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Social Parasites

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Summary of recent advances

Protozoan parasites cause tremendous human suffering worldwide, but strategies for therapeutic intervention are limited. Recent studies illustrate that the paradigm of microbes as social organisms can be brought to bear on questions about parasite biology, transmission and pathogenesis. This review discusses recent work demonstrating adaptation of social behaviors by parasitic protozoa that cause African sleeping sickness and malaria. The recognition of social behavior and cell-cell communication as a ubiquitous property of bacteria has transformed our view of microbiology, but protozoan parasites have not generally been considered in this context. Works discussed illustrate the potential for concepts of sociomicrobiology to provide insight into parasite biology and should stimulate new approaches for thinking about parasites and parasite-host interactions.

Keywords

Cell-cell communication; social behavior; Trypanosoma; Plasmodium

Introduction

Social behaviors are most widely recognized in the communication and cooperation observed in metazoans, ranging from navigation strategies and group hierarchies in insect communities to complex social networking in humans and other primates. However, communication and cooperation among individuals in a group also occurs at the cellular level, as illustrated in collective motility of migrating cells during wound healing, tissue morphogenesis and tumor metastases. Moreover, cell-cell communication and cooperative behavior is not restricted to higher animals and recent years have seen a surge in the study and understanding of social interactions and their underlying mechanisms in microbial systems.

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Social interactions among microbes give rise to multicellular groups having emergent behaviors that are not possible in single cells [1-3] [4-8]. For example, quorum sensing enables synchronization of gene expression and cellular activities to allow a population to act as a group [1]. Surface-associated behaviors such as biofilm formation and swarming motility allow microbes to establish communities with enhanced protection against external agonists and promote colonization and penetration of biotic and abiotic surfaces [9-13]. Cell-cell signaling during sporulation in myxobacteria and slime molds directs group motility behaviors and developmental programs in which cellular differentiation gives rise to multicellular forms having distinct cell types with specialized functionalities, thereby enhancing survival through division of labor [14,15]. In extreme cases, multispecies biofilms and microbial mats constitute complex microbial ecosystems where numerous microbes communicate, cooperate and battle with each other [16]. Ultimately, the goal is to enhance survival and proliferation of the organism and when the microbe is a pathogen, this has dire consequences for the host [5,17,18].

In the bacterial world, cell-cell communication is the rule and considering social behavior as a ubiquitous property of bacteria has transformed our view and understanding of microbiology [1-3]. Social behaviors are also well-documented in eukaryotic microbes [19] [5,6,20]. However, despite the tremendous influence that the paradigm of "sociomicrobiology" has had on our understanding of microbiology, one group of microbes, the parasitic protozoa, seem to have been left without an invitation to the party. Studies of these organisms generally consider them as individual cells in suspension cultures or animal models of infection, while social interactions are largely unstudied.

Parasitic protozoa are etiologic agents of several major human maladies, including malaria, epidemic dysentery, Leishmaniasis and African sleeping sickness, that affect over half a billion people worldwide. Parasites also limit economic development in some of the poorest regions on the planet and are thus major contributors to the global human health and economic burden. Parasites have complex life cycles requiring transmission through multiple hosts, survival in diverse environments and a wide variety of cellular differentiation events. Hence, there are numerous facets of parasite biology that may benefit from, or may even depend upon, social interactions. In this review, we highlight recent work on social behavior in two well- studied parasites, *Trypanosoma brucei* that causes sleeping sickness and *Plasmodium* parasites that cause malaria. In addition to uncovering underappreciated aspects of parasite biology, these studies illustrate the potential for sociomicrobiology concepts to advance understanding of the biology, transmission and pathogenesis of parasitic protozoa.

Cell-cell signaling and cell density-dependent behavior

The protozoan parasite *Trypanosoma brucei* is the etiologic agent of African trypanosomiasis, which causes widespread mortality and morbidity of humans and livestock in sub-Saharan Africa. These parasites are transmitted to the bloodstream of a mammalian host through the bite of a tsetse fly vector. In the mammalian host, *T. brucei* must balance competing objectives of promoting parasite proliferation and limiting pathologic consequences to preserve the host as nutrient source (Figure 1). In addition, as a vector-borne pathogen, *T. brucei* must ready itself for survival in the tsetse vector and must maintain sufficient parasite density in the bloodstream to permit transmission during a tsetse blood meal [21,22]. Parasitemia is controlled in part via host immune defenses, but *T. brucei* is an expert at evading these defenses and thus benefits from differentiation of proliferating "slender" form parasites into growth-arrested "stumpy" forms [23-25]. Differentiation into non-dividing stumpy forms is irreversible in the bloodstream and premature commitment to this pathway would jeopardize maintenance of the infection [23,26]. Control is provided via

