we dare to reintroduce substantial plasticity levels in the adult thalamus or cortex in order to cure amblyopia. The human visual system is far more complex than that of the rodent, and we have no clue yet how enhancement ofthalamic or cortical plasticity may affect visual perception. Although therapeutic applications will have to wait, this new study by Stephany et al. [1] makes an important contribution to the amblyopia research field by forcing us to rethink how visual acuity and ocular dominance are related. The study also illustrates that we have been left in the dark for too long about the role of the thalamus in ocular dominance plasticity. Let’s put the thalamus in the spotlight to get a better picture of its function!

REFERENCES


Microsporidia: A Single Horizontal Gene Transfer Drives a Great Leap Forward

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Horizontal gene transfer from bacteria to eukaryotes is the subject of much debate. A recent study reveals the instrumental role that the acquisition of bacterial nucleotide transporters played in the evolution of the ubiquitous, intracellular eukaryotic parasites, the microsporidia.

Since their discovery ~150 years ago [1], microsporidia have retained a unique position among unicellular (that is, protist) parasites, mostly due to their dissimilarity to other eukaryotes. Their developmental stages lack some key features, such as mitochondrial cristae and a stacked Golgi apparatus. Instead, they developed unusual morphological structures, such as a long extrusive polar tube and a membranous polaroplast (Figure 1A), which together allow the injection of the sporoplasm into the host cytoplasm, an unusual yet highly efficient mechanism of cell infection (Figure 1B). No wonder microsporidia were considered the most
hosts or syndromes with high affinity and selectivity [5]. Next, the authors proceeded to study the function of members of the diversified NTT family in three microsporidian species, some of which (*Encephalitozoon* spp.) belong to the most common human parasites, with prevalence up to 30% of immunocompetent and asymptomatic individuals [7]. All three species carry several NTTs in their genomes that functionally diversified following gene duplications. By a range of assays using radiolabeled and cold purine and pyrimidine nucleosides, nucleotides and nicotinamide derivatives, Dean et al. [5] demonstrated that microsporidia use NTTs for import of NAD+ and purine nucleotides. Indeed, microsporidia lost the capacity to synthesize both purine and pyrimidine nucleotides and consequently must obtain them from the host, yet the importer(s) for pyrimidine nucleotides remain(s) unknown. The acquisition of NTTs by microsporidia via HGT was undoubtedly a transformative moment in their long evolutionary history. As a consequence, endogenous pathways for energy generation and nucleotide biosynthesis were lost, turning microsporidians into ‘energy parasites’ with minimalistic eukaryotic genomes and mitochondrion-derived mitosomes shrinking into tiny vesicles with the sole function of iron-sulfur cluster synthesis [8]. Due to their cryptic existence, the presence and diversity of microsporidia are chronically underestimated; yet it is likely that each mammalian and fish species hosts its own, one or several, microsporidia [9] and the same may apply to insect hosts. Such massive expansion of microsporidia seems to coincide with the diversification of their hosts and the acquisition of NTTs. Microsporidia tend to infect metabolically active tissues and within the host cells often accumulate around mitochondria, likely due to the high concentration of ATP. During the multiplicative phase of their life cycle, microsporidians do not cause visible harm to the host cell, thus resembling an intracytoplasmic symbiont rather than a typical parasite [10] (Figure 1C). Moreover, efficient acquisition of energy from the host and consequent genome streamlining allows extreme parasitism — such as the infection of mammalian enterocytes, which live for only ~3 days — during which dozens of spores are produced from a single sporoplasm (Figure 1D). Indeed, some species have a doubling time of only 3.3 hours, comparable to yeast in a rich medium [11].

Taken together with previous studies on microsporidian NTTs, the work by Dean et al. [5] provides possible explanations of some additional unique aspects of microsporidian biology, such as the absence of an extant group linking them with fungi or their morphological uniformity despite their extreme diversity. The HGT of NTTs was such a transformative event that an intermediate stage might never have ever existed, or went extinct if it did. Moreover, once microsporidia acquired the capacity to steal ATP, GTP and/or NAD+, a novel ‘exploit and kill’ strategy was established within the eukaryotic realm, opening to these cunning parasites niches in a virtually unlimited number of host species, with which they just co-evolved, without any need to tweak and/or further improve their main features. Furthermore, we propose that via their NTTs microsporidia sense the level of host ATP, and respond by multiplying when ATP is abundant. Furthermore, its drop would signify exhaustion of resources, and signal to the parasite that it should produce spores, the only stage that survives outside of the host cell (Figure 1). Consequently, further research of NTTs might allow the identification of this long elusive sporulation signal. HGT is extremely common in bacteria and archaea and has been instrumental in

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**Figure 1. Unique morphology and host-parasite interaction.**

(A) Uniform morphology of a microsporidian spore; AD, adhesive disk; PF, polar filament; PP, polaroplast; V, vacuole. (B) A still healthy host cell carrying an injected sporoplasm (colored). (C) A host cell containing a fast-dividing merogonial stage of the microsporidium consuming host ATP. (D) An ATP-depleted host cell turned into a bag of spores; N, host nucleus.
We will not conceal that there are several uncertainties in interpreting single-gene phylogenetic trees often spanning millions of years ago. In our view, methodological advancements, including this [5] and previous work [4,15,16] on NTTs in Microsporidia, settle at least three arguments with respect to HGT between bacteria and eukaryotes.

