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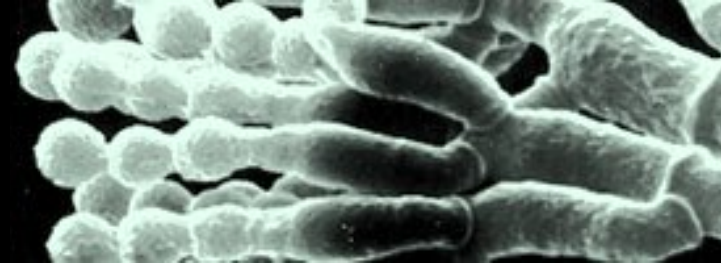

Hiding in plain sight: how parasites have evolved to outsmart their hosts

Hannah Bialic

Endoparasites are unicellular (such as protozoan or amoebozoan) or multi-cellular (such as helminthic) organisms that must reside within a host to gain nutrients, grow and survive. There are numerous parasites that can infect plants, invertebrates, and mammals – including us. Parasites have evolved for millennia alongside and within their human hosts. This co-evolution has greatly influenced how the human immune system has developed and it has also driven parasite evolution to develop methods of evasion. The parasites discussed in this article have also evolved to infect both an intermediate host and a definite host, which allows these parasites to separate their asexual reproduction from their sexual reproduction and increase their evolutionary fitness.

Many parasites have complex life cycles that require multiple hosts – such as the helminthic parasite *Schistosoma*. The schistosome (as shown in Figure 1, with detailed information on its development), requires a snail for part of its life cycle, where it matures until it exits the snail and swims in fresh water as a cercaria. At this life cycle stage, the parasite can penetrate human skin, travel through the circulatory system, and mature into its adult form. Once mature, the adult schistosome will pair with a mate, and begin to produce eggs, which are then passed out with the host's faeces.

Female *Schistosoma* can produce up to 300 eggs a day, which is 300 future cercariae. Schistosomiasis affects up to 200 million people a year in over 78 countries and is a disease of poverty, which means this disease, like many neglected tropical diseases, disproportionately affects low- and middle-income countries. Although this parasite is treatable with the drug praziquantel, emerging drug resistance and other multi-

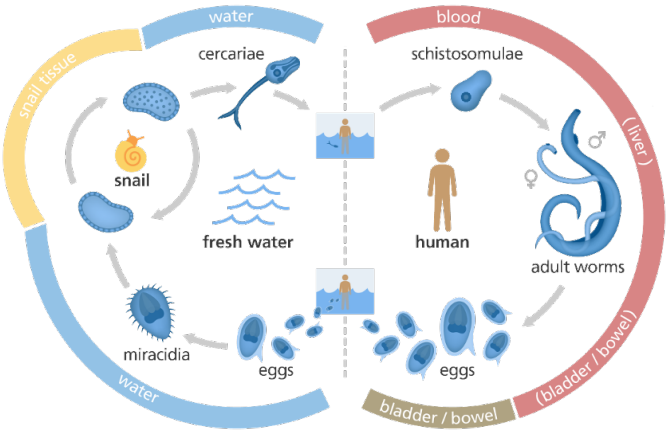

Figure 1. The *Schistosoma* life cycle diagram shows the multiple stages of development for the schistosome within its various environments. The snail is the intermediate host, which is the host that allows for growth and development into an infectious form via asexual reproduction. For this stage of the life cycle, schistosome eggs mature into miracidia before infecting their intermediate host, within which they mature into cercariae and re-enter the freshwater supply. The human host is the definitive host, which provides an environment for the parasitic worm to reproduce via sexual reproduction. During this stage in the life cycle the cercariae puncture the skin and travel through the circulatory system to the liver. This is where they mature into their adult sexual stage and pair up. They migrate to the bladder or the bowel to begin producing eggs which then – if defecated into the water – can begin the cycle anew.

Image credit: Genome Research Limited

It is not only the age, shape and motility of a parasite that changes during its life cycle. Parasites also change their molecular composition as they mature. They differentiate into new cell types, turn different genes on and off – termed a *gene-expression profile* – and produce different molecules that can help them survive and thrive within their host environment[1]. These molecular fluctuations are necessary for the parasite to survive the constant attack of the host immune system, in this case our immune system, which has evolved over the millennia alongside parasites and other pathogens to protect us from infection.

Our immune system consists of two components, innate and adaptive immunity. The innate immune system is non-specific and is responsible

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for protecting our body against general threats. It is comprised of physical barriers to infection such as skin, and nonspecific chemical and cellular barriers. The adaptive immune system is highly specific and is responsible for generating a protective response against pathogens such as bacteria, viruses, and parasites. Adaptive immunity is extremely complex and involves various mechanisms of communication – termed *signalling* – and cell types. If a pathogen enters the human body, bits of that pathogen – termed *antigen* – are picked up by immune cells to provide a blueprint for producing highly specific antibodies. Antibodies then bind the pathogen and act as a beacon for other immune cells to target and destroy it.

This complex system is reliant on efficient communication between the cells fighting infection, the lymph nodes – where antibodies are produced by B cells – and the rest of the body. This communication is accomplished through different small molecules that can either ramp up inflammation and immune cell attack or calm it back down – for when the infection is under control. This is a constant balance between immunostimulation and immuno-suppression. Parasites have evolved multiple ways to disrupt that balance and inhibit our immune response so that they can evade detection.