a postulated quorum sensing-type system in which a soluble, parasite-derived “stumpy induction factor” (SIF) accumulates as parasite cell density increases and triggers parasite differentiation only after a sufficient parasitemia has been achieved [23,24]. The nature of SIF and the SIF signaling pathway are not known, but cyclic nucleotide signaling has been suggested to be involved [24,25]. Stumpy-form parasites are pre- adapted for survival in the tsetse midgut, while slender forms are not. Thus, SIF-dependent slender-to-stumpy differentiation limits maximum parasite density in the mammalian host and simultaneously modulates parasite preparation for survival in the next host, optimizing probability of transmission [22,23].

Recent work has provided insight into slender-to-stumpy differentiation and its contribution to *T. brucei* disease progression and transmission. Previously, studies were limited by subjective parameters for distinguishing slender from stumpy-form parasites. MacGregor and colleagues [21] used a stumpy-specific marker, PAD [27] to conduct a quantitative analysis of trypanosome population dynamics during chronic infection in mice. They demonstrated that stumpy forms dominate the parasite population throughout late stages of infection. The quantitative nature of the approach enabled mathematical modeling, which provided overwhelming support for a quorum sensing mechanism. Moreover, the authors were able to make specific predictions for the cell types that produce SIF and define kinetic parameters for its production, activity and turnover. These data will facilitate efforts to identify the SIF molecule(s). Because SIF is produced only by a subset of cell types in the population, the system has the capacity to make qualitative as well as quantitative assessments of population dynamics. Interestingly, the findings also have implications for immune evasion strategies employed by *T. brucei*, because stumpy forms do not undergo antigenic variation [28]. Overall, the results emphasize the importance of parasite-parasite communication as a critical element in disease progression and transmission.

Another fascinating example of parasite surveillance of its own population during infection comes from studies of sex ratio adjustment in the malaria parasite *Plasmodium chabaudi* [29]. Malaria affects an estimated 247 million people worldwide [30]. Malaria parasites are transmitted through the bite of an *Anopheles* mosquito. In the transmission cycle, male and female gametocytes are produced in the mammalian bloodstream and taken up during a mosquito blood meal. Within the mosquito, gametocytes mature, then fuse and complete their life cycle in a series of steps that culminate in formation of infectious parasites in the mosquito salivary gland. The ratio of female to male gametocytes varies and is biased toward females. This sex ratio distribution contributes to parasite fitness and influences parasite evolution, but the factors controlling it are unknown. In multicellular animals, gamete sex ratio distribution is governed by rules of social evolution theory, which predict that sex ratios are dictated by population diversity [31,32]. In essence, at low population diversity, female gametes outnumber males and as population diversity increases, the ratio of females to males decreases. In an elegant series of experiments, Pollitt and colleagues tested this theory in mixed *Plasmodium* infections using different numbers of *Plasmodium* genotype variants [33]. They found that the parasites adjusted their sex ratio in response to the presence of unrelated genotypes in the parasite population. Their results indicate that not only can malaria parasites sense population density during an infection, but they can also sense diversity in the population and adjust their behavior in response. In addition to resolving a long-standing question about *Plasmodium* biology, the studies offered a test of one of the basic tenets of social evolutionary theory, thus emphasizing another aspect of the value in applying social biology concepts to parasite biology.

Life on a surface and social motility in *T. brucei*

Most microbes are associated with surfaces in their natural environments and engage in surface-induced social behaviors, such as biofilm formation and various forms of social motility [5,6,8,12,13]. These group activities facilitate surface colonization, defense and efficient use of nutrients [34] [11,13]. *T. brucei* is extracellular in both hosts and spends most of its lifecycle in direct contact with host tissue surfaces. Within the tsetse in particular, parasite movement across, and colonization of tissue surfaces are critical for development and transmission [35,36] [37]. Currently, *T. brucei* is studied almost exclusively in suspension cultures and little is known about how life on a surface influences parasite behavior.

With bacteria and fungi, cultivation on semisolid agarose matrices has proven valuable for studies of social behavior [12] [5,13]. Oberholzer, Lopez and colleagues thus employed semisolid agarose matrices to study surface behavior of procyclic-form (insect life cycle stage) *T. brucei* [38]. They discovered a novel group behavior, termed social motility, in which parasites assembled into multicellular communities with emergent properties that are not evident in single cells. Initially, parasites collect into small groups that move en masse across the agarose surface and grow larger through recruitment of other cells (Figure 2). At the periphery of the inoculation site, groups of parasites collect in nodes of high cell density and then advance outward, forming radial projections (Figure 3). The number and spacing of radial projections is generally consistent from one group to the next and patterns formed resemble those generated during surface colonization by swarming bacteria [12,13]. The events of *T. brucei* social motility occur in defined stages as summarized schematically in Figure 3A.

