molecules farnesol and dodecanol inhibit serum-induced filamentation in *C. albicans* downstream of Cdc35 in the signal transduction pathway [10]. However, these molecules were not able to block Hsp90-induced filamentation, suggesting that Hsp90 regulation must occur downstream of the generation of cAMP. In addition, the *efg1* transcription factor mutant still underwent filamentation in response to Hsp90 inhibition, showing that repression of filamentation also occurs through other downstream targets of PKA.

Previous studies on *C. albicans* temperature-mediated morphogenesis are illuminated in the light of these observations. Soll and colleagues [11] showed that, in defined media, simultaneous increases in medium pH (from 4.5 to 6.5 or above) and temperature (from 25°C to 37°C) were required to induce efficient yeast-to-hypha transitions. Induction of hypha formation was much less efficient following a change in medium pH alone and the kinetics of germ-tube formation were shown to be temperature dependent. Conditions where hyphae have been generated following culture in media at 25°C have also been reported, but the kinetics of conversion were much slower [12]. These observations all seem to be accommodated by the hypothesis that temperature controls morphogenesis by influencing the available cytoplasmic pool of Hsp90 for repression of the PKA pathway that induces hypha formation.

As with all new insights, more questions are immediately suggested. How is hyphal growth maintained at 37°C when, presumably, Hsp90 levels recover after heat shock? What other components of the network of signal transduction pathways are also influenced by Hsp90? The authors show that strains of *C. albicans* that have depleted Hsp90 levels are attenuated in virulence. How is this best explained in the knowledge that about 10% of the proteome may be affected by Hsp90 and therefore many virulence-related functions may be affected simultaneously?

Finally, it is interesting to note that temperature-mediated regulation of *C. albicans* is atypical of other human fungal pathogens in so far as it is the hyphal and pseudohyphal filamentous forms that are promoted at 37°C. In *Histoplasma capsulatum*, *Paracoccidioides brasiliensis*, *Cryptococcus neoformans*, *Penicillium marneffei* and many other dimorphic fungi, it is the yeast form that is found in human tissues while mycelia exist outside the human body [1]. Might it be that in these cases Hsp90 or other molecular chaperones maintain positive regulators of yeast development in an inactive state until the temperature is elevated? Alternatively, Hsp90 could act by repressing negative regulators of hyphal development in these other organisms. The paper published here provides a conceptual framework for framing testable hypotheses that may eventually explain why temperature is a major determinant of fungal morphology in most pathogenic fungi.

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The Aberdeen Fungal Group, School of Medical Sciences, University of Aberdeen, Aberdeen AB25 2ZD, UK.
E-mail: n.gow@abdn.ac.uk

DOI: 10.1016/j.cub.2009.03.027

Organelle Division: Dynamin-Related Proteins in Apicomplexans

Establishing an infection within a host requires efficient invasion and division. In the intracellular parasite *Toxoplasma gondii*, these functions are mediated by dynamin-related proteins with a unique evolutionary history.

Wesley A.J. Webster and Geoffrey I. McFadden*

To be a successful intracellular parasite, you have to get your own insides right before you get inside anyone else's. The phylum Apicomplexa, which includes *Toxoplasma gondii* and *Plasmodium falciparum*, the causative agents of toxoplasmosis and malaria, respectively, are intracellular parasites that have mastered the arts of invasion and division. Indeed, the name for the phylum denotes their specialised complex of invasion machinery at their apical end. In a recent issue of *Current Biology*, Breinich *et al.* [1] demonstrate a role for a dynamin-related protein (Drp) in pinching off parts of the *Toxoplasma* parasite's endomembrane system to form membranous sacs that are a vital part of the apical complex and essential for invasion. A companion article in the same issue by van Dooren *et al.* [2] reports that another Drp has been put to work to divide a relict plastid, the apicoplast, an organelle related to plant chloroplasts. Apicoplasts have generated much excitement as

a potential target for new drugs to combat malaria and toxoplasmosis, for which existing therapies are becoming less and less useful due to resistance. The implication of two Drps, which act as pinchases by using GTP hydrolysis to constrict membranes [3], in the biogenesis of internal membranous compartments reveals a new paradigm in parasite cell biology that was essential to their success as invaders of host cells.

