Why are parasitic diseases a largely neglected area of research?

Parasitic diseases are typically endemic in low-income populations in developing and often very poor regions of the world. As a result, most governments of countries where these diseases are widespread are unable to offer financial support for the much-needed research, and the universities and research institutions lack proper infrastructure to conduct meaningful investigations into these diseases. Furthermore, large pharmaceutical companies are unwilling to fund studies in neglected diseases because if vaccines or new drugs are developed, the financial returns are unlikely to be as high as those from more affluent western countries.

What can be gained from understanding host-pathogen interactions?

A clear understanding of host and parasite factors that regulate disease outcome (susceptibility or resistance) could provide novel drug targets for therapeutic and immunotherapeutic purposes. In addition, it could aid vaccine designs and strategies to protect against infection and prevent disease.

According to your investigations, which parasite-derived factors enhance invasion, contribute to the takeover of the host immune defence system or otherwise alter the immune response?

In Leishmania infections, several parasite-derived molecules contribute to successful invasion, establishment and disease pathogenesis. We are particularly interested in two key molecules and the role they play in infection. First, we have spent a great deal of time working on phosphoglycans, which are glycoprophosphate conjugates (phosphate-containing sugar molecules) expressed on the surface of both the promastigote (insect) and amastigote (mammalian) life stages of the parasite. These molecules are major virulent factors that help the parasite to evade several host defence molecules, such as the complement proteins. In addition, these molecules also influence host dendritic cells and macrophages, which are key for initiating inflammation and immunity.

We are also interested in arginase, an enzyme produced by the parasite that is closely related to its mammalian homologue. This enzyme acts to deplete the availability of the amino acid arginine in the host, thereby limiting nitric oxide production, which is a key effector molecule for killing the parasites in infected cells.

What is the link between your research interests in sepsis and septic shock and your investigations into leishmaniasis and African trypanosomiasis?

Sepsis is a systemic inflammatory response caused by decreased tissue perfusion and oxygen delivery as a result of infection. If left unchecked, sepsis can progress to septic shock, which can lead to severe multi-organ dysfunction syndrome and death. Death is usually associated with excessive inflammation and unregulated release of proinflammatory cytokines leading to systemic inflammatory response syndrome (SIRS), akin to sepsis. Regulation of inflammation is an effective way of controlling death in mice infected with Trypanosoma congolense. Indeed, we recently showed that Berenil, one of the major drugs for treating trypanosomiasis, exerts its protective effects, in part, by dampening excessive inflammatory responses. Similarly, inflammation contributes immensely to the pathogenesis of leishmaniasis. Thus there is a common link between sepsis and these infectious diseases.

Could you elaborate on the methodologies you are employing to advance understanding of sepsis and septic shock?

We have successfully developed a laboratory model of lipopolysaccharide-induced acute inflammation leading to septic shock in mice. We have also developed an Escherichia coli-induced model of inflammation in mice. We are using both models to interrogate the role of regulatory T cells, a subset of T cells that act to restrain and/or suppress excessive immune activation, and phosphoinositide 3-kinase (PI3K), a key intracellular signalling enzyme, in ameliorating sepsis and acute inflammatory responses.

Are you involved in designing appropriate clinical interventions to prevent and treat sepsis and septic shock?

We are not; however, we are aware of ongoing studies aimed at expanding autologous human regulatory T cells in vitro, for in vivo infusion to treat autoimmune disorders. We envisage situations where this could also be done for the management of sepsis and septic shock in patients.
HUMAN LEISHMANIASIS ARE a complex spectrum of diseases with over 10 million cases and an estimated 350 million people at risk of becoming infected globally each year. The effects of the condition range from small self-healing ulcers and skin lesions to large disfiguring scars or even death, depending on the species of Leishmania involved. These single-celled protozoan parasites are spread by sandflies and can be found in South America, Africa, the Middle East, Asia and parts of Europe bordering the Mediterranean. There are three main types: cutaneous, mucocutaneous and visceral, in order of increasing severity and mortality, with visceral leishmaniasis often having a 100 per cent fatality rate within two years without treatment. Despite this significant health and societal burden, there is currently no effective vaccine against these diseases that is licensed for use in humans – all the existing treatments either cause major side effects or are only effective in specific circumstances.

