PHOSPHOSIGNALLING IN MALARIA PARASITES: OPPORTUNITIES FOR ANTIMALARIAL DRUG DISCOVERY

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Almost half the world population lives in countries where malaria, caused by Apicomplexa of the genus *Plasmodium*, is endemic, and several hundred million cases (leading to 1-3 million deaths) are reported yearly. The parasites have developed resistance against available chemotherapeutic agents, making the search for alternative drugs a priority. Apicomplexa are phylogenetically vastly distant from the Opisthokonta, the phylum including animals and fungi. This phylogenetic distance is reflected by important divergences in the properties of protein kinases (PKs), at the following levels : (i) ***individual enzymes***; in addition to enzymes that do not cluster within any of the established PK families, many parasite PKs which clearly belong to known families nevertheless display atypical characteristics, e.g. in putative regulatory sites. (ii) ***organisation of signalling pathways***. For example, malaria parasites are the only eukaryotes so far to have been described as lacking 3-component MAPK pathways. (iii) ***kinome***. For example, malaria parasites possess a complement of calcium-dependent protein kinases (CDPKs), a family found in plants and ciliates but not in mammalian cells, as well as a novel group of 20 members that appears to be strictly specific to Apicomplexan parasites. A broadly similar picture is emerging with respect to proterin phosphatases. The differences between phosphosignalling pathways of parasites and those of their hosts suggest that specific inhibition of the former can be achieved, a notion that has recently been compounded in the case of *Plasmodium* by structural data demonstrating exploitable divergences between host and parasite PKs. Strategies for anti-parasitic chemotherapeutic intervention based on phosphosignalling inhibition include **(i) *targeting PKs of the parasite*:** Many PKs from protozoan parasites display activity in *vitro* as recombinant enzymes, and can be used in medium/high throughput screening operations. (ii) ***targeting host cell signalling***: Many protozoan pathogens are obligate intracellular parasites, and in some instances an essential role for host cell signalling in the infection has been identified. (iii) t***argeting transmission by the arthropod vectors***. Most of the important protozoan parasites require transmission by arthropod vectors; in many instances, complex developmental transitions of the parasite's life cycle occur in the vector. Inhibiting this process would be useful in the context of disease control.

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