The apical complex is a core set of conserved invasion machineries comprising a conoid, rhoptries and the micronemes [4]. The conoid is cytoskeletal, but the membranous rhoptries and micronemes appear to derive from vesicles generated from the Golgi. Breinich *et al.* [1] show that an unusual Drp, *Tg*DrpB, is essential to microneme and rhoptry formation. The authors show that *Tg*DrpB initially accumulates as a cytoplasmic pool in close proximity to the Golgi, but, during daughter cell formation, *Tg*DrpB is recruited to the Golgi to produce special vesicles that carry the ammunition of the invasion machinery [1]. Parasites with reduced *Tg*DrpB expression fail to form rhoptries and micronemes and are completely disarmed as parasites — no ammunition, no invasion. Without *Tg*DrpB, the hapless *Toxoplasma* are virtually paralysed, unable to egress from the host cell, unable to glide across the substrate to find a new host cell, and unable to invade a new host. Essentially, the loss of *Tg*DrpB destroys the occurrence of future invasions.

The discovery of the apicoplast in Apicomplexa transformed our view of the evolutionary path these protists have marched on their road to becoming virulent intracellular parasites. A past life as photosynthetic symbionts of animals now seems likely, and the apicoplast apparently remains as an anomalous — but potentially exploitable — evolutionary hangover from an earlier incarnation. Apicomplexans acquired plastids by secondary endosymbiosis and belong to the group Alveolata, which also includes ciliates and dinoflagellates. Like all plastids, apicoplasts cannot arise *de novo*; they must be passed on from generation to generation. Failure to do so will result in crippled parasites unable to infect new hosts [5]. Exactly why apicoplasts are essential to the infection cycle is a mystery, but it certainly makes them attractive targets for therapy. Kill the apicoplast and you kill the infection. In plants and red algae, the fission of plastids uses a mixture of the prokaryote-derived GTPase FtsZ that constricts from the inside, and the Drp ARC5 that acts as a pinchase to finally cut the dumbbell-shaped plastid into two halves [6]. ARC5 was apparently recruited to plastid division from the host repertoire of GTPases, whereas FtsZ was incumbent in the cyanobacterial endosymbiont. With the notable exception of apicoplasts, all known plastids utilise FtsZ for division, but apicomplexans lack both FtsZ and orthologues of ARC5 [7]. How their plastids divide was a complete mystery. Van Dooren *et al.* [2] filled this gap by investigating a somewhat unusual Drp paralogue from *Toxoplasma gondii*, *Tg*DrpA, to see if it has a role in apicoplast division. *Tg*DrpA localises to punctate regions on the apicoplast surface during division, eventually concentrating at the point where the apicoplast schisms. During daughter cell formation, dividing *T. gondii* apicoplasts become attached to the mitotic appraratus (centrioles); and the growth of the triple-membrane pellicle around daughter cells, along with the separation of nuclei during mitosis, appears responsible for the elongation and initial constriction of the apicoplast [6] (see Figure 8 of [2]).

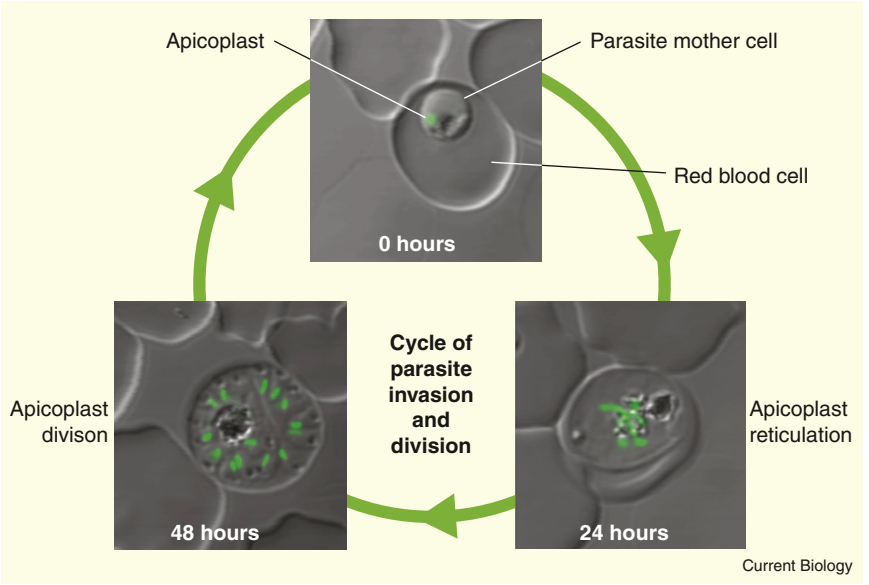

Figure 1. The apicoplast of *Plasmodium falciparum* throughout the intra-erythrocytic cycle. A single apicoplast (green) is present in the mother cell post infection (0 hours). As the cell matures, the apicoplast reticulates into elongated branches (24 hours). Multiple division sites around the branched apicoplast are necessary to ensure faithful segregation of the organelle into daughter merozoites (48 hours). Recruitment of dynamin-related proteins to these division sites would occur during this phase of the cell cycle.

