distinct segments located at distant sites on a chromosome (also reported in [2]), whereas a gene encoding a dynein heavy chain is present in four distinct segments, three of which are spliced together. Clearly, it would now be worthwhile to re-examine the genome and transcriptome of this protist to determine whether there are perhaps numerous genes that were missed because the entire genes were not contiguous. If this is true for *Giardia*, for how many other organisms whose genomes have already been, or are yet to be, sequenced might it also be the case?

Giardia may be an early-branching eukaryote or it may represent an organism that was simplified from a more complex ancestor that was more typical of other protists. In either case, this discovery suggests the interesting possibility that some now contiguous genes could have evolved in non-contiguous pieces, the transcripts of which could be spliced together. In this model, the separate pre-mRNAs are brought together by base pairing and subsequently spliced to give the precision needed for the mRNA to contain an open reading frame. The current contiguous genes could then have arisen by DNA transposition, thus forming introns that could splice at the sites previously used in *trans*.

There has been much debate about whether genes were put together by assembling exons [11], or whether introns are more recent invaders into eukaryotic genes [12]. If the primitive exons were relatively ancient, they presumably were already transcribed, and they may even have been trans-spliced together to create chimeric mRNAs before the subsequent assembly of the genes. In this idea, some current introns may be present at locations where early pre-mRNAs were spliced together. Of course, all of this requires that genes were not already contiguous in the earliest eukaryote, a debatable proposition.

Finally, there are numerous reports of low-level trans-splicing in human cells (e.g. [13], although some may be artifacts of template switching during reverse transcription [6,14]). The actual trans-splicing events appear to be 'mistakes' of the splicing machinery, but they can sometimes have far-reaching consequences. For example, trans-splicing forms a chimeric mRNA in normal endometrium. In endometrial cancer cells, an identical mRNA is expressed from a chimeric gene formed by DNA rearrangement [15]. Could the trans-spliced mRNA have acted as a 'guide' for this DNA rearrangement [16] much like RNA-guided DNA rearrangement in *Oxytricha* [17]? Perhaps trans-spliced mRNAs like those seen in *Giardia* could have guided the formation of contiguous genes later in evolution. Did RNA lead, and DNA follow? The answer is presumably lost in history, but the discovery in the *Giardia* genome of gene fragments whose RNA products must be trans-spliced together provides a possible new perspective on the role of the spliceosome.

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Circuit Assembly: The Repulsive Side of Lamination

Identifying the mechanisms that shape neuronal circuit architecture remains a major challenge. A recent study shows that repulsive signaling between parallel visual pathways helps organize their connections into laminar circuits in the inner retina.

Daniel Kerschensteiner

In many parts of the nervous system, parallel pathways relay distinct information from one stage of processing (or circuit) to the next. In their target fields, axon terminals of parallel pathways often occupy separate layers [1]. This laminar separation of incoming axons facilitates the formation of pathway-specific connections with local interneurons and dendrites of outgoing projection neurons which target the same layer. Matsuoka *et al.* [2] have now reported evidence that complementary expression of repulsive ligands and their receptors helps guide the laminar separation of parallel circuits in the inner retina.

In mice (and similarly in other vertebrates), twelve types of bipolar

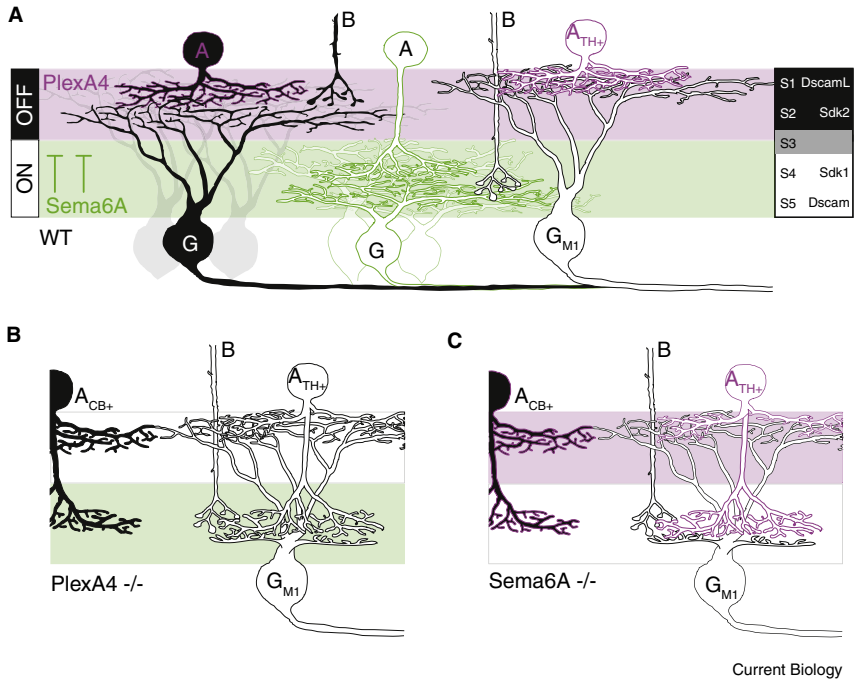

Figure 1. Repulsive and adhesive cues for laminar circuits in the inner retina.

