In this issue

Malaria research

This issue of *Current Science* brings out a special section on malaria to highlight research done in India. The special section has papers on drug resistance, the need for improved drug therapy, and on molecular biology of *Plasmodium* species. A commentary by V. P. Sharma and interviews with Sharma and V. S. Chauhan about the state of research on malaria in India also appear in this issue of the journal.

The two most common species of human malaria parasite in India are *Plasmodium falciparum* and *Plasmodium vivax*, where the former shows resistance to most commonly used antimalarial drugs. Prevalence of drug-resistant parasite varies from region to region in India. There is continuous drug pressure on the parasite leading to the selection of population with higher level of drug resistance. The judicial usage of drugs can control/ slow down the development of drug resistance in the parasite population. But this requires continuous surveillance. Molecular methods for surveillance should be employed by the malaria control programme at a larger scale to evolve the effective drug policy for each region. See **page 696**.

The review by Padmanaban *et al.* (**page 704**) highlights the need and efforts to contain malaria through improved drug therapy. The absence of a vaccine against malaria makes therapy heavily dependent on drugs. Since the parasite has developed resistance to front line antimalarials, artemisinin (ART) derivative-based combination therapy has become the main focus. In that context, studies with mice have shown that ART–curcumin combination has a unique mechanism of action against the parasite. Curcumin not only synergizes with ART to directly kill the parasite, but also acts as an immunomodulator to prevent parasite recrudescence. This has potential to be tested in human trial to prevent parasite recrudescence/relapse seen in infections with *P. falciparum* and *P. vivax*. In addition, the combination has potential to be tested against cerebral malaria, since curcumin has demonstrated anti-inflammatory potential. In addition to improving curcumin bioavailabilty, there are also efforts to identify new pharmacophores that would eventually be needed as a substitute for ART.

Regulation of gene expression is textbook knowledge in many organisms. However in the malaria parasite *P. falciparum*, these fundamental biological processes are still being studied. A highly AT-rich genome, the complex life cycle and the inability to culture all stages of the parasite in the lab have all contributed to this paucity of information. Nevertheless, recent progress, in the field has led to several new insights. The article by Aishwarya Narayan *et al.* (**page 712**) reviews the current knowledge on regulation of gene expression particularly transcription, post-transcriptional events such as splicing and translation. These are discussed in the context of potential strategies for therapeutic intervention.

DNA replication is one of the most fundamental biological processes. Studying this aspect of DNA metabolism in parasite like *P. falciparum* may give insight into its complex life cycle and its successful existence and exploitation of different environments. The review by Pallabi Mitra *et al.* (**page 725**) is an attempt to compile all the available information and observations pertaining to the DNA replication proteins in the intra-erythrocytic asexual cycle of *P. falciparum* and a comparative analysis of the same with respect to other well-studied eukaryotic model systems. Although DNA replication is a highly conserved process, several unique features in the parasite DNA replication proteins have been observed which may be helpful in understanding the parasite biology and pathogenesis.

Apicomplexan parasites have complex life cycles that have adapted to the host systems that they infect. For example, *Plasmodium* spp, responsible for causing malaria in humans, require two different hosts (human and mosquito) to complete their life cycles, have three different invasion states (sporozoites, merozoites and ookinete) and shuttle between two hosts with vastly different body temperatures (mosquito at ~25°C and malaria patients ~39°C). Considering the complexity of its life cycle, the around 23.3 Mb parasite genome that codes for ~5000 proteins appears rather small. How does the parasite manage such vast functional needs with so few molecular components? The answers probably lie in certain unique features of the parasite translation machinery and the parasite's ability to chemically modify the proteome with post-translational modifications (PTMs). In the article on **page 741**, Sharma and Jarori review the current status of our knowledge of this field and the emerging trends and challenges in understanding the translational machinery of the parasite and identifying the nature and regulation of PTMs in *Plasmodium*. Importantly, the article discusses the various lacunae in our understanding of these mechanisms and suggests approaches that might help in filling the gaps in our knowledge.

The malaria parasite has an intriguing plastid (apicoplast) with an algal origin whose presence is critical for parasite survival and growth. The product of the apicoplast-specific DOXP pathway isoprenoid biosynthesis has recently been identified as the sole essential metabolite required for parasite survival in the blood stages. The apicoplast harbours a reduced DNA genome and is the site of other biochemical pathways that have significant roles in different stages of the malaria infec-

tion cycle. Several of these are identified as potential sites for drug intervention. See **page 749**.

In living systems, cellular metabolism is orchestrated to take advantage of nutrient availability in its niche and to cater to specific growth requirements. Free living organisms, in general, have bypass mechanisms for a given pathway. In contrast parasitic organisms – having evolved in very specific environments of the host – utilize available nutrients and hence, have altered metabolic fluxes and pathways. *P. falciparum*, the causative agent of malaria, during its intra-erythrocytic stages is microaerophilic in nature with mitochondria not contributing significantly to adenosine triphosphate production. However, the parasite expresses the enzymes of the tricarboxylic acid (TCA) cycle and those of the electron transport chain indicating an alternate function for these pathways. In this context, fate of metabolites produced by diverse pathways that feed into the TCA cycle needs examination. The review article by Vijay Jayaraman *et al.* (**page 757**) puts in perspective novel features of glycolysis, the TCA cycle and other mitochondrial processes operating in the parasite. In most cells fumarate generated from the purine nucleotide cycle (PNC) anaplerotically feeds into the TCA cycle. In the absence of conventional mitochondrial pathways, the article discusses the possible fates of fumarate generated through an active PNC operating in the parasite.

Malaria parasites invade and multiply within erythrocytes during the blood stage of the parasite life cycle. A family of erythrocyte binding proteins (EBPs) plays a key role in mediating interactions with host receptors during invasion. The article by Chitnis (**page 767**) reviews our current understanding of the role of EBPs in host cell invasion. Biochemical, molecular, structural and genetic approaches have been used to understand the functional roles played by EBPs in erythrocyte invasion by *Plasmodium* merozoites. The article also reviews efforts to develop blood stage vaccines for *P. vivax* and *P. falciparum* malaria based on EBPs. Parasite proteins such as EBPs that mediate host cell invasion are localized in apical organelles of *Plasmodium* merozoites. Studies to understand the signalling mechanisms that trigger their release to the merozoite surface to enable receptor-engagement during invasion are also described. A clear understanding of such signalling mechanisms may provide novel drug targets to block invasion and protect against malaria.

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G. Madhavan
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