of the ancient siblings contains a story not only about the evolution of light reception, but also about the evolution of life-style and general biology in the different phyletic lines.

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DOI: 10.1016/j.cub.2005.01.027

Leukocyte Adhesion: What's the Catch?

A recent study shows that the leukocyte adhesion molecules known as selectins form 'catch' bonds, the dissociation rate of which decreases with increasing applied force. The ability of selectins to switch between catch and slip bonds, where dissociation increases with force, can explain the shear threshold effect, in which leukocyte adhesion goes through a maximum with increasing shear rate.

Daniel A. Hammer

Much of what we now understand about the behavior of biological adhesion molecules under applied force was predicted by two theoretical physicists. George Bell [1] postulated that applied force would increase exponentially the dissociation rate of a biological adhesive bond; this model has been used extensively to model the force-dependent behavior of adhesion molecules, such as the tethering of leukocytes on selectin surfaces [2]. Micah Dembo [3] then postulated that force need not increase dissociation rate, but could actually *decrease* it. Likening the possible behavior of adhesion molecules to a child's 'finger prison', he postulated that applied force could entrap a dissociating ligand, extending the time for dissociation.

An example of this behaviour may now have been found. Yago *et al.* [4] have shown that selectin molecules and leukocyte ligands interact via catch bonds for at least some range of shear rates, and related the behavior to the 'shear threshold' effect [5]. The shear threshold effect is when adhesion goes through a maximum with shear rate [6]. At low shear rates, cells are incapable of binding; as the shear rate increases past a threshold,