Initially, it was proposed that these external physical forces literally chopped the apicoplast in two, but it now appears that DrpA achieves the final schism in a sphincter-like constriction [2]. Parasites expressing *Tg*DrpA dominant-negatives still manage to stretch out the apicoplast across the two, new-forming cells but fail to cleave it in two. The tension eventually wrenches the apicoplast off the centrioles and it snaps back to the middle of the forming daughter cells. Reducing *Tg*DrpA expression in *T. gondii* blocks the completion of cytokinesis, most likely due to apicoplast division failure [2]. Thus, the role of *Tg*DrpA is analogous to the one played by the Drp *Cm*Dnm2 of the red alga *Cyanidioschyzon merolae* [8], yet another Drp recruited to plastid division from an ancestral pinchase previously employed for cytokinesis [9]. Curiously though, DrpA, which occurs in all the apicomplexans, is not obviously related to any of the Drps that play the role of plastid fissures in plants; DrpA appears to have been recruited to the task exclusively by Apicomplexa. This raises the question of how a more complex structure (four membranes as opposed to two) can divide within an organism that threw away the molecular machinery originally evolved to separate the progenitors?

Why did the apicomplexans evolve new plastid division machinery and dispense with the old system that had served well for all other plastid-containing organisms? The answer might lie in the extraordinary form of cell division, known as schizogeny, common to apicomplexans. Schizogeny involves multiple rounds of mitosis without cytokinesis to produce a multinucleate, unicellular schizont that then undergoes an unusual cytokinesis to produce numerous daughter cells, as many as 10,000 in extreme cases [10]. When the apicoplast was first visualised during schizogeny [11], it was found to go through a remarkable branched and reticulate stage not previously seen in plastids of any other organism, which typically divide by binary fission like their bacterial ancestors. Could the new system of DrpA-mediated cleavage have arisen in conjunction with this bizarre form of plastid division during schizogeny? Apicoplast scission is a fast-paced, highly synchronistic event and visualisation of this phase is rare (Figure 1). Perhaps a key factor underlying the incorporation of host Drps into the organelle division machinery was the coupling of Drp activation and the expression of cell-cycle-dependent factors, thus swinging the balance of division control toward the host. Perhaps, also, the time-honoured system of binary fission orchestrated by FtsZ and the Min proteins was no longer suited to the production of thousands of infectious parasite schizonts. The division of mitochondria [12], primary plastids [8] and secondary plastids [13] show that the expression of division proteins is tied closely to daughter cell formation. Controlling the division of the red algal endosymbiont was key to the establishment of the apicoplast and probably its unusual division mode in parasite schizogeny. It remains to be seen what other proteins are responsible for the concurrent fission of the four apicoplast-bounding membranes. Are membrane-anchored proteins involved and is there sequential division of plastid membranes, as observed in the secondary plastids of the diatom *Phaeodactylum tricornutum* [14]?

The dynamins *Tg*DrpA and *Tg*DrpB are essential, and their co-option to organelle biogenesis were key innovations for the parasitic lifestyle of apicomplexans. More *Drp* genes exist in Apicomplexa and we look forward to learning what their roles are. We are also avidly following the search for the ultimate origins of the highly adaptable dynamins, which would appear to derive from prokaryotic ancestors [15]. Just as tubulin derives from FtsZ, dynamins might also be a little piece of technology that eukaryotes stole from prokaryotes. Ironically, it now appears that parasitic eukaryotes have not only used this technology against their hosts to generate an invasive apparatus but also enlisted it to control their prokaryotic endosymbionts, the apicoplasts.

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Plant Cell Biology Research Centre, School of Botany, University of Melbourne, Victoria 3010, Australia.
*E-mail: gim@unimelb.edu.au

DOI: 10.1016/j.cub.2009.02.044

Critical Periods: Motion Sensitivity Is Early in All Areas

Recent work shows that global motion sensitivity, a property of extrastriate cortex, can be altered by early visual deprivation, while binocularity, a property of primary visual cortex, is still plastic. This contradicts the hypothesis that critical periods end later at higher levels of the system.

Nigel W. Daw

There are critical periods for development of the nervous system. These have been best illustrated by observations on the visual system, where optical or motor problems affecting vision lead to compensatory changes in the connections and physiology of the visual cortex before the age of eight or so, but not after that. The critical period depends on the form of the optical or motor problem, the level of the visual system being studied, the technique used to study the problem, and the previous visual history of the animal [1]. Two recent papers, one in this issue of *Current Biology* by Mitchell *et al.* [2] working with cats, and the