also suggested[13] a link between them.

Fifty years after a military mission unexpectedly made one of the most remarkable discoveries in high-energy astronomy, we are still struggling to unify the physical models of GRBs. Greiner and co-workers' findings add another twist to the tale of γ-ray astronomy, which will undoubtedly be followed by others in the next few years, when gravitational-wave detectors start surveying high-energy phenomena in the sky. ■

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PROTISTOLOGY

How to build a microbial eye

Dissection of the subcellular eye of microorganisms called warnowiid dinoflagellates reveals that this structure is composed of elements of two cellular organelles — the plastid and the mitochondrion. SEE LETTER P.204

THOMAS A. RICHARDS & SUELY L. GOMES

The ancient Greek physician Galen described the key anatomical features of the eye[1], including the retina, lens, cornea and iris. Yet arguably the first true understanding of how the vertebrate eye works came in the early seventeenth century, with mathematician Johannes Kepler's demonstration that vision occurs as an image projected on to the surface of the retina[2]. As such, an eye can be defined as a cornea and/or a lens that forms an aperture allowing light arising from a specific direction to pass on to a sensory surface that processes this signal into a chemical message. But animals were not the only organisms to evolve such systems — analogous structures and biochemical responses exist in cells of several eukaryotic microorganisms (cells that package most of their DNA in a nucleus), allowing these microbes to move in response to light[3]. On page 204 of this issue, Gavelis *et al.*[4] describe the subcellular features that make up the eye-like structures of warnowiid dinoflagellates, which in anatomical terms are remarkably similar to vertebrate eyes.

Warnowiid dinoflagellates are unicellular plankton that have not been cultured in the laboratory, but that are known to possess a remarkably complex eye-like structure, called the ocelloid. Ocelloids consist of distinct components similar to key parts of vertebrate 'camera-type' eyes: a cornea, a lens (called a hyalosome) and a pigmented cup or retina-like structure. Gavelis *et al.* studied warnowiids isolated from marine waters in Japan and Canada, and demonstrate that the anatomy of ocelloids is built from reconfigured plastids and mitochondria (Fig. 1a). These are subcellular compartments seen in many eukaryotic groups that formed in the distant past through the intracellular incorporation of symbiotic bacteria; these organelles usually contain their own genomes and typically function in energy transformation.

Specifically, Gavelis and colleagues show that the retinal body of ocelloids arises from a membrane network derived from plastids, and that multiple mitochondria form a cornea-like surface across a lens structure. To test these microscopy-based observations, the authors microdissected the warnowiid

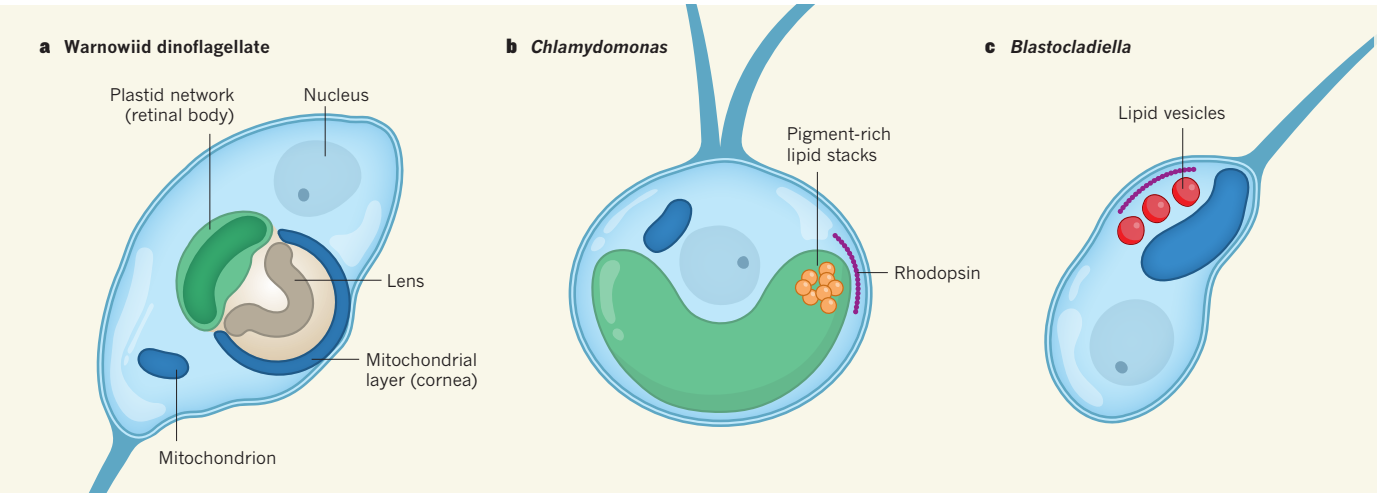

Figure 1 | Eyes across the tree of life. a, The eye-like ocelloids found in unicellular organisms known as warnowiid dinoflagellates have a 'camera-like' complexity that resembles that of animal eyes. Gavelis *et al.*[4] show that two of these components in warnowiids have arisen through the reconfiguration of membrane-bound organelles that are usually used for cellular energy transformation: the cornea is formed from a layer of mitochondria and the retinal body is derived from a network of plastids. **b**, **c**, Microorganisms from other branches of the tree of life also contain eye-like structures, although these are anatomically simpler. **b**, The eyespots of *Chlamydomonas* algae comprise stacks of pigment-rich lipid molecules, located inside the cell's plastid, which shades light from one side of light-sensitive rhodopsin proteins. **c**, The eyespots of *Blastocladiella* fungi are lipid-filled vesicles close to the cell's main mitochondrion that are overlaid with rhodopsin proteins.

retinal body and sequenced its DNA, which contained a much higher proportion of DNA of plastid origin than equivalent samples from the whole cell.

