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Editorial overview: Host-microbe interactions: Parasites

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This is the 11th issue of Current Opinion in Microbiology's collection of reviews on host–parasite interactions and I am honored to edit the new decade's first issue. After I was approached to take on this task, I went back and reread previous issues and was impressed not only by the impact and significance of those reviews but of their timeliness. These reviews also highlighted two important motivations that drive most of our research. First, parasites cause severe and life-threatening human diseases that exact significant health and economic tolls. New treatments against these infections are still needed since the current ones are limited by emerging drug resistance, poor efficacy, and intolerable side effects. In addition, the development of effective vaccines has remained elusive. Second, parasites have evolved unique strategies to successfully co-exist with their hosts. This includes modulation and evasion of immune responses as well as manipulation of host signaling, metabolism, and gene expression. While the study of how parasites co-opt their host cells is important for drug development studies, they also reveal novel biological mechanisms that spurs discovery in other eukaryotes. As an example, Trypanosomes dramatically modify mitochondrial transcripts by inserting and deleting uridines to create a final mRNA. This was the first mechanism of RNA editing, which is now considered a widespread eukaryotic mechanism to modify mRNAs.

The goal for this issue of Current Opinion in Microbiology: Host–Parasite Interactions was to continue this tradition of high quality reviews with a particular focus on intracellular parasites subversion and manipulation of host cellular functions to create a niche in which they can successfully complete their life cycles. Two main themes have emerge from these reviews. The first (Szumowski and Troemel, Duque and Descoutex, Hakimi and Bougdour, Tweten et al., Kaushansky and Kappe, and West and Blader) focus on how parasites co-opt and/or manipulate cellular functions and structures to successfully grow within their host cells. The second (Dantzler et al., and Ueno and Lodoen) centers on understanding how parasites disseminate to different tissues.

A majority of the reviews in this issue focus on apicomplexan parasites, a large number of which cause human diseases. *Plasmodium* spp is the most important member of this phylum since those species that infect humans are the causative agents of malaria. *Plasmodium* is transmitted as a sporozoite via mosquito bites and the injected sporozoites traffic to the liver. Once in the liver, sporozoites infect hepatocytes and develop into merozoites, which are then released and enter the blood stream to establish a blood stage infection. Liver stage development is therefore a complicated process during which the parasite must first exit the bloodstream, traffic through liver sinusoidal vessels, and then select a hepatocyte to infect.

Kaushansky and Kappe review recent developments findings for each step in this transformation with a particular focus on the interaction between the parasite and its host hepatocyte. This includes recent developments in sporozoite invasion of the hepatocyte as well as in defining how the parasite modifies the hepatocyte to facilitate its development towards becoming merozoites. They end their review by highlighting recent studies that use either primary human hepatocyte cell culture model or humanized liver murine models. These advances are significant since previous studies primarily used rodent malaria species for liver-stage studies; however, now research on *Plasmodium* species that infect human is possible because of these humanized models.

Like *Plasmodium*, *Toxoplasma gondii* is an apicomplexan that must modify its host cell by targeting a variety of processes including membrane trafficking, cytoskeletal architecture, and transcription. Although host cell transcription can be controlled by parasites activating extracellular receptors, recent work has revealed that *Toxoplasma* injects proteins from specialized secretory organelles directly into the host cell. Initial work suggested that proteins secreted from rhoptries were the only effectors that entered the host cell cytoplasm; however, recent findings reveal that dense granule proteins also traffic to the host cytoplasm. Hakimi and Bogdour discuss recent advances in these effector proteins and how modulation of host immune responses is an important way that these proteins may impact virulence.

To complete their life cycles, both *Toxoplasma* and *Plasmodium* must traverse through several types of membranes when it egresses from its host cells or when it spreads from one anatomical position to another. These traversals require the disruption and/or rupture of various types of membranes and a family of perforin-like proteins (PLPs) have emerged as the proteins that mediate membrane rupture. Wade and Tweten discuss the mechanisms that PLPs use in forming membrane pores and how the PLPs may contribute to parasite growth and survival.