Several features of *T. brucei* social motility indicate cell-cell communication governs the behavior. First, coordination among individuals to enable group movement is striking, e.g. Figure 2 and movie M1, and in some cases, group movements occur only when other parasites are detected nearby, suggesting cell-cell communication within and between groups. Additionally, individual cells within each radial projection are highly motile (Movie M2) and can freely move out and back from lateral edges, yet the group advances only at its leading edge. This indicates that polarized migration of the group is governed by parasites ‘choosing’ to move in a specific direction and suggests that parasite-derived signals may govern spacing of adjacent projections. In support of this idea, radial projections continue to advance unless they encounter a separate group of parasites, in which case movement is halted or diverted to avoid contact (Figure 3B). Adjacent projections alter their course in parallel, indicating that signaling between groups controls group movement. The zone of avoidance is a direct function of parasite number, suggesting that a diffusible substance(s) is responsible, as has been reported for swarming motility in bacteria [39,40]. Overall, the work demonstrates the capacity of protozoan parasites to engage in group activities and reveals a level of complexity and cooperativity to trypanosome behavior that was not previously recognized. The findings also offer a convenient assay for studying environmental sensing in these organisms, which is an understudied problem.

Conflict, Competition and Cross-Kingdom Interactions

Wherever there is interaction among individuals, there is potential for conflict and competition. Bacteria engage in all manner of intercellular warfare and competition, ranging from growth inhibition and cytolysis of competing species, to bacterial cannibalism [1,4,8,39,41]. In an interesting case of sibling rivalry, neighboring colonies of *Paenibacillus dendritiformis* mutually inhibit each other’s growth through secreted signaling molecules while growth inhibition does not occur in a single colony [39]. The behavior bears strong

resemblance to the avoidance behavior observed in *T. brucei* social motility (Fig. 3), suggesting that procyclic form trypanosomes produce secreted factors that affect neighboring cells. Another instance of parasite-parasite competition has been reported for mixed *T. brucei* infections in mice [42] in which mutual competitive suppression was observed between co-infecting *T. brucei* strains of varying virulence. The authors report that mutual suppression of parasite growth in the host is correlated with extended host survival, suggesting that the less virulent strain reduces the pathogenic impact of the more virulent strain. The extent of mixed infections for *T. brucei* in the field is not known, but for some parasites, such as *Plasmodium*, the majority of natural infections are expected to involve multiple strains [43].

It is taken as de-facto knowledge that host-parasite interactions influence infection outcome. However, parasites are not the only microbes present in their hosts. The influence that the microbial flora of the mammalian host or insect vector exerts on parasite biology, transmission and pathogenesis is mostly unknown. For evolutionary ecologists, the influence of an organism's microbial flora on infection is well-known [44]. Recent work has demonstrated for both *T. brucei* and *Plasmodium*, that the presence or absence of specific bacterial symbionts in the insect vector is associated with refractoriness to parasite infection [45,46]. Thus, as is the case for bacterial pathogens [18], cross-kingdom social interactions exert significant influence on the biology of pathogenic protozoa.

Summary and Perspective

Protozoan parasites cause tremendous human suffering worldwide, but strategies for therapeutic intervention are limited. Recent studies illustrate that the paradigm of microbes as social organisms can be brought to bear on questions about parasite biology, transmission and pathogenesis. In addition to uncovering novel aspects of parasite biology, these studies suggest alternative strategies for therapeutic intervention may include targeting parasite-parasite communication. Experimentally tractable parasite systems also provide opportunities for empirically testing rules that govern social behavior.

Microbes derive a variety of benefits from social interactions and group behaviors (Figure 4). A focus of future efforts should be to determine which of these benefits apply in specific parasite systems. It will also be important to elucidate the underlying mechanisms. At a minimum, systems are required for production, perception and transduction of extracellular signals, whether diffusible or cell contact-mediated. Proteomic analyses of parasite surface proteins will facilitate efforts to define these systems [47] [48,49]. Exolipids are used as surfactants in bacterial surface motility [13] and parasites express abundant glycolipids and glycoproteins on their surface. Cyclic nucleotide signaling plays a major role in the regulation of social behaviors in other organisms [6,24,50] and has been implicated in *T. brucei* SIF signaling [24] and social motility (unpublished observation). Combined with other similarities discussed above, these observations indicate that mechanistic insights may come from comparing social behaviors in bacteria and parasitic protozoa.

