

nary radiation. As the pulsar observations of Weisberg *et al.* (1) demonstrate, even weak amplification can produce astounding effects. Comets provide another example. When a comet approaches the Sun, the rising rate of heating causes ice evaporation and the production of OH, whose population distribution is controlled by interaction with solar ultraviolet radiation. Because the heliocentric velocity of the comet varies during its motion around the Sun, the Doppler effect shifts different solar lines into and out of match with the OH transition frequencies. At some locations the net outcome is population inversion, at others the opposite. As a result, the detected OH lines can oscillate between emission and absorption as the comet moves around the Sun. Since 1973, these striking oscillations have been observed in many comets (4).

Weak amplification can even offer advantages. Weak OH maser emission at 1720 MHz is always accompanied by absorption at the 1612 MHz transition, and the sum of these conjugate features is zero. When such

cancellation is observed, the two detected features must originate from the same region, removing a critical uncertainty for sources at cosmological distances (distances of billions of light years). This approach has recently been used to place limits on the possible variation of fundamental constants, such as the electron-proton mass ratio, during the evolution of our universe (5).

As demonstrated by galaxy NGC 4258, maser radiation can provide unique information about small details in the structure of the emitting astronomical sources. Strong maser radiation is emitted during both the very early and very late stages of the life of a star, providing invaluable information on stellar evolution. For example, recent analysis of methanol maser observations established the existence of a circumstellar disk around a newly formed star (6). The disk structure is extremely smooth, providing a glimpse of the state of our own solar system before the planets condensed out of its protoplanetary disk.

To fully understand the structure of an astronomical source, one needs data at different regions of the electromagnetic spectrum. Thanks to masers, data at radio wavelengths are much more detailed than at any other wavelength. Facilities are under construction and in the planning stages to extend high-resolution astronomy from radio to infrared and even visible wavelengths. As these regions of the electromagnetic spectrum are combined with maser observations, we will gain valuable insight into the detailed structure and inner workings of a wide range of astronomical objects.

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GENETICS

Themes and Variations in Apicomplexan Parasite Biology

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The eukaryotic phylum Apicomplexa comprises more than 5000 species of parasitic protozoa (1), including the *Plasmodium* parasites responsible for malaria. *Toxoplasma gondii* is well known as a source of congenital neurological birth defects, while *Cryptosporidium* and *Cyclospora* (along with *Toxoplasma*) have emerged as opportunistic infections associated with immunosuppressive conditions (including AIDS), and as sources of human infection through contaminated food or water supplies. Many apicomplexan parasites are also of veterinary importance, including *Babesia*, *Eimeria*, *Neospora*, *Sarcocystis*, and *Theileria*. *Theileria parva* and *T. annulata* are cattle pathogens, responsible for East Coast fever and theileriosis. Acute lymphoproliferative disease or anemia can lead to death, imposing significant constraints on cattle farming in sub-Saharan Africa (2).

Theileria parasites are also of considerable biological interest, as the only eukaryotic pathogens known to transform lymphocytes (3). Parasite sporozoites invade lymphocytes, escape from the invasion vacuole,

interact with the host cell cytoskeleton (4), and alter cellular signaling pathways (5) through mechanisms that are incompletely understood. Further insight into their fascinating biology comes from two reports in this issue, by Gardner *et al.* on page 134 (6) and Pain *et al.* on page 131 (7), that describe effectively complete genome sequences for *T. parva* and *T. annulata*, respectively.

The availability of two *Theileria* genomes, along with numerous sequences for other apicomplexans (8–13), provides a rich trove of data for comparative analysis (see the Table) (14). Consistent with observations in other parasites, the *Theileria* genome is reduced in both metabolic complexity and size (~4000 genes, 8.4 Mb) relative to the genomes of other eukaryotes. Absent genes suggest metabolic deficiencies in the synthesis of purines, polyamines, fatty acids, and porphyrin, among other pathways (6). The parasites are able to carry out glycolysis, and probably the tricarboxylic acid cycle, although how these pathways are linked is unclear. Moderate levels of synteny are observed between *Theileria* and *Plasmodium* genomes (6).

Apicomplexan parasites pursue diverse life-history strategies, infecting virtually all animals, from mollusks to mammals (1). Some parasite life cycles are relatively sim-

ple, involving only a single host (see the figure), whereas others require sexual recombination in a vector species for transmission. Some parasites are specialists, restricted to particular species and tissues, whereas others are generalists. For example, *Plasmodium falciparum*, which causes the most lethal form of malaria, infects only great apes (including humans), and is transmitted only by anopheline mosquitoes. In contrast, *T. gondii* can infect almost any tissue of warm-blooded animals, causing disease in immunodeficient hosts (including AIDS patients and human and animal fetuses).

The complex life-cycle stages of apicomplexan parasite infection are characterized by persistent themes, with subtle variations. Extracellular “zoite” forms are usually motile, and include an “apical complex” that gives the phylum its name, including organelles associated with host cell attachment, invasion, and establishment of an intracellular “parasitophorous vacuole” (15). *Theileria* sporozoites and merozoites are unusual in being nonmotile, and appear to invade host cells passively, in an orientation-independent manner (4). Consistent with these observations, organelles usually found in the apical complex are modified: The distinctive cytoskeletal “conoid” (16) is absent; the micronemes (17), whose secretion is associated with cell adhesion, are altered or absent; and the apicoplast (18, 19), a secondary endosymbiotic organelle that may play a role in establishing the parasitophorous vacuole, shows reduced function. *Theileria* has retained the rhoptries, however; these secretory organelles (17) are also part of the apical complex, and are suspected to function in modifying the parasite’s intracellular