(A) Schematic illustrating the parallel ON and OFF circuits formed between the bipolar cell (B) axons, amacrine cells (A) and retinal ganglion cell (G) dendrites in the inner plexiform layer of the retina. Sema6A and PlexA4 show complementary expression in the ON and OFF zones of the inner plexiform layer, respectively [2]. PlexA4 is expressed by amacrine, Sema6A by both amacrine and ganglion cells. In addition to ON and OFF zones, the inner plexiform layer can be divided into five anatomically distinct sublaminae (S1–S5). Several cell adhesion molecules (Sidkick 1 and 2, Sdk1 and 2; Down syndrome cell adhesion molecule, Dscam; Dscam like, DscamL) show restricted expression on neurons that target one particular sublamina and are thought to help establish layer specific connections [5–7]. (B,C) In the absence of either PlexA4 (B) or Sema6A (C), dopaminergic amacrine cells (thyrosinhydroxylase-positive, TH+) and type M1 ipRGCs (G_{M1}) which normally form ectopic ON circuits in S1 send aberrant and overlapping processes to S4/S5 [2]. In addition, a group of calbindin-positive (CB+) amacrine cells begins to invade S4/S5 [2]. These are depicted as OFF amacrine cells in the schematic, but their response type remains to be confirmed.

cells relay photoreceptor signals from the outer to the inner retina. Seven are excited by increases in light (ON) and five by decreases in light (OFF), generating parallel ON and OFF pathways which are critical to many aspects of visual processing [3,4]. The axons of each bipolar cell target specific bands (or sublaminae) in the retina's inner plexiform layer: ON types in the inner and OFF types in the outer half (Figure 1A). There they form pathway- and cell-type-specific connections with amacrine cells (~30 types), a diverse class of local interneurons, and the dendrites of retinal ganglion cells (~20 types), the output neurons of the eye [3,4].

Based on the expression patterns of molecular markers, five anatomical sublaminae (S1–S5) are commonly distinguished in the inner plexiform layer (Figure 1A) [4]. In recent years, neurons that target the same inner plexiform layer sublamina have been shown to express identical homophilic cell adhesion molecules on their surface [5,6]. Genetic removal or ectopic expression of these cell adhesion molecules were found to blur and misdirect, respectively, the laminar targeting of neurites in the inner plexiform layer [5–7]. While adhesive interactions through matching cell surface molecules provide a mechanism for synaptic partners to recognize each other and maintain contact, they do not readily explain how neurites and connections become confined to a specific sublamina of the inner plexiform layer, how the different sublaminae acquire stereotypic positions, or how the inner plexiform layer is divided into ON and OFF zones?

The results reported by Matsuoka *et al.* [2] identify semaphorin-mediated repulsion between neurons in the inner retina as one of the answers to these questions. Semaphorins form one of the largest and phylogenetically most conserved groups of guidance cues. In higher vertebrates, ~20 different semaphorins are divided into five classes (Sema3–7) on the basis of structural differences [8,9]. Thus, some semaphorins are secreted (for example, Sema3A–G) and act at a distance, whereas others span the plasma membrane (for example, Sema6A–D) or are linked to it by glycosylphosphatidylinositol anchors (for example, Sema7A) and act in a contact-dependent fashion [8,9]. By far the most prominent receptors of semaphorins are plexins, a family of transmembrane proteins with nine members grouped into four classes (PlexA–D) [8,9]. The cytoplasmic signaling domain of plexins can activate a variety of pathways, several of which converge to alter cytoskeletal dynamics. While semaphorin–plexin signaling can influence many aspects of neuronal morphology, it is best known as a mechanism for repulsive neurite guidance [8,9].

To assess whether semaphorin–plexin signaling contributes to the formation of laminar circuits in the inner plexiform layer, Matsuoka *et al.* [2] analyzed the distribution of lamina-specific markers in knockout mice of each of the nine plexin receptors. They found that dopaminergic amacrine cells, which normally are confined to the outermost portion of the inner plexiform layer (S1), extend branches deep into the ON zone (S4/S5) in mice lacking PlexA4 (Figure 1B), but maintain normal stratification in the other plexin receptor knockout mice. Do the aberrant processes of dopaminergic amacrine cells contact inappropriate synaptic partners or meet their normal partners in an unusual place? Dopaminergic amacrine cells are exceptional in that they receive input from intrinsically photosensitive retinal ganglion cells (ipRGCs, type M1) [10]; amacrine cells are generally presynaptic to retinal ganglion cells, not *vice versa*. Matsuoka *et al.* [2] show that the aberrant projections of dopaminergic amacrine cells colocalize in S4/S5 with equally misplaced processes of M1 ipRGCs.

