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Parasitism as a lifestyle: Ultimate intimacy between Apicomplexan protozoans and metazoan hosts

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Given the many gaps to fill for reaching the most relevant knowledge on parasitism as a lifestyle, the contributions of this BOC issue focus on datasets highlighting the sustained reciprocal cross-talks between single-celled eukaryotic parasites and their hosts, which account for the completion of the microbe developmental program. We have chosen to emphasize on a few members of the otherwise huge phylum of unicellular obligate parasites known as Apicomplexa. The 6000 or so species already named reveal just the tip of the enormous iceberg since they could cover about only 0.1% of the estimated diversity across Apicomplexa. Despite this limitation, Apicomplexa parasites have already been found in most aquatic and terrestrial ecosystems, hence they are seen amongst the most successful group of living eukaryotic microorganisms perpetuating on earth.

At the base of Apicomplexan phylogenies are the gregarines, which establish mostly in a wide range of freshwater, marine, and terrestrial invertebrates and, in view of their huge diversity, undoubtedly represent major assets to untangle the evolutionary transition from free-living ancestors to cells with ectotherm metazoan hosts-dependent lifestyle. Therefore, this thematic BOC issue starts with the strong advocacy by Boisard and Florent for integrating system biology and multi-omics exploration of gregarines as promises to illuminate the repertoire of adaptive capacities shaped by Apicomplexans to secure perpetuation within ectotherm and endotherm metazoan hosts over co-evolutionary processes.

Once gregarine put on stage, a following theme of this issue concerns the remarkable journey that allows the cosmopolitan *Toxoplasma gondii* upon colonization of the vascularized *lamina propria* of the small intestine to reaching through the blood vascular beds distant tissues, the most studied being the striated muscles, the brain and the retina. As free motile cells or embarked on migratory mononuclear myeloid cells, the protozoans eventually access long-lived cells and co-constructs dynamic intracellular niches in which is generated the *T. gondii* host to host transmissible population. A mini-focus for this emerging topic by Ólafsson and Barragan addresses how upon entry, *T. gondii* subverts integrin-related signalling pathways of human and murine mononuclear hosting phagocytes. In particular in immature dendritic cells, *T. gondii* alters cytoskeletal and migratory properties of the hosting cell that eventually impact on parasite dissemination throughout the hosts, hence on the extent of tissue damages that shape disease hallmarks.

Aside from the striking shift induced by *Toxoplasma* on the motile behaviour of host leukocytes, in the BOC issue are also spotlighted the *Theileria* Apicomplexa members, in particular by emphasizing on the unique ability of some species to hijack the cell cycle machinery of various leucocytic cells in a range of wild and domestic ruminants including cattle. The mini-review from Tajeri and Langsley discusses the current understanding of how *Theileria* spp. transform leucocytes into proliferative and highly tissue-invasive cells thereby leading to a deadly process reminiscent of the malignant leukaemia. The authors focus on the about two handfuls of known parasite effectors that upon secretion appear ideally poised to rewire leucocyte regulatory pathways,

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Credit: B. Touquet, Team "Biomechanics of Host-Parasite Interactions" I. Tardieux

hence impacting on host cell gene expression by mimicking proto-oncogene or oncogene products.

As masters of subversion, Apicomplexans have sharpened their molecular weapons to exploit the hosting cell resources while avoiding their defence systems. Once intracellular, several Apicomplexan species timely play with distinct organelles of their hosting cells. Briefly, owing to a unique subcortical force-generating machinery and force-transmitting device, *T. gondii* actively enters into a non-fusogenic parasitophorous vacuole (PV) hence providing protection against the harmfulness of the endocytic pathway and paralyzing other constitutive and inducible potentially biocidal functions of host cells. However, once settled within the PV, the same *T. gondii* subverts major controllers of the vesicular trafficking process including the microtubule tracks and the Rab small GTPase protein family. In the mini-review by Coppens and Romano, not only we learn how *T. gondii* re-routes and intercepts cargos from multiple Rab vesicles to access essential nutrients from their hosting cells but also how other Apicomplexan such as *Theileria* and *Plasmodium* differentially modulate expression and function of host cell Rab-vesicles in light of their own parasitic intracellular lifestyle.

The perpetuation of Apicomplexa parasites relies on their capacity to unfold more or less numerous successive developmental processes. These differentiation events allow fine-tuned adjustment of the parasites to the fluctuating conditions encountered at the micro- to macro-metre scales, when the

latter colonize distinct hosting cells and tissues from distinct -ectotherm and endotherm- host organisms. Exemplary is the case of *Plasmodium* spp. which reproduce sexually only in the midgut of blood feeding hosts, namely the *Anopheles* spp. mosquitoes. Following gamete fusion and zygote formation in the *Anopheles* midgut lumen, *Plasmodium* ookinetes cross the midgut epithelium and initiate several developmental stages, which eventually reach the salivary glands prior to be deposited with the saliva content in the vascularized dermis of the endotherm metazoan hosts upon blood feeding. Finally, Hajkazemian et al. bring us to consider in an integrative evolutionary framework the challenges met by *Plasmodium* to make it through to the insect salivary gland niche, and reciprocally, the impact on the mosquito host fitness, a key determinant of *Anopheles* population dynamics in their various ecosystems.

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