Growing up and studying Veterinary Medicine in Nigeria, where parasitic diseases are common, Dr Jude Uzonna, from the University of Manitoba, Canada, is fully aware of this vast problem. He was driven to research by the social and economic impact of another, very similar, disease. African trypanosomiasis, also known as sleeping sickness, is characterised by a ‘zombie-like state’ and, as the name suggests, is prevalent in Africa, including his home country of Nigeria. Whilst this disease is much less widespread than leishmaniasis, inflicting around 500,000 people, it is fatal in humans if left untreated. Moreover, livestock infection and mortality causes annual losses of US $3.75 billion in sub-Saharan Africa. Uzonna saw an opportunity where he could apply his knowledge and skills to help combat African trypanosomiasis, its associated poverty and the closely associated but more problematic leishmaniasis: “I was convinced that concerted cutting-edge research could provide possible drug targets or vaccines to curtail or eradicate the harmful infections”.

Vaccinating for parasites

Research from the University of Manitoba, Canada, is using an array of proteomic and reverse immunology techniques alongside genetically modified model systems to elucidate the regulation of immunity in parasitic disease to ultimately develop effective vaccines.
Although recent control efforts have resulted in a decrease in the number of new cases of African trypanosomiasis, the incidence of leishmaniasis has increased steadily over the past 10 years. With its prevalence associated with environmental change, in the absence of effective vaccinations and treatments, this pattern is likely to continue.

CONCERTED EFFORT

Recent successes from Uzonna’s team have significantly advanced research in this field such that the realisation of a vaccination is now on the horizon. By investigating the interaction between Leishmania parasites and the immune system of their hosts, the researchers have uncovered the requirement for the persistence of live parasites to ensure sustained immunity. It is known that in mice, as in humans, when a primary major Leishmania infection is cleared, patients develop long-lasting immunity to reinfection. This is known as infection-induced immunity. It has been shown that infection-induced immunity is less effective if the host is completely cleared of live parasites. With this in mind, Uzonna realised that successful vaccination must in some way mimic live parasite persistence in the host.

To this end, the group is using a genetically modified parasite that was unable to produce phosphoglycans – key sugar molecules on the cell surface required for parasite virulence – for vaccine studies. In mice, these parasites persist without causing disease and induce protection against virulent challenge – a key advance on the road to effective immunisation in humans. These observations help to explain the previous failures in vaccine development that make use of non-living parasites – which are rapidly cleared from the body but fail to provide immunity following subsequent infection. These findings may also prove to be insightful for the increase in susceptibility of individuals who received this failed first generation vaccine.

IMMUNOLOGY

This potential inroad into vaccine development has led Uzonna’s group to further probe the nature of the immune response that leads to this protection. The researchers began by demonstrating that both effector and central memory T cells are required for optimal secondary immunity and also identified a key enzyme in their regulation, phosphoinositide 3-kinase (PI3K); all of which furthers scientific understanding of the pathological mechanisms of leishmaniasis.

The function of regulatory T cells (Tregs) is an area of study which has brought the team members some of their greatest success. Their work went against the current accepted notion about anti-Leishmania immunity; that any observed hyper-resistance was due to a strong T cell and inflammatory response. However, Uzonna’s group found that lower levels of PI3K led to hyper-resistance, not accompanied by the expected strong T cell response. “We showed that the PI3K regulates the expansion and function of Tregs and that in their absence, a strong T cell response is not necessary. In fact, our studies suggest that the strong T cell response may be pathologic and is only necessary to overcome the activity of Tregs that act to dampen immunity,” Uzonna elaborates.

Using various reverse immunology and proteomic studies, the researchers have also identified a number of peptides and antigens applicable for vaccinations. These highly immunogenic and protective antigens were shown to produce striking protection in vaccinated mice and, with the help of collaborators, the team has demonstrated this strong response in infected and recovered human patients. These immunological and proteomic techniques subsequently led to the development of the first Leishmania-specific tetramers capable of identifying Leishmania-specific T cells, at the clonal level, over an entire course of infection. This reagent will be critically relevant in the study of memory responses in Leishmania infection.

CHALLENGES FOR THE FUTURE

Despite these innovative findings, progress is much slower than it could be. If discoveries like these were being made for diseases endemic in wealthier countries there would likely be a prompt uptake of research in the area and treatments would begin the clinical trial procedure much more rapidly. However, the lack of funding to develop vaccinations for these diseases, which are preventing the improvement of socioeconomic conditions in less economically developed countries, has not deterred Uzonna, who values the importance of vaccinations.

Certainly, the Manitoba team is well on its way towards developing cost effective vaccinations and treatments for these parasitic diseases, but there is still much left to do. The investigators are using multiple international collaborations to validate their findings in human patients and using multiple methodologies and interdisciplinary expertise to get to the heart of these complex problems. Even if these vaccinations – arising from their paradigm-challenging findings – turn out to be ineffective in human trials, their collaborations and determined research will surely lead to more clinical targets. It is therefore likely that these diseases will soon be effectively treatable in humans and livestock in countries of economic disadvantage.

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