Bacteria to eukaryote HGT exists. Above all, it has been shown by numerous independent research groups that HGT between bacteria and eukaryotes occurs and bacterial genes in eukaryotic genomes can come from donors other than mitochondrial and plastid ancestors [13,14]. Of course, it is not as common and active a process as HGT amongst bacteria and archaea, but the relative rarity of something does not mean that it should be disregarded as nonexistent or insignificant. This is particularly important for parasites where horizontally transferred genes can be explored as potentially unique drug targets [15,17–19].

Bacteria to eukaryote HGT is relatively common. Several percent of all genes in unicellular eukaryotes [13–15,17–19] or asexual multicellular eukaryotes such as bdelloid rotifers [20] are frequently reported to be of HGT origin. Multicellular eukaryotes have a much lower proportion of HGTs likely due to their segregated germ line [14]. In parasitic protists, conservative estimates usually report less than 2.5% of all genes to be of HGT origin [15,17,18] (Figure 2).

Functional bacteria to eukaryote HGTs are adaptive. Mechanisms of gene transfer from bacteria to eukaryotes do not hugely differ from mechanisms for HGT amongst prokaryotes [13]. However, eukaryotic genes are fundamentally different from bacterial and archaeal genes, for example by having spliced introns. These differences usually result in the introduced genes in eukaryotes ending up as non-functional DNA [14]. Nevertheless, the remaining few HGTs that become functional often allow eukaryotes to adapt to novel environments. The gene can then evolve and co-diverge with its particular host as any native gene would — gene duplication and specialization can fine-tune or expand its function. Evolution of the NTT gene duplication, as reconstructed by Dean et al. [5] for distinct clades of Microsporidia, provides a fascinating example of what can possibly happen with HGTs post-acquisition.

One particular group of eukaryotes that took advantage of HGT to expand into and persist in novel ecological niches are parasites. Free-living eukaryotes represent an untapped resource of essential nutrients. Bacteria are very proficient at using this resource, and eukaryotic parasites often borrow genes from bacteria to parasitize other eukaryotes. In Microsporidia, diverse species were shown to carry between 0.34% and 2.11% of genes to be of HGT origin [15] participating mostly in nucleic acid synthesis and salvage (Figure 2). Proteomes of other protist parasites reveal overrepresented HGTs involved mostly in metabolism of amino acids, sugars, nucleotides, cofactors and vitamins, lipids, and anaerobic energy metabolism [17]. Such HGTs were found in almost all evolutionarily successful parasitic lineages such as Plasmodium, Toxoplasma, Cryptosporidium, Trypanosoma, Leishmania, Trichomonas, Giardia, and Entamoeba (Figure 2). The most illuminating example is Blastocystis with ~2.5% of its genes acquired by HGT, allowing this parasite to adapt to the hostile environment of the animal gut [18].
From the perspective of animal hosts of microsporidia, we can conclude that it is rather fortunate that HGT of NTTs from bacteria to parasitic eukaryotes has been relatively rare [17] as otherwise no eukaryote would be safe from diverse microsporidia-like ‘super-parasites’ stealing its ATP, GTP and NAD³.

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Developmental Biology: Neurons That Divide Together Wire Together

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Retinotopic maps represent a fundamental organizing principle of visual system wiring. A recent study illustrates how careful coordination of developmental strategies can simultaneously create a diverse array of cell types and establish a complex wiring diagram.

If you have ever assembled an elaborate home entertainment system, you are likely familiar with how challenging it can be not only to plug all of the wiring into the correct ports, but also to make sure that the setup is space-efficient, modular, and reproducible. Yet this task is analogous to a problem all developing nervous systems must solve on a much larger scale: the adult human central nervous system, for example, is estimated to have hundreds of trillions of synapses [11]. What developmental strategies do nervous systems use to wire complex circuits?

A recent study by Pinto-Teixeira et al [2], along with two related studies [3, 4], illustrates how simple developmental processes can be combined to produce, differentiate, and wire a large population of neurons with complex synaptic connections (Figure 1).