The 'yin and yang' of malaria parasite development

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Dr. Tewari in insectory. Credit: The University of Nottingham

Scientists searching for new drug and vaccine targets to stop transmission of one of the world's deadliest diseases believe they are closer than ever to disrupting the life-cycle of this highly efficient parasite.

Dr Rita Tewari in the School of Life Sciences at The University of Nottingham has completed what she describes as a 'Herculean study' into the roles played by the 30 protein phosphatases and 72 kinases –

enzymes that act as the 'yin and yang' switches for proteins – as the malaria parasite develops in the body and then in the mosquito gut.

Research is published today, Wednesday July 9 2014, in the academic journal *Cell Host and Microbe*, describes the work that has just been completed into the role of protein phosphatases.

Dr Tewari said: "This latest study identifies how protein phosphatases regulate parasite development and differentiation. Our research provides a systematic functional analysis for all the 30 phosphatases in *Plasmodium berghei* – the parasite responsible for causing malaria in rodents. These enzymes work in tandem with the protein kinases identified by the same team in a complementary study carried out in 2010. If we can find out what proteins are essential for these parasites to develop and divide, maybe we can target those proteins and arrest them with drugs or vaccines."

Dr Tewari's new research was carried out in collaboration with the Medical Research Council's National Institute for Medical Research (MRC-NIMR) in London, together with colleagues at Oxford University, Imperial College, London and King Abdullah University of Science and Technology, Saudi Arabia.

Dr Tony Holder, Head of the MRC-NIMR Division of Parasitology, said: "Inhibitors of protein kinases are already used in treatments for other diseases and there is growing interest to develop phosphatase inhibitors as drugs. Identifying the key kinases and phosphatases in the parasite life cycle will define the targets for drug development to treat human malaria and prevent its transmission in communities by the mosquito."

Malaria sufferer becomes malaria researcher

Born and brought up in Dehli, Dr Tewari had malaria seven times as a child. It remains one of the most deadly scourges of the developing world – killing up to one million people and causing clinical disease in 300 to 500 million people every year. In humans the deadliest form of malaria is caused by the single cell parasite *Plasmodium falciparum*. Disrupting the lifecycle of the malaria parasite could save the lives of millions of people.

Dr Tewari now leads her own malaria research laboratory at The University of Nottingham with her own mosquito insectary.

Her laboratory has received well over £1.2m from the MRC, UK for its research into malaria parasite biology. It has taken her team, together with collaborators at Imperial College London, eight years to identify every one of the protein phosphatases and protein kinases responsible for malaria parasite development.

High tech research to go back to basics

Malaria parasite development and cues controlling it is still not fully understood. What Dr Tewari's team is trying to do is understand the basic developmental biology of these parasites.

Using a number of molecular cell biology and biochemical techniques, Dr Tewari and her team found that half the phosphatase genes (16) could not be 'knocked out' suggesting some of these genes could be future drug targets as their presence is critical to parasite growth.

Dr Tewari said: "Interestingly, out of the genes that could be knocked out (14), six were found to be crucial for sexual development and hence could be drug targets for parasite transmission to and from the mosquito. The research gathered here using the mouse malaria parasite can be directly related to the human malaria parasite, as many of the genes

share a very similar homology and symptoms of the diseases are very similar.

A molecular Taoism

Protein kinases and phosphatases are crucial for many stages of the malaria parasite lifecycle. They are two families of enzymes that play crucial roles in regulating many cell processes – the 'yin and yang' of cell development.

Dr David Guttery, first author on the manuscript and now at the University of Leicester, said: "Building on our previous research on the protein kinases, this study represents a complementary view of the protein phosphorylation mechanism and gives us tantalising clues to the major players in this pathway. It will be exciting to see in the future which proteins are targeted by the protein kinases and phosphatases, and whether they act upon each other too."

Understanding a complex parasite life-cycle

When the female mosquito bites and ingests infected blood, parasite gamete fertilisation takes place in the mosquito gut. The parasites then colonises the mosquito, multiply and migrate to the salivary glands, so that when the mosquito bites again they are injected into the human host. The parasite is then transported to the liver when it multiplies again and within 48 hours millions of parasites are released to invade into red blood cells, producing high fever and sickness and potentially overwhelming its host.

Dr Tewari said: "Resistance to anti-malarial drugs is increasing. As a result, the race to uncover new vaccines and more effective drugs to treat disease and block malaria transmission is becoming ever more

important."

Earlier this year, the journal *Nature Chemistry* published a landmark study involving Dr Tewari, which showed the potential of the enzyme N-myristoyltransferase as a possible therapeutic target.

Dr Tewari's group has also published high impact papers interpreting the functions of two unique protein phosphatases - PPKL and SHLP1 – which could help in the design of new drugs to treat malaria.

Research 'packs a powerful punch'

Dr Tewari's group is also focusing on the role of diverse proteins involved in parasite cell shape and polarity, which are important for motility and host cell invasion. It also studies proteins that play a crucial role in cell-cycle progression and division as the parasite multiplies. The aim is to identify the best drug or vaccine targets along the way.

David Brook, Professor of Human Genetics and Director of Research in the School of Life Sciences, said: "This is another example of the outstanding research being conducted by Rita and her group. It's another paper in a leading international journal from a growing list of such papers. Despite being a small research group, Rita's lab packs a powerful punch and they are really putting Nottingham on the world map for malaria research. "

Provided by University of Nottingham