Many parasites must develop into transmissible forms in humans and often do so in specific environmental niches. For example, *Toxoplasma* is acquired through digestion of either oocysts (released in feline fecal matter after sexual development within the cat intestine) or from tissue cysts that develop within the muscle of an infected host. In humans and other intermediate hosts, the parasite must disseminate from the gut to other tissues such as the brain where it develops back into tissue cysts. Ueno and Lodoen discuss recent advances in *Toxoplasma* dissemination including work from their own lab utilizing microfluidic devices that allows assessment of how shear stress contributes to dissemination. In addition, they compare and contrast *Toxoplasma* dissemination to other parasitic (*Plasmodium falciparum* and *Trypanosoma brucei* spp.) and fungal pathogens that also interact with and in some cases, penetrate into the brain vasculature.

During blood-stage growth, a portion of *Plasmodium* parasites differentiate into gametocytes, which is the form taken up by a mosquito during a blood meal, and that undergoes sexual replication and sporozoite development within the insect vector. Here, Dantzler et al. discuss the parasite and host factors that contribute to gametocytogenesis and review the evidence that the decision for a parasite's commitment to undergo gametocytogenesis is likely not random but rather is dictated by a combination of factors,

including host- and parasite-derived factors delivered within exosomes, activation of specific transcriptional networks, and metabolic factors. They discuss that the early stages of gametocytogenesis do not occur in the blood as previously thought, but rather occurs in the bone marrow after an infected red blood cell adheres to the vasculature within this compartment.

The complex life cycles that *Plasmodium*, *Toxoplasma*, and other parasites use to successfully infect a host and cause disease often entails hematogenous dissemination to a variety of tissues that have different metabolic environments. Oxygen levels within a tissue can vary dramatically based upon a variety of factors including proximity to the vasculature. Like almost all other types of cells, parasites must sense changes in oxygen availability and then respond by adapting their metabolism and other cellular activities. With coauthor Dr. West, we discuss the various strategies and proteins that different protozoans use to sense oxygen and how oxygen availability affects the growth and virulence of parasites.

Leishmania are a large group of kinetoplastid parasites that causes leishmaniasis, which represents a spectrum of diseases and kills ~30,000 people each year. In humans, the parasite primarily resides in macrophages and to successfully grow in such a hostile cell the parasite has developed numerous mechanisms to disarm its host cell's defenses. Duque and Descoteaux discuss these mechanisms and highlighting the function of the metalloprotease GP63 as a regulator of antigen presentation, cytokine production, and function of the nuclear pore complex. In addition, they discuss how the parasite modifies host cell metabolism to help generate its replicative niche within the macrophage.

The final review in this issue is on host interactions with Microsporidia, which are important human and agricultural pathogens. Microsporidia are a large group of eukaryotic pathogens whose relation to protozoans and fungi has been a source for some debate. In general, these pathogens have been studied less than the others reviewed herein primarily because of the difficulty in culturing them. Recent genome sequencing efforts and the development of new infection models have spurred much recent work. Szumowski and Troemel discuss how these efforts revealed that Microsporidia infection regulates a large number of transcriptional targets within a host, egress from their host cells by commandeering host endosomal trafficking, and alter host behavior.

These eight reviews represent some of the exciting advances that we are seeing in the study of host-parasite interactions. Collectively, they also highlight common themes that are either established or are emerging. As examples, host cell transcription, metabolism, and membrane trafficking are host cell processes that are commonly targeted needed for intracellular pathogens to create their replicative niches. Yet the diverse ways that each pathogen uses to regulate these processes and the different array of host proteins that are altered by each infection to effect these changes reflects the diversity of the biology of these parasites.

Biography

Ira Blader is an Associate Professor of Microbiology and Immunology at the University at Buffalo's School of Medicine and Biomedical Sciences. He obtained his Ph.D. in neuroscience/cell biology from the University at Alabama at Birmingham and then completed a postdoctoral fellowship at Stanford University where he started his work on interactions between *Toxoplasma gondii* and its host cell. In 2003, he established his laboratory at University of Oklahoma Health Sciences Center and in 2013 moved to the University at Buffalo. His laboratory's research interests include identifying host cell pathways critical for parasite growth, determining how *Toxoplasma* senses oxygen, and defining how the parasite impacts the structure and function of the central nervous system.