Parasite-host interactions

Dr Nishith Gupta is working towards understanding intracellular parasitism and developing therapeutic strategies for the inhibition of parasites. Here, he discusses the field, his daily challenges, the importance of technology and collaboration, and of an interdisciplinary approach

Why parasite-host interactions?

Intracellular parasites reprogramme their host cells to create a safe haven for their survival. Conversely, triggers from the host cell can influence these pathogens to replicate, die, differentiate, or undergo dormancy and sexual reproduction. A successful parasitism requires efficient access and allocation of host resources. We would like to know how different parasites manipulate their host cells to eventually win the Armageddon.

What are the primary objectives of your research?

Most protozoan parasites have adapted to highly convertible life styles, which often comprise development in more than one type of host or tissue, switching between fast-replicating (acute) and quiescent (dormant) modes, and asexual-sexual conversion. We endeavour to delineate the impact of host-parasite metabolism on parasite growth and differentiation. In a nutshell, our studies explore the metabolic basis of parasitism, host cell tropism and stage switching. We have selected three complementary parasite models based on solicited questions, experimental feasibility and their comparative value. *Toxoplasma* and *Plasmodium* species have proven useful to examine the pathogen-host interactions occurring during the asexual phase. *Eimeria falciformis*, a monoxenous parasite with a short life cycle in the mouse (an established research model), has been pivotal in identifying host determinants of the parasite's sexual development and to study *in vivo* parasite-host interactions.

Could you elaborate on the basic research being carried out in this area?

One key process is the transaction of host- and parasite-derived metabolites across biological membranes and macromolecular biogenesis within the parasite. To reproduce, a parasite must generate a significant amount of biomass (proteins, nucleotides and lipids) and energy. Moreover, when a parasite switches between the proliferating and quiescent modes, it must rewire metabolism to accommodate cell division or dormancy. Equally, metabolic cues can influence the gene expression and stage switch. Our work strives to appreciate the evolutionary framework and regulation of carbon metabolism, and its impact on the parasite growth, pathogenesis and nutritional adaptations in discrete host niches.

What are the advantages of studying mutual interactions in addition to just the parasite and host cell individually?

Because the parasites we study are not able to survive without their host cells, it is important to address both partners to understand the underlying concepts of intracellular parasitism and to develop drugs. Studying the pathogen, host and their interactions provides a prevailing insight into their coevolution, and identifies drug targets at different cellular levels. I have also been amazed to discern quite a few analogies between our laboratory studies on the parasite-host relationships, and the binary interactions we face in our daily life.

How does technology help advance your investigations?

Our work uses a combination of classical and state-of-the-art methods on three singular parasites to study both facets of pathogen-host interactions in an integrated manner. More recently, we have begun exploring the metabolic basis and control of epigenetic modifications during parasite differentiation. This involves a combination of contemporary transcriptomics, metabolomics and epigenetics experiments along with more conventional methods of molecular genetics, biochemistry and cell biology. We have also been pioneering the use of optogenetic tools in infection research to modulate the parasite or host processes in a specific, dynamic and spatiotemporal fashion.

What are your daily activities and challenges?

Most of my activities are scientific, such as managing and mentoring the laboratory, experimental troubleshooting, writing and reviewing grants and publications, presenting our research, and teaching and training students. Infection research, particularly with the human pathogens and animal models, must overcome numerous ethical and practical issues. This includes obtaining appropriate work permissions, setting up the laboratories and techniques, recruiting the right workforce, ensuring their safety and finding suitable cooperation partners. This is what I admire about science though; taking up intellectual challenges and resolving them fruitfully. I see problems as precious opportunities to improve my workforce and myself. Every single day feels different and rewarding in terms of the work we do.

How important is an interdisciplinary, collaborative approach to your research?

Our interdisciplinary work has been a prerequisite to ask and answer appropriate questions while ensuring a competitive advantage. Of late, our wet-lab work has amalgamated with theoretical biology to systematically model conjoined cellular networks of the parasite and its host cell. We have benefited immensely from our diverse cooperation partners. I believe that a collaborative approach has become the lynchpin of modern science, research and technology. All our ongoing projects have one to two partner labs with a frequent exchange of ideas, resources, technologies and personnel.