Some parasites, such as *Plasmodium*, the unicellular protozoan parasite which causes malaria, have evolved the ability to take refuge inside our cells. Malaria is a serious and potentially life-threatening tropical disease with enormous global health impact that is transmitted by the female anopheles mosquito. 250 million cases of malaria occur worldwide annually and it is one of the leading causes of child mortality. There is a worldwide effort by countless governments, funding agencies, researchers and policymakers to eliminate malaria. However, there is still a long road ahead to preventing or curing this destructive parasitic *Plasmodium*, once it enters its host through a mosquito bite, enters our red blood cells. Red blood cells are known as an immunological privileged site because they are not subjected to immune regulation. Red blood cells have one job – to deliver oxygen around the body. To ensure they can carry as much oxygen as possible, they have little room for anything else. They don't have a nucleus and they don't possess the molecular machinery necessary to alert the immune system when they are infected[2]. The *Plasmodium* parasite has evolved to exploit this. Once inside the red blood cell, *Plasmodium* can continue its life cycle, dividing until ready to burst out and continue to the next life cycle stage (as shown in Figure 2).

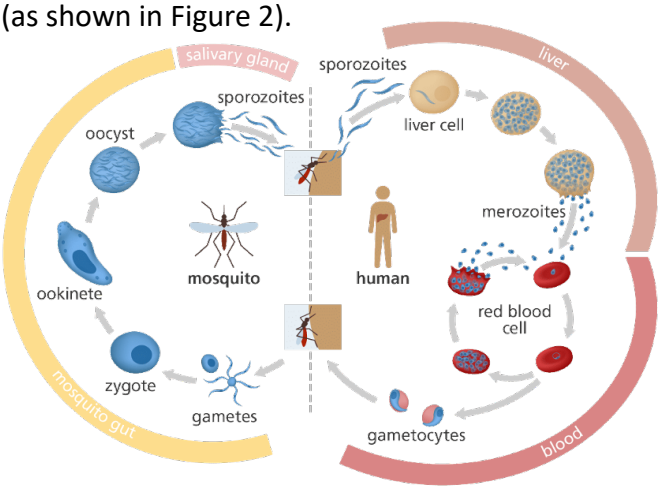

Figure 2. The *Plasmodium* life cycle diagram depicts the multiple stages of development for the *Plasmodium* parasite within its various host environments. In this example of parasitic infection, the human is the intermediate host. Sporozoites are deposited into the circulation system after a mosquito takes a blood meal. The parasite then travels to the liver. It infects and manipulates liver cells to allow for a rapid asexual reproduction cycle before the parasites exit the liver and return to the blood stream. Once in the circulation, some merozoites infect red blood cells where they reproduce until they burst out of these cells – causing fevers associated with the disease. Some of the merozoites are taken up by a new mosquito as it feeds which, as the definitive host, allows the Plasmodia to reproduce. First, the ingested merozoites mature into their adult sexual forms within the mosquito gut. Next, male and female parasites fuse to form an ookinete, which then develops further into sporozoites. The sporozoites migrates to the mosquito salivary glands, ready to begin the cycle anew.

Image credit: https://www.yourgenome.org/facts/what-is-malaria

Leishmania is another parasite which also employs this Trojan Horse tactic. *Leishmania* is a unicellular protozoan parasite that is transmitted through the bite of an infected sandfly and causes

three forms of the disease Leishmaniasis in humans and other mammals – cutaneous, mucosal and visceral. If left untreated, visceral Leishmaniasis will result in death in over 90% of cases. Leishmaniasis affects over 12 million people worldwide and, as another disease of poverty, disproportionately affects low- and middle-income countries across South America, Africa and Asia. Once within its host, *Leishmania* is ingested – termed *phagocytosed* – by a macrophage, one of our innate immune cells. *Leishmania* parasites have evolved the ability to resist the antimicrobial factors that macrophages would normally initiate to chemically destroy what they have phagocytosed. This allows *Leishmania* to hide within our own immune system and continue to survive and multiply[3].

Parasites can also be masters of disguise, hiding from the immune system in plain sight. Some species of *Schistosoma* cloak themselves in a host's self-antigen to avoid recognition by the immune system[4]. Another parasite that has evolved the ability to mask its presence is the unicellular protozoan parasite *Trypanosoma*. This parasite is transmitted by the tsetse fly and causes the debilitating disease called Human African Trypanosomiasis or African Sleeping Sickness. Sleeping sickness occurs in two stages and unfortunately it is regularly mis-diagnosed as malaria – due to a similarity in symptoms – during the first stage of the disease. The second stage of the disease regularly results in death, either from the infection itself or the toxicity of the drugs used for treatment, so early and correct diagnosis are key. Trypanosomes are coated in proteins called 'variant-specific glycoproteins'(VSGs) and although these proteins are highly immunogenic (i.e. they generate a large immune response), they are also extremely varied. The variation is so extreme that, once the immune system has generated a specific response to one coat of VSGs, Trypanosomes 'change coats' and slip past the immune system[5]. Due to the complex and dynamic nature of VSG gene recombination, the potential variations for this VSG coat are limitless[6].

Parasites and their hosts have evolved in parallel, with every new evasion tactic trying to circumvent our complex and adaptive immune system. There are laboratories around the world conducting research to better understand how parasites evade these immune responses, so that we can develop treatments that inhibit those tactics and allow our immune system to prevail.

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Hannah Bialic obtained her Bsc in Biochemistry from Northeastern University in Boston, Massachusetts (2017) and her Msc in Immunology and Inflammatory Disease from the University of Glasgow (2018). She has since worked in rheumatology, neuroimmunology, virology and parasitology. Currently she is the public engagement manager at the Wellcome Centre for Integrative Parasitology, in which she works with Human African Trypanosomiasis, Malaria, Leishmaniasis, Schistosomiasis and Toxoplasmosis. She will soon be returning to lab work in the fall of 2023 and pursuing a PhD in the field of pathobiology soon after.