Microbial social behavior was once considered to be a cottage industry of only a few species, but is now recognized to be ubiquitous among bacteria. Likewise, the few examples of social behavior in parasites discussed here may be just the tip of the iceberg and much more lies beneath the surface that is yet to be explored.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

Protozoan parasites cause tremendous human suffering worldwide, but strategies for therapeutic intervention are limited >Recent studies illustrate that the paradigm of microbes as social organisms can be brought to bear on questions about parasite biology, transmission and pathogenesis >This review discusses recent work demonstrating adaptation of social behaviors by parasitic protozoa that cause African sleeping sickness and malaria >The recognition of social behavior and cell-cell communication as a ubiquitous property of bacteria has transformed our view of microbiology, but protozoan parasites have not generally been considered in this context >Works discussed illustrate the potential for concepts of sociomicrobiology to provide insight into parasite biology and should stimulate new approaches for thinking about parasites and parasite-host interactions.

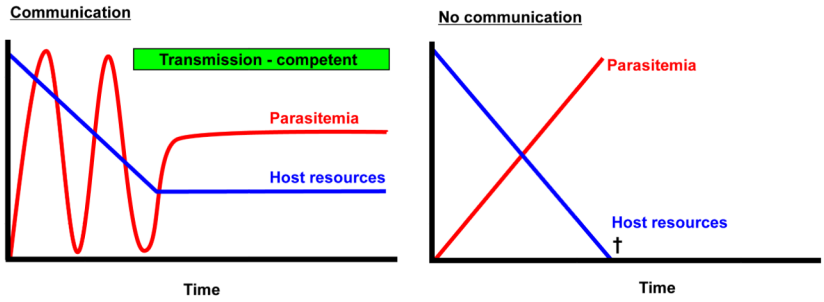

Figure 1. Cell-cell communication benefits *T. brucei*

Parasite-parasite communication (chart on left) via cell density-dependent signaling controls *T. brucei* differentiation from proliferating forms that are adapted for survival in the bloodstream to growth-arrested, transmission competent forms that are adapted for survival in the tsetse vector. By linking differentiation to population density, the parasite avoids depletion of host nutrients and prevents premature commitment to a developmental form that is not optimized for survival in the mammalian host. Without density-dependent cell-cell communication (chart on right), continued parasite proliferation would deplete host resources and thus reduce chances for transmission.

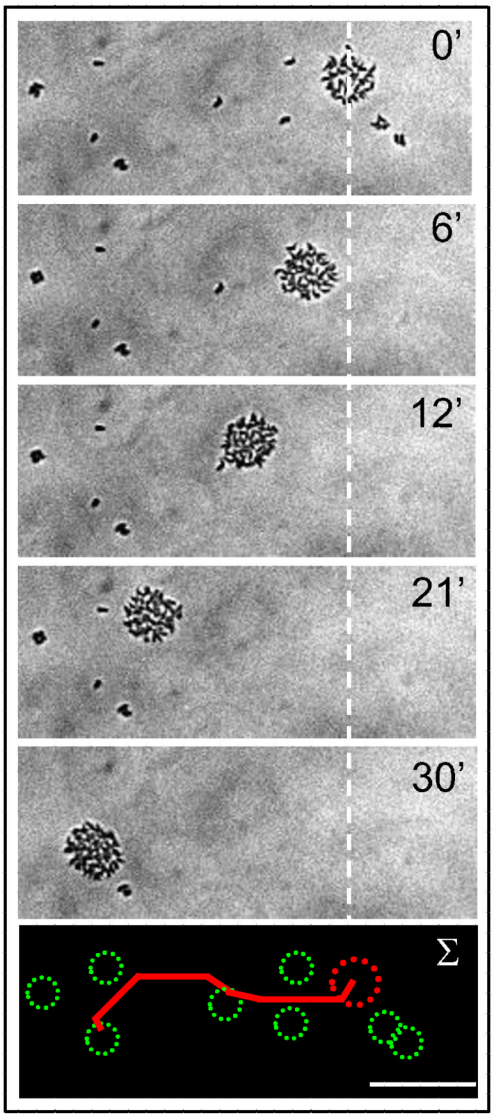

Figure 2. *T. brucei* cooperative motility on a surface

In response to surface exposure, *T. brucei* cells assemble into small groups that migrate en masse across the surface and enlarge through recruitment of other cells. Panels are time-lapse images (see movie M1) showing movement of a group of parasites (top right of top panel) across the surface of a semisolid agarose plate, with dashed white line indicating starting position of the group. Bottom panel shows summary. Elapsed time is indicated in minutes. Scale bar is 100 um.