DR NISHITH GUPTA

Exploiting the host

Ongoing research at the **Humboldt University**, Berlin, seeks to understand the processes by which intracellular parasites exploit their hosts, specifically looking at the metabolic interactions occurring during symbiosis

PARASITISM IS A non-mutual relationship between two different organisms where a parasite lives at the expense of its host instead of seeking out its own resources. Parasites may be facultative, whereby the organism is not obliged to act as a parasite – it can also satisfy its cellular needs by independent means. Obligate parasites, on the other hand, have no choice but to exploit their host to complete the processes critical to their life cycle. Particularly relevant and interesting parasites include intracellular pathogens, which co-opt individual host cells and utilise their cellular machinery to acquire the necessary resources.

Obligate intracellular parasites infect a wide range of hosts, including both wild and domesticated animals and also humans. Infection can either be asymptomatic or elicit trivial symptoms, and it is often the case that those infected are unaware of their newly acquired parasites – indeed, remaining undetected is a viable strategy for a parasite and underlies its evolutionary success. In many cases, however, parasites produce debilitating symptoms, which can lead to fatality. There is a sizeable yearly socioeconomic burden attributable to parasites. It is therefore imperative to build a complete understanding of how they survive and reproduce in order to develop treatments and to improve the lives of those affected by parasitic infections.