Another unusual aspect of the circuits between dopaminergic amacrine cells and M1 ipRGCs is that both cells receive out-of-zone input from axon stalks of a subset of ON

bipolar cells passing through S1 (Figure 1A) [11,12]. Interestingly, the axon terminals of these ON bipolar cells stratify in S4/S5 [11,12], the region to which dopaminergic amacrine cells and M1 ipRGCs mistarget in the absence of PlexA4 [2]. Thus, it seems most parsimonious to conclude that PlexA4 signaling does not determine the specificity of synaptic connections but instead selectively protects their laminar organization. The observation that PlexA4 is expressed by dopaminergic amacrine cells, but not M1 ipRGCs, further indicates that amacrine cells provide laminar cues which retinal ganglion cells follow [2]. A leading role for amacrine cells in inner plexiform layer organization was previously suggested by a study of the zebrafish mutant *lakritz*, in which amacrine cells were found to establish admirably normal lamination patterns in the absence of retinal ganglion cells [13].

Which ligand signals through PlexA4 receptors to keep the neurites of dopaminergic amacrine cells from straying towards the ON zone of the inner plexiform layer? Matsuoka *et al.* [2] excluded contributions from class 3 semaphorins (Sema3) because genetic removal of neuropilin-1 or neuropilin-2, obligatory co-receptors of plexins in Sema3 signaling [8,9], did not affect inner plexiform layer lamination. Instead, Matsuoka *et al.* [2] found that PlexA4 (amacrine cells only) and Sema6A (amacrine cells and retinal ganglion cells) show strikingly complementary expression in the OFF and ON zones of the inner plexiform layer, respectively. Moreover, in mice lacking Sema6A, dopaminergic amacrine cells, M1 ipRGCs and a group of calbindin-positive amacrine cells show identical targeting defects to those observed in *PlexA4*$^{-/-}$ mice (Figure 1C). Finally, whereas both *Sema6A*$^{+/-}$ and *PlexA4*$^{+/-}$ mice have normally patterned inner plexiform layers, dopaminergic amacrine cells extend aberrant processes into S4/S5 in *Sema6A*$^{+/-}$ *PlexA4*$^{+/-}$ double heterozygous mice, a genetic confirmation that Sema6A signals through PlexA4 to regulate inner plexiform layer lamination [2]. The narrowness and abrupt boundaries of ON and OFF zones in the inner plexiform layer may explain the choice of a contact-dependent (Sema6A) rather than diffusive (Sema3) cue for repulsion.

Several OFF amacrine cells — for example, OFF starburst amacrine cells and VGluT3-positive amacrine cells — appear to stratify normally in the absence of PlexA4 [2]. These amacrine cells may use additional plexins to detect Sema6A or respond to a different repulsive cue. However, it is worth noting that the circuit which most clearly becomes displaced when Sema6A–PlexA4 signals are missing is the one known ectopic circuit (the ON circuit in OFF zone) in the inner plexiform layer. Both dopaminergic amacrine cells and M1 ipRGCs normally receive input from the stalks of ON bipolar cell axons passing through the OFF zone [10–12] and send aberrant processes towards the laminar target of these axons in the absence of Sema6A–PlexA4-mediated repulsion. Thus, the mistargeting of dopaminergic amacrine cells and M1 ipRGCs may highlight how adhesive (for example, cell-adhesion-molecule-mediated) interactions between synaptic partners [5–7] collaborate with the repulsive interactions described by Matsuoka *et al.* [2] to define the spatial layout of inner plexiform layer circuits, while additional signals [14,15] refine the patterns of synaptic connectivity in the confines of this layout. Interestingly, plexins were originally identified as the antigen to an antibody that disrupted retinal lamination in cultured frog eyes [16,17], and semaphorin–plexin signaling has been shown to guide laminar targeting elsewhere in the nervous system [9,18] arguing for a conserved role of these cues in establishing laminar circuit architecture.

A final question emerging from the study of Matsuoka *et al.* [2] is: why the effort to keep an ON circuit out of the ON zone of the inner plexiform layer? There are five known types of melanopsin-expressing intrinsically photosensitive retinal ganglion cells (M1–M5 ipRGCs) [19]. All except M1 ipRGCs stratify their dendrites at least partially in the ON zone of the inner plexiform layer, and all (as far as tested), including M1 ipRGCs, receive input from cone photoreceptors via ON bipolar cells. Interestingly, cone input to M1 ipRGCs is much weaker than to other ipRGCs [20], most likely because of their reduced contact opportunities with ON bipolar cells in the OFF zone. Thus, one might speculate that Sema6A–PlexA4 signaling serves to protect M1 ipRGCs from excessive cone input which might interfere directly with their ability to photoentrain circadian rhythms or could homeostatically suppress expression of melanopsin, which appears to be inversely correlated with the level of cone input to ipRGCs [19]. This can now readily be tested in the mice described by Matsuoka *et al.* [2], who in their new study have shown us the repulsive side of retinal lamination.

