Malaria: Targeting parasite and host cell kinomes

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The spread of drug resistance in *Plasmodium falciparum* renders the development of novel control tools an urgent task, especially with respect to as yet unexploited classes of targets to prevent cross-resistance. Based on (i) the success of protein kinase-selective inhibitors to treat various cancers and their prospects in other diseases [1], and (ii) the divergences between mammalian and *Plasmodium* protein kinases (PKs) [2], the kinome of the parasite has been proposed as an attractive target for novel antimalarials.

The *P. falciparum* kinome was characterised shortly after publication of the *P. falciparum* genome [3]. This revealed that although some *Plasmodium* PKs are clear orthologues of mammalian PKs, the vast majority are either "orphan" enzymes (i.e. they do not cluster within any of the established eukaryotic PK families) or "semi-orphan" (i.e. they belong to an established PK family but are sufficiently divergent as to prevent detection of orthology to specific mammalian PKs). Thus, most *Plasmodium* PKs are divergent from mammalian enzymes at the level of primary structure, suggesting that species-selective inhibition is achievable. Structural data published for two *P. falciparum* kinases [4, 5] confirm that the catalytic pockets of these divergent enzymes offer unique opportunities selective inhibition. Several laboratories have produced active recombinant *P. falciparum* kinases that can be used in inhibition assay, and species-selective inhibition has actually been obtained in a few instances, even in the case of enzymes that have orthologues in human cells [6]. Furthermore, high throughput screens have been performed, albeit so far with only a very small number of target PKs. Thus, Kato and co-workers [7] identified an inhibitor of the calcium-dependent protein kinase PfCDPK1 (which has no orthologue in mammalian cells) that was used as a tool to reveal a role for the kinase in invasion of the host erythrocyte by the parasite.

Reverse genetics (knock-out) approaches are used to assess the essentiality of kinases in both *P. falciparum* and the rodent malaria model *P. berghei*. This led to the identification of PKs as being required for asexual proliferation in erythrocytes, and therefore representing potential targets for curative antimalarials. In contrast, many *Plasmodium* PKs are dispensable for the asexual cycle, but have essential roles in infection of the mosquito vector, and thus represent targets for transmission-blocking intervention.

Recent data identified a role for host cell PKs in parasite survival. Prior to proliferation in erythrocytes, malaria parasites injected by the mosquito first undergo multiplication in hepatocytes. Prudencio and co-workers [8] performed a human kinome-directed siRNA screen on infected hepatocytes, and identified 5 host cell PKs that caused significant reductions in infection when silenced by RNAi. This appears not to be restricted to the hepatoytic stage of infection: intriguingly, recent pharmacological and biochemical data from our laboratory implicate host erythrocyte signaling pathways in parasite proliferation. This suggests that human as well parasite PKs might represent targets for antimalarials, which has important implications in terms of strategies for developing new tools for the control of malaria.

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