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## **Social motility in African trypanosomes: fact or model?**

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## **Abstract**

African trypanosomes grown on agarose plates exhibit behaviours akin to social motility. This phenomenon has not been observed *in vivo* so far but recently turned out to be instrumental in the definition of two specific stages of the parasite cycle and as a tool to probe for trypanosome sensing functions.

## Text

*Trypanosoma brucei* is an extracellular flagellated parasite responsible for sleeping sickness in humans and *nagana* in cattle in Africa. It is exclusively transmitted by the bite of tsetse flies where its complex development involves several strictly organized differentiation and migration steps in distinct organs [1]. Although trypanosomes are protists, they can exhibit community behaviours as reported in the mammalian bloodstream, where the proliferative slender cells can trigger their differentiation into the tsetse-adapted stumpy form upon production of a “stumpy induction factor” once they have reached a threshold density (review in [2]). The existence of collective or social behaviour could also be considered when trypanosomes develop in the insect vector where they are subjected to drastic micro-environmental changes along the digestive tract, marked by high variations in population density and by migration steps from one tissue to another (review in [1]).

Social motility (SoMo) is an energy-requiring process that allows colonies of bacteria to crawl over a solid surface in an organized manner. Social motility is implicated in a wide range of biological functions in biofilm-forming bacteria (e.g. *Pseudomonas*, *Vibrio*...), in fruiting-body forming bacteria (e.g. *Myxococcus*) or in eukaryotes such as *Dictyostelium*. Strikingly, comparable patterns of social motility were observed when the culture-adapted procyclic stage of *T. brucei* was allowed to develop on agarose plates [3]. There, individual trypanosomes gather into multicellular communities that grow larger through recruitment of other cells. At the periphery of the colony, parasites assemble in nodes of high cell density and from there they advance outward. Movement is polarized such that cells move outward but not laterally, leading to the formation of thin projections radiating away from the centre (Figure 1A). Importantly, these gliding movements require directional motility mediated by the flagellum [3]. When cells in radial projections encounter a separate group of parasites they halt or divert their movement so that contact is avoided, implicating cell-cell signalling in the control of trypanosome group behaviour [3]. This first report of SoMo *in vitro* provoked agitation in the community and raised the intriguing question: does SoMo really occur *in vivo*? If yes, where would SoMo take place and what would be its significance? If the answer is no, the existence of SoMo would nevertheless remain of high interest because it would imply trypanosome abilities for group behaviour, cell-to-cell interactions and responses to the environment.

The recent publication of Imhoff and co-workers could bring fuel to both hypotheses [5]. From the observations of *in vitro* differentiated parasites, they associated SoMo to a specific stage of parasite development in the tsetse fly. After a blood meal, trypanosomes colonise the posterior region of the fly midgut lumen and express two major surface glycoproteins called EP and GPEET procyclins. These parasites are designated as early procyclic. To establish a mature infection, trypanosomes cross the peritrophic matrix in order to colonise the ectoperitrophic space. At this stage, GPEET is down-regulated and EP becomes the major surface protein of the so-called late procyclic form. Imhof *et al.* demonstrated that social motility is a feature of the early procyclic form *in vitro* that is invariably absent in the late procyclic form (Figure 1B-C) [5]. These findings could suggest that SoMo happens specifically in the parasites present during the early phase of midgut infection. The authors postulate that ordered group movement on plates could reflect the migration of parasites from the midgut lumen into the ectoperitrophic space within the vector. The hypothesis is tempting knowing that motility is essential for trypanosome development in the insect vector [4]. However, SoMo remains to be proven *in vivo* and direct observation appears technically challenging due to the high parasite density in a compacted and complex environment whose accessibility for *in vivo* imaging is limited.