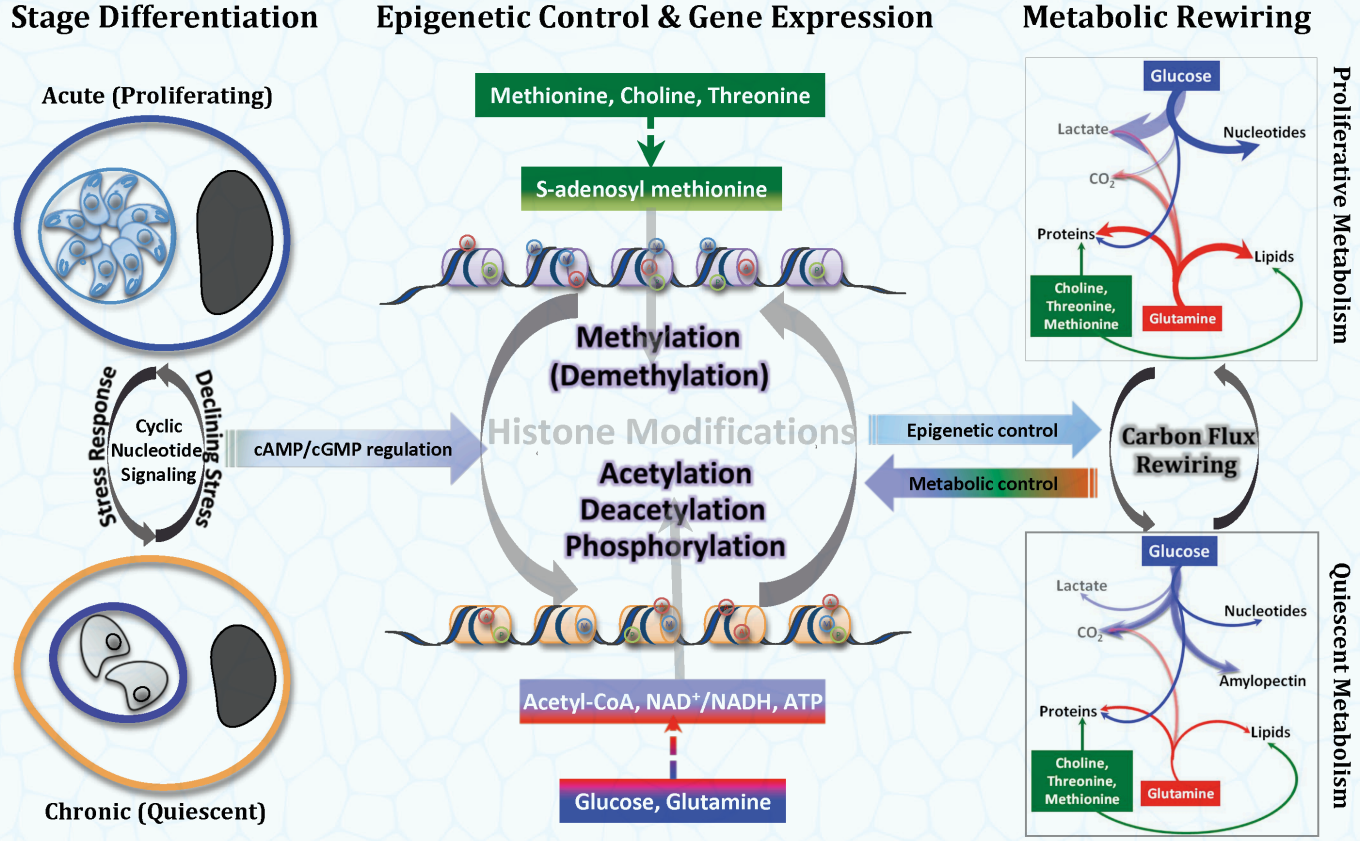
PARASITES OF INTEREST

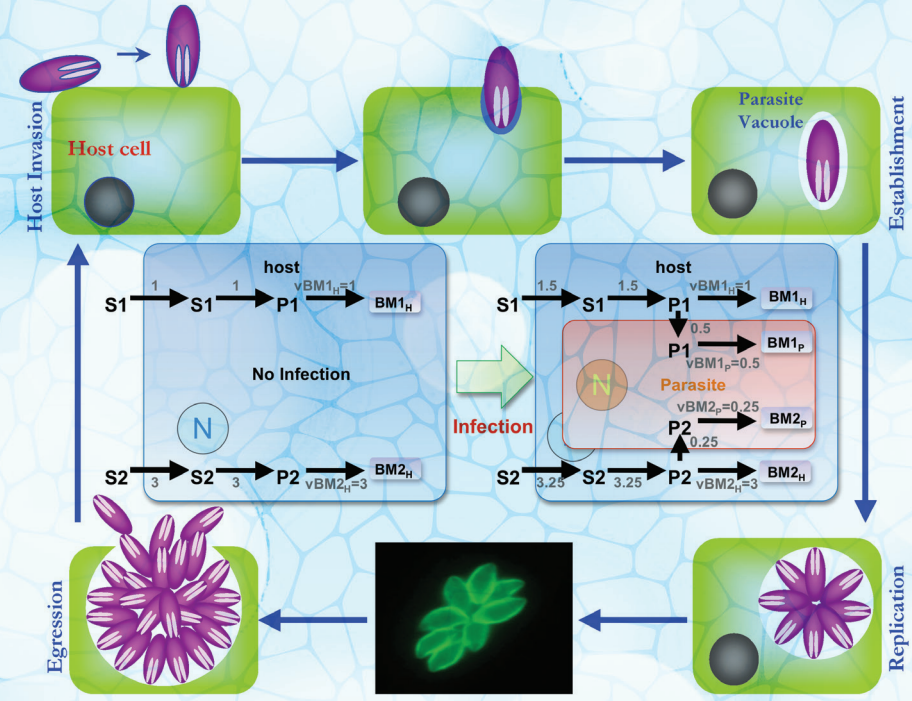
Dr Nishith Gupta of the Department of Molecular Parasitology at the Humboldt University, Berlin, works at the forefront of this field. He seeks to identify the interplay between pathogen and host metabolism to better understand intracellular parasitism. In particular, he studies three different parasite genera of the protozoan-apicomplexa phylum, *Toxoplasma, Plasmodium* and *Eimeria*.

Toxoplasma gondii is considered to be one of the most successful pathogens on Earth due to its infective diversity, and is found in nearly all warm-blooded vertebrates. About one-quarter of the world's population is seropositive to this parasite. The parasite infection is generally asymptomatic or produces mild flu-like symptoms, but in immuno-suppressed individuals, such as those affected by HIV/AIDS and ageing, or patients undergoing organ transplants, it can lead to cerebral and ocular toxoplasmosis and eventual death. It also causes spontaneous abortion during pregnancy, and cognitive defects in newborns. *Eimeria* species inflict gastrointestinal diarrhoea (coccidiosis) in a variety of animals including poultry. *Plasmodium* is the culprit parasite responsible for malaria, which kills about 1 million people annually.