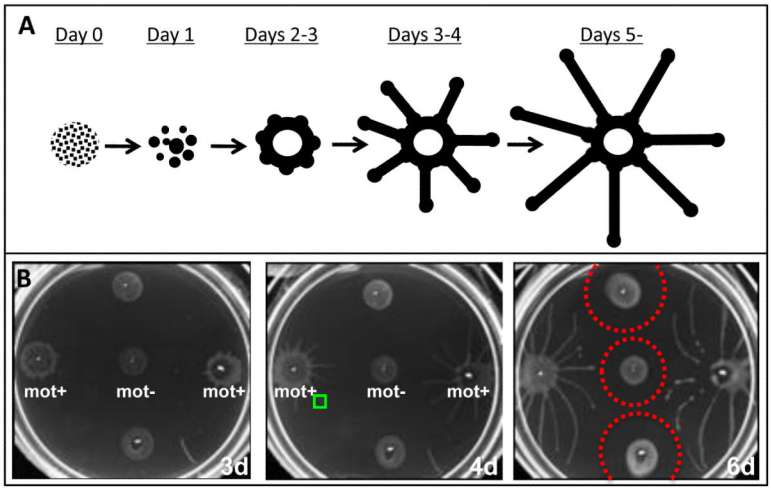

Figure 3. Social motility in *T. brucei*

When cultivated on semi-solid surfaces, *T. brucei* engages in complex social interactions that culminate in the formation of characteristic colony patterns. (A) Schematic diagram of the main steps of social motility in *T. brucei*, with parasites represented in black. Initially, individual parasites (Day 0) form small groups (Day 1). These groups move *en masse* across the surface and grow through recruitment of additional parasites. Groups assemble at the periphery of the inoculation site, concentrating in nodes (Days 2-3). From these nodes, parasites advance outward, forming radial projections (Days 3-5) that are regularly-spaced and advance at the leading edge only (Days 5+). (B) Suspension cultures of wild type (mot +) or motility mutant (mot −) parasites were inoculated on semisolid agarose and imaged at 3, 4 or 6 days (3d, 4d, 6d) post inoculation. Social motility requires active parasite motility, as motility mutants (mot-) fail to undergo social motility. Individual cells in each projection are highly motile (see movie M2, corresponding to a region represented by the green box in panel B4d). Projections can sense neighboring cells and halt or redirect their movements to avoid contact, resulting a zone of avoidance (dotted red circles in panel B6d). Adapted from [38] with permission.

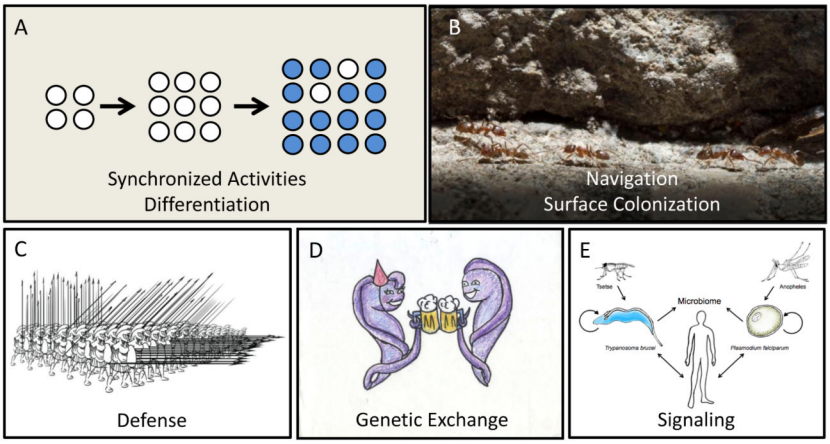

Figure 4. Benefits of social behavior

(A) Cell density signaling mechanisms enable synchronization of cellular activities thus preserving group level behaviors (blue circles) for when they are most advantageous. Additionally, not all individuals are equally receptive to the signals thus allowing for differentiation within a population (white among blue circles). (B) Cell-cell communication and cooperative motility facilitate colonization of tissue surfaces and navigation through specific host compartments. (C) Group defensive strategies protect against environmental agonists. (D) Social interactions facilitate genetic exchange. (E) While the current review has primarily considered social behavior in the context of parasite-parasite signaling, cell-cell communication also occurs between the parasite and vector, host, and host microbiome, all of which will impact parasite transmission and pathogenesis. Studying these interactions is also expected to provide insight into the signal transduction pathways utilized by parasites.