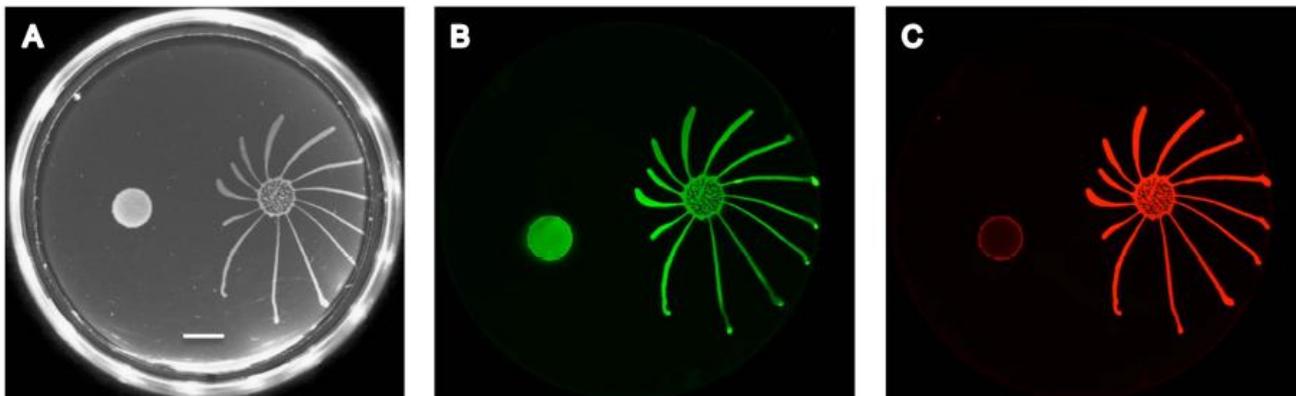
Although the study does not demonstrate the existence of SoMo *in vivo*, it contributed to a much better definition of the difference between early and late procyclic forms that were previously mostly defined by the presence of different procyclin proteins [6]. The different SoMo phenotypes prompted Imhof *et al.* to investigate the extent of differences using SILAC, revealing unexpected differences in protein expression profiles. For example, the calcium-binding proteins calflagins and the two hexokinases are significantly enriched in early procyclic cells grown in culture or isolated from tsetse flies, whereas two adenylate cyclases showed opposing patterns [5]. These data indicate that early and late procyclic forms have different biological properties and that they should be considered distinct stages of the life cycle [5].

Despite the fact that they are the major surface proteins, neither EP nor GPEET are essential for social motility [5, 7]. Similarly, two other unrelated null mutants for the MAP kinase kinase 1 [8] and the membrane-spanning phosphoprotein PSSA-2 [9], that are defective in infecting the salivary glands, were shown dispensable for SoMo [5]. However, none of these proteins is required for colonisation of the fly midgut, leaving open the possibility that SoMo somehow reflects the ability of parasites to initiate the early phase of the midgut infection.

Whatever the answer of its possible occurrence during the natural development of trypanosomes, SoMo represents an interesting model to efficiently probe for a combination of parameters such as proliferation, motility and sensing in the same assay. This is how Lopez *et al.* who were investigating sensing capabilities of trypanosomes recently demonstrated the contribution of specific flagellar receptor-type adenylate cyclases (ACs) to SoMo [10]. RNAi-mediated knockdown of AC6 did not lead to discernable effect on individual cells in liquid culture but instead caused an amazing phenotype on agarose plates where the number of projections from the same input material increased by 2-3 fold, what was coined a “hyper-social” phenotype. Remarkably, mutation of the AC6 catalytic domain phenocopied the knockdown phenotype, demonstrating that loss of AC activity was responsible for the phenotype. This contribution of AC could be correlated with the observed down-regulation of two other ACs in the early procyclic forms by Imhof *et al.* [5].

In conclusion, the existence of social motility *in vivo* remains to be demonstrated but the recent work by Imhof *et al.* points to a specific stage where to direct investigations. In the meantime, SoMo is turning out a promising tool for probing candidate molecules potentially involved in sensing.

**Figure 1.** Only GPEET-positive procyclic trypanosomes exhibit SoMo. Trypanosomes grown in medium with (“early procyclic”, right colony) or without (“late procyclic”, left colony) glycerol were inoculated on an agarose plate. (A) Photograph of the community 5 days post plating. Scale bar is 1cm. (B–C) A community lift incubated with anti-EP (green, B) and anti-GPEET (red, C) antibodies. SoMO is only observed in the population expressing GPEET. (Adapted from [5])



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Figure

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