WHAT CAN WE LEARN FROM METABOLISM?

Intracellular parasites rewire host metabolism for their reproduction. A successful parasite must be able to access the host cell's resources and allocate them towards its own cellular demands, which vary depending on the parasite's phase. This requires a crosstalk between the metabolic networks of both organisms. Through study of how they interact, and how parasites deal with changes in host cell metabolism, one can learn how to manipulate them and develop strategies to inhibit parasite growth. Gupta's work aims to understand the functioning of intertwined host-parasite networks in different parasitic infections. Moreover, his group is studying metabolic transformation and network interactions occurring when a parasite switches between its replicative and non-replicative stages.





BIOLOGY MEETS MATHEMATICS TO EXPLORE PARASITE-HOST INTERACTIONS

PARASITE EVOLUTION AND METABOLISM

Some parasites, such as *Toxoplasma* are highly promiscuous, meaning that they are able to infect a multitude of different vertebrate hosts and survive in virtually any nucleated cell. This contrasts with *Plasmodium* and *Eimeria* species, which are highly tissue- and cell-specific parasites. Through the course of evolution, these parasites have gained or lost metabolic pathways, optimising their life cycles with that of their host cell. For example, *Toxoplasma*, *Plasmodium* and *Eimeria* express about 400-700 metabolic enzymes. When compared to a typical mammalian host cell expressing about 1,400 enzymes, the data implies multiple metabolic dependencies of these parasites as well as their unique adaptation to parasitism. Gupta's research group strives to clarify the relationship between the parasites' metabolic capacities and their ability to infect different hosts. If appropriate metabolites are not available in a host, then the parasite will not be able to survive and reproduce in that particular environment. This could provide clues as to how the aforementioned parasites are adapted specifically to different hosts and tissues, and may suggest new drug targets.

INITIAL FINDINGS AND THE IMPACT

Significant progress has already been made in these research endeavours. Gupta and colleagues have identified and characterised quite a few metabolic enzymes required for parasite growth. In particular, the team has demonstrated that disrupted synthesis of certain membrane lipids arrests *Toxoplasma* reproduction and decreases parasite-induced lysis of host cells. These findings could therefore have important implications in designing novel therapeutics. His group has also developed a transgenic yeast (*Saccharomyces cerevisiae*) model for screening potential antimalarial drugs, and unearthed key metabolic strategies of apicomplexan parasites. Of particular note is the investigation and comparison of sugar metabolism in *Toxoplasma* and *Plasmodium*. The researchers have shown a divergence in their carbon usage, with *Toxoplasma* demonstrating an unprecedented level of nutrient flexibility, which perhaps underlies its comparatively much wider host range. Additionally, *Toxoplasma* has also been shown to have a greater plasticity in its membrane biogenesis that parallels to a free-living metazoan cell. Such a versatile and autonomous sugar and lipid metabolism might ensure the survival and growth of *Toxoplasma* in a variety of nutritional milieus encountered in different host cells.

These findings help us understand the intracellular parasitism and pathogenesis, and, if applied successfully, have the potential to improve clinical intervention

The research group's engagement with *Eimeria* has also identified several host factors regulating parasite development. The work shows how this parasite subverts a key immune and metabolic pathway of the mouse host to promote its own life cycle. Last but not least, similarities have also emerged between the metabolic functioning of replicating parasites and cancer cells. Thus, Gupta's research has the potential to bridge the fields of parasitology and tumour biology – the consequences of which have yet to be seen.

INTELLIGENCE

PARASITOLOGY

OBJECTIVES

- To investigate the metabolic interactions between the single-celled obligate intracellular parasites (namely *Toxoplasma*, *Eimeria* and *Plasmodium*) and their host cells
- To reveal the metabolic processes that underlie a successful reproduction and stage differentiation in these pathogens

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NISHITH GUPTA finished his MSc in Biotechnology at the Banaras Hindu University (India); PhD in Microbial Biochemistry from the University of Leipzig (Germany); and subsequent postdoctoral training in Molecular Parasitology from the National Jewish Medical and Research Centre (Denver, USA), and Humboldt University (Berlin, Germany). He currently works as a research group leader at the Humboldt University of Berlin.