Focus on biological signalling to defeat malaria

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Millions of people die each year of malaria – a disease transmitted by the Anopheles mosquito. There are major barriers in vaccine development as well as increased resistance to currently available therapies. New biological targets for drug and vaccine development are thus direly needed. Now the EU-funded project, MALSIG, completed in 2012, may have paved new routes for malaria control. The project worked to understand the regulatory pathways of the malaria parasite life cycle. Project coordinator Gordon Langsley, researcher in an INSERM unit called the Institute Cochin, in Paris, France talks to youris.com about how targeting kinases and their corresponding substrate proteins might be one way to develop new drugs to treat and prevent malaria.

Why did you aim to develop new routes for antimalarial drug development instead of approaches to overcome existing drug resistance?

We decided not to work on the molecular basis of existing antimalarial drug resistance, partly because that is quite well understood. Instead, our idea was to investigate new biological processes as therapeutic targets. But if we are going to propose that blocking regulatory pathways can be an anti-malarial strategy, then we have to understand how these pathways work.

Why are kinases a useful target in antimalarial drug

development?

Kinases are enzymes. They regulate different developmental steps in the malaria parasite life cycle. Since parasite kinases are significantly different from human kinases, the logic is that you can develop drugs that target the parasite kinases, but not the human kinases.

We also targeted kinases because there has been a lot of drug development in cancer with them. Some of these early cancer drug leads were not very efficacious against the human enzymes, but the idea is that they could work against the parasite enzymes.

Would inhibiting kinase pathways be a form of antimalarial treatment, prevention or both?

It can be both. If you inhibit a kinase that regulates the parasite invasion of liver cells, referred to as hepatocytes, that's prevention. Infection begins with the parasite proliferating in the liver. If you inhibit a kinase that blocks parasite entry into a red blood cell, that would be therapy. All of the symptoms in patients are associated with this next step of infection. If you blocked transmission of the parasite to mosquitoes, that would be what you call 'altruistic therapy'. This is because you are actually preventing the next person from getting infected.

What is the next step in developing antimalarial drugs based on kinase inhibition?

Many of the malaria parasite kinases have been characterised. But which proteins each kinase phosphorylates is still a big black box. Phosphorylation is the process that turns proteins on and off and therefore alters their function and activity. These regulatory pathways.

But if inhibiting the kinase is enough to stop the parasite, why do you need to know which proteins the kinase is phosphorylating?

There are a large number of proteins phosphorylated by one kinase. For example, we know Protein kinase A, or PKA, phosphorylates myosin A, a protein. We also know that myosin A is involved in parasite motility. But we don't know if myosin A is the crucial protein that regulates motility. So you could develop a drug that would inhibit PKA. But you might have a biological effect outside of those of myosin A.

Do you mean there might be unwanted drug side effects?

Yes. It is basically what the Food and Drug Administration or other regulatory bodies always ask: you have this drug that blocks this kinase, but are there any "off-target effects"?

What is the biggest obstacle that could prevent the development of such drugs to treat malaria?

At some point malaria research funding has to stop being 'conscience funding.' My hope for the future is that the funding bodies – the governments, the Wellcome Trust, the Gates Foundation – do not diminish their funding for malaria research. And if anything, they increase it.

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