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Genome Evolution: Horizontal Movements in the Fungi

Fungi possess robust cell walls and do not engulf prey cells by phagotrophy. As a consequence they are thought to be relatively immune from the invasion of foreign genes. Nonetheless, a growing body of evidence suggests gene transfer has amended the metabolic networks of many fungal species.

Thomas A. Richards

Horizontal gene transfer (HGT) involves transmission of genetic material between organisms [1,2]. This pattern of inheritance contrasts with the typical transmission of genetic material from parent to offspring. HGT is usually detected using phylogenetic trees to identify gene ancestries that contradict established species' phylogenies by placing one species, or group of species, *within* a clade of unrelated species [2]. Such analyses have demonstrated that HGT has occurred at a very high frequency among prokaryotes [1], especially among genes classified in the 'operational' category (e.g., genes of intermediary or secondary metabolism). By comparison, 'informational genes' (genes involved in transcription, translation and replication) appear to undergo a much lower frequency of transfer [3]. HGT is thought to occur at a lower frequency in eukaryotes because several cellular characteristics act as partial barriers to the incorporation of foreign genetic material (e.g., the membrane-bound nucleus, segregation of reproductive and somatic cell lines in multicellular organisms, and differential intron processing) [2]. Nonetheless, a new study by Slot and Rokas [4] reported in a recent issue of *Current Biology* highlights the potential for transfer of large clusters of genes between distantly related fungi.

Fungi are extremely successful eukaryotic microbes, especially in terrestrial environments where they constitute the principal recyclers of biomass and establish important commensal and pathogenic interactions with both plants and animals [5]. Biological innovations that underpin this success include possession of a robust chitin-rich cell wall and an osmotrophic feeding habit (secretion of enzymes to break down complex polymers in the extracellular environment followed by uptake of metabolic subunits). These cellular adaptations are linked: the chitin wall reinforces the fungal cell and enables it to resist substantial osmotic pressures produced during osmotrophic feeding and growth of fungal hyphae in diverse and heterogeneous environments. These adaptations drive the high metabolic rate, fast growth, and ecological success of the Fungi [6]. However, as a consequence of this lifestyle, fungi have lost the ability to perform phagocytosis and therefore cannot engulf and digest prey cells like many other eukaryotes. This is a key factor when we consider biological processes that may underlie HGT, because phagotrophy has been suggested to be a major source of gene transfer into eukaryotes [7]. In support of the 'you are what you eat' hypothesis, phylogenomic analysis of unicellular eukaryotes that feed by phagotrophy has demonstrated that these microbes have obtained genes from their prey, thereby establishing phagotrophy as a route for HGT into eukaryotic genomes [8,9]. Conversely, these observations suggest that key adaptive strategies and cellular characteristics of fungi constitute additional barriers to HGT. Does this mean that HGT has played an insignificant role in the evolutionary diversification of the Fungi?

A growing body of data suggests this is not the case, with several studies identifying the transfer of individual or small clusters of genes into fungal genomes (e.g., [10–18]). The recent study by Slot and Rokas [4] goes further still by demonstrating that HGT can move large clusters of genes between fungi, providing radical additions to the metabolic network of the recipient. Slot and Rokas identified the HGT of a 23-gene cluster from the *Aspergillus* lineage to *Podospora*. These two groups are distantly related members of the Pezizomycotina, a subphylum within the Ascomycota [5,19], (Figure 1). The 23-gene cluster includes genes that putatively encode the entire sterigmatocystin synthesis pathway, a toxic and mutagenic compound and a precursor of aflatoxins. Gene-by-gene phylogenetic analysis demonstrated all 23 *Podospora* genes branched with genes from *Aspergillus.* Taking into account differential gene loss, these phylogenetic results are in direct contradiction to the species phylogeny [19], (Figure 1) and are consistent with HGT between these fungi. Furthermore, the "remarkable microsynteny and sequence conservation" [4] of the gene cluster shared by both the *Aspergillus* and *Podospora* provides additional evidence to support the HGT hypothesis. These data change our perception of how HGT operates in fungi by demonstrating that HGT can convey large chunks of genome that encode entire metabolic pathways between distantly related fungi in a single event.

Although HGT is thought to occur at a comparatively low frequency in the Fungi, these new data support two hypotheses relating to gene transfer and fungal genome evolution. Fungal genes encoding intermediary and