MALARIA

Differential parasite drive

Giel G. van Dooren and Geoffrey I. McFadden

Our knowledge of the inner workings of malaria parasites comes largely from lab-based studies. But parasites growing in humans may have greater metabolic flexibility than those growing in Petri dishes.

Malaria parasites kill more than a million people every year. These minuscule organisms, belonging to the genus *Plasmodium*, ensconce themselves inside our red blood cells. They eat our oxygen-carrying haemoglobin protein, and sup on the rich supply of glucose in our blood plasma. Hidden from our immune system within our own cells, they multiply exponentially, inducing anaemia, acidity of the blood, low blood sugar, fluid build-up in the lungs, seizures and blockage of brain capillaries — complications that can kill a person within ten days of being infected by a malaria-carrying mosquito. Until now, we believed that malaria parasites burned the