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COMPARATIVE BIOLOGY OF THE APICOMPLEXA

| Genus (genome size; no. available) | Transmission vector (definitive host) | Apical organelles* | | | | Intracellular compartment | Distinctive biology | Function of expanded gene families |
|--|--|--------------------|-----|----|-----|---------------------------|--|---|
| | | Co | Mn | Rh | Ap | | | |
| <i>Cryptosporidium</i> (9 Mb, two genomes) | None required | + | + | + | - | Feeder organelle | Extreme metabolic reduction, and nutrient salvage from host | Surface antigens (mucins) Transporters |
| <i>Toxoplasma</i> (65 Mb, one genome) | Cats (not required for asexual transmission) | + | + | + | + | Parasitophorous vacuole | Long-term persistence in brain and other tissues | Parasite surface antigens Nutrient salvage? |
| <i>Plasmodium</i> (23 Mb, six + genomes) | Mosquitoes | - | + | + | + | Parasitophorous vacuole | Modification of infected RBCs mediates cytoadherence/sequestration | RBC surface proteins Nutrient salvage? |
| <i>Theileria</i> (8 Mb, two genomes) | Ticks | - | (-) | + | (+) | Cytoplasm | Lymphocyte transformation | Parasite surface antigens Lymphocyte transformation? |

*Co, conoid; Mn, micronemes; Rh, rhoptries; Ap, apicoplast. Parentheses reflect the absence of micronemes in at least some zoite stages and reduced metabolic function of the apicoplast (6).

home for survival (20). In the case of *Theileria*, rhoptry secretion coincides with lysis of the invasion compartment, releasing parasites into the host cell cytoplasm (3, 4).

In addition to the insights that they provide into basic metabolic pathways, genome sequences also highlight phylogenetically restricted genes, which are often linked to distinctive aspects of organismal biology. Large families of surface antigens are commonly found in pathogen genomes, and are likely to play an important role in antigenic variation

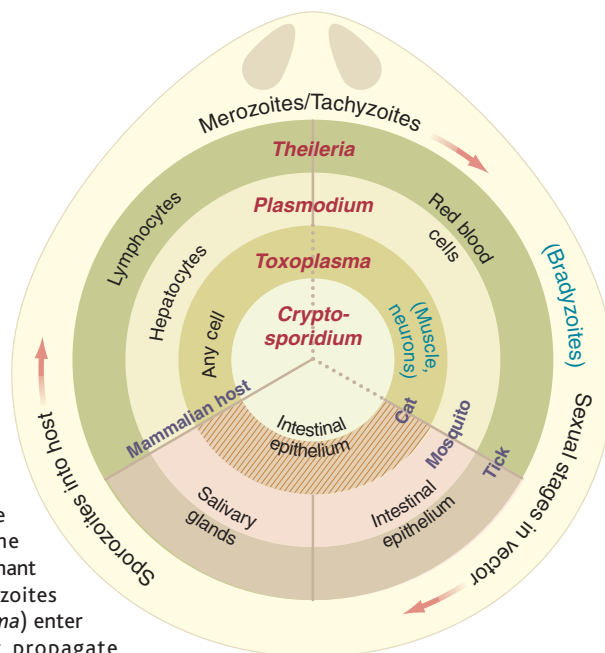
and immune evasion (12–14, 21, 22). *Plasmodium* genomes even encode proteins targeted into the infected red blood cell (23, 24). These include variable surface antigens that mediate cytoadherence and sequestration of *P. falciparum*-infected red blood cells within capillaries of the brain and placenta, leading to severe disease and death (22). Expanded numbers of transporters and extensive horizontal gene transfer in the *Cryptosporidium* genome (12–14, 25) may reflect the extreme need for nutrient salvage in

this parasite, and provide several attractive targets for this untreatable opportunistic pathogen that afflicts immunosuppressed individuals. Expanded families of secreted *Theileria* proteins may play a role in evading immune recognition or regulating host cell transformation, highlighting targets for drug or vaccine development (2). Several individual genes specific to the *Theileria* genome are also suggestive of roles in modulating the host cell cytoskeleton and the immune response (6, 7).

Overall, the range and depth of genomic-scale data sets available for multiple apicomplexan parasite species provide an extraordinarily rich resource for studying the evolution and function of eukaryotic cells, organelles, and host-pathogen interactions.

Parasite life cycles compared.

Concentric circles diagram the differentiation of various apicomplexan parasites, as they traverse multiple stages of their complex life cycle. Radial lines indicate distinct invasion events, in which parasites enter new host cells (broken lines correspond to invasion events that do not require entering a new tissue type). Sporozoites enter the mammalian cells indicated in the upper left sector. *Theileria* transforms lymphocytes to induce a life-threatening lymphoma; other sporozoites produce little pathogenesis, although the hepatocytic stages of some *Plasmodium* species may lie dormant for long periods of time. Merozoites (called tachyzoites in *Toxoplasma*) enter new cells, where they may propagate indefinitely (except for *Cryptosporidium*), causing significant anemia or tissue destruction. *Toxoplasma*-infected cells can also differentiate into latent bradyzoite tissue cysts, particularly in muscle and brain. The pink-shaded region at the bottom indicates sexual stages in ticks (*Theileria*), mosquitoes (*Plasmodium*), or cats (*Toxoplasma*), although *Toxoplasma* bradyzoites may also be transmitted without sexual recombination, via carnivory. *Cryptosporidium* requires no vector species for transmission. The outermost shape depicts a generic merozoite, with rhoptries of the apical complex at the top.



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