Although ocelloids are exceptionally complex, warnowiids are not the only microbial cells with eye-like subcellular structures. A diversity of eukaryotic microorganisms perceive light using different kinds of eyespots. One such structure is the eyespot of the green alga *Chlamydomonas reinhardtii* (Fig. 1b), a unicellular relative of land plants. This eyespot is located at the edge of the alga's plastid and is made up of lipid globules, rich in orange carotenoid pigments, that are stacked in compartments inside the plastid envelope. As such, this globule layer is thought to provide directionality and contrast by shielding and reflecting light from one side of the organism on to two light-sensitive proteins called type 1 rhodopsins that localize with this eyespot[5–7]. These two proteins have intrinsic light-gated cation-channel activity (and are therefore named channelrhodopsins) and have been demonstrated to act as photoreceptors that trigger movement in response to light[5–7].

Cryptophyte algae such as *Guillardia theta* also build eyespot structures that are located in plastids[8], and movement of these cells in response to light is mediated by the function of at least two type 1 rhodopsin proteins[9], similar to *Chlamydomonas*. The alga *Euglena gracilis* also has an orange-red eyespot, although, in contrast to the previous examples, this structure is associated with the base of the flagellum[3], the cells' swimming propeller. The photoreceptor in *Euglena* has been identified as a photoactivated adenylyl cyclase[10] protein.

In yet another branch of the tree of life are the eyespot-like structures of the swimming spores of Blastocladiomycota fungi (Fig. 1c). These structures are lipid-filled vesicles called side-body complexes that are located close to the large mitochondrion of these fungal cells[11]. The side-body complex is overlaid with type 1 rhodopsin proteins. In *Blastocladiella emersonii*, the type 1 rhodopsin photosensor contains a guanylyl cyclase domain, which allows the protein to control the production of cyclic GMP (ref. 12), a key chemical messenger in vertebrate vision. Recent work[13] on warnowiid ocelloids has also suggested that messenger RNA encoding a type 1 rhodopsin is associated with the retinal body.

These examples demonstrate the wealth of subcellular structures and associated light-receptor proteins across diverse microbial groups. Indeed, all of these examples represent distinct evolutionary branches in separate major groups of eukaryotes[3]. Even the plastid-associated eyespots are unlikely to be the product of direct vertical evolution, because the *Chlamydomonas* plastid is derived from a primary endosymbiosis and assimilation of a cyanobacterium, whereas the *Guillardia* plastid is derived from a secondary endosymbiosis in which the plastid was acquired 'second-hand' by intracellular incorporation of a red alga[14]. Using gene sequences recovered from the warnowiid retinal body, Gavelis *et al.* investigated the ancestry of this organelle by building phylogenetic trees for the plastid-derived genes. Their analysis demonstrated that this modified plastid is also of secondary endosymbiotic origin from a red alga.

Although derived independently, there are common themes in the evolution of these eye-like structures. Many of them involve the reconfiguration of cellular membrane systems to produce an opaque body proximal to a sensory surface, a surface that in four of the five examples probably involves type 1 rhodopsins. Given the evolutionary derivation of these systems, this represents a complex case of convergent evolution, in which photo-responsive subcellular systems are built up separately from similar components to achieve similar functions. The ocelloid example is striking because it demonstrates a peak in subcellular complexity achieved through repurposing multiple components. Collectively, these findings show that evolution has stumbled on similar solutions to perceiving light time and time again. ■

The ocelloid demonstrates a peak in subcellular complexity achieved through repurposing multiple components.

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MYELOID DISEASE

Another action of a thalidomide derivative

Lenalidomide effectively treats a blood disorder caused by the 5q chromosomal deletion. A study shows that the drug binds to its target, CRBN, to promote the breakdown of an enzyme encoded by a gene in the 5q region. SEE ARTICLE P.183

TAKUMI ITO & HIROSHI HANDA

Around 60 years ago, thalidomide was developed as a sedative and sold in more than 40 countries. But the drug was soon banned because of its association with serious developmental defects, such as limb deformities, in children whose mothers had taken it while pregnant. Now, thalidomide is being re-evaluated and is recognized as an effective treatment for myeloma, a cancer of plasma cells of the immune system. Moreover, derivatives of thalidomide have been developed; these compounds, which include lenalidomide and pomalidomide, make up a class of immunomodulatory drug termed IMiDs[1]. As well as being effective against myeloma, lenalidomide can treat[2] a type of myelodysplastic syndrome (MDS) — a disorder of blood stem cells (haematopoietic cells) — that is caused by a deletion of the long arm of chromosome 5. In this issue, Krönke *et al.*[3] (page 183) provide a model of lenalidomide action in the context of this mutation.

The protein CRBN was identified as a direct target of thalidomide through affinity-bead technology[4]. CRBN functions as a substrate-recognition component of an E3 ubiquitin ligase enzyme complex that catalyses the conjugation of ubiquitin molecules to specific substrate proteins, thereby marking the proteins for degradation. CRBN is also bound by lenalidomide and pomalidomide[5,6] and is now regarded as a primary target of IMiDs — this binding is required for both the damaging and the therapeutic effects of the drugs. Previous research[7–9] showed that lenalidomide and pomalidomide promote the degradation