Master 2 proposal

Exploring the interactions between the mucus, parasites and immune cells

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Duration: 5-6 months

Expected starting period: Jan 2025

Co-supervision and contact
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Context and aims
This is an interdisciplinary project at the interface between biology and physics of host-parasite interactions. The aim is to study the interactions between coccidia, a large group of multilayered-wall protected parasites (Dumètre et al., 2013), and mucus, a viscous and sticky fluid that covers the surface of several epithelia to protect them against external pathogens. The mucus forms the first physical barrier that is believed to prevent parasite infection. Yet, in some cases, parasites manage to infect the underlying epithelium. The cascade of events that leads to a successful infection remains largely unknown. The questions addressed in this project are:
(i) how do parasites interact with mucus? And what is the role of rheological properties of mucus in these interactions?
(ii) do immune cells patrolling close to the mucus barrier target parasites?
(iii) are interactions between the mucus, parasites and immune cells detrimental or beneficial to the parasites in the infection of the epithelium?
To answer these questions, we will 1) use *in vitro* models of mucosal epithelium challenged by oocysts of the model coccidia *Cryptosporidium* and *Eimeria*, which are non-pathogenic to humans, to study mucus-parasite interactions, and 2) introduce phagocytic cells, such as neutrophiles or macrophages, to study the complex interplay between mucus, parasites and immune cells in the context of parasite infection.

Proposed approach
We will use two type of model systems: (i) Artificial mucus, whose rheological properties can be tuned to mimic the mucus barrier in small intestine, which is a primary site of infection by many digestive coccidia *in vivo*. This system will allow to finely characterize and quantify the adhesion and fate of the parasites facing the mucus as a function of the parasite surface biochemistry, mechanics and adhesion, and of the mucus composition and rheology.
(ii) A bronchial mucosal epithelium, reconstituted *in vitro* at the air/liquid interface from human primary cells, in which the mucus is propelled via the continuous beating of active cilia exposed by the epithelial ciliated cells. This system will enable to study to what extend muco-ciliary clearance is efficient to fight against parasite infection or whether specific mucus flow patterns (e.g. vortices), previously observed in air/liquid interface cultures (Loiseau et al., 2020), lead to the trapping and a local increase of parasite concentration thus enhancing the probability of infection of the epithelium and/or contact with the patrolling immune cells (see below). This approach could help better understand how *Cryptosporidium* parasites infect airways.
In a second step, phagocytic cells (macrophages and neutrophiles) will be introduced into each of these systems to investigate whether these cells target and eliminate the parasites or serve as Trojan horses to allow the parasite infecting the epithelium as shown previously with the coccidian *T. gondii* (Freppel et al. 2016; Ndao et al., 2020).
We will combine cell biology techniques, video-microscopy, confocal microscopy and advanced image processing (based on machine learning) to image and quantify interactions and fate of the parasites in these systems.

Student profile

Physicist or biologist, with an interest in quantitative biology and biophysical experiments. Programming knowledge (Python) would be a plus. Curiosity, independence and tenacity are some of the "must have" for such an interdisciplinary project.

References

Dumètre A et al. Mechanics of the *Toxoplasma gondii* oocyst wall. Proc Natl Acad Sci U S A. 2013;110: 11535–11540. doi:10.1073/pnas.1308425110

Freppel W et al. Macrophages facilitate the excystation and differentiation of *Toxoplasma gondii* sporozoites into tachyzoites following oocyst internalisation. Sci Rep. 2016;6: 33654. doi:10.1038/srep33654

Loiseau E et al., Active mucus–cilia hydrodynamic coupling drives self-organization of human bronchial epithelium, Nat. Phys., 2020. https://doi.org/10.1038/s41567-020-0980-z

Ndao O et al. Dynamics of *Toxoplasma gondii* oocyst phagocytosis by macrophages. Front Cell Infect Microbiol. 2020;10: 207. doi:10.3389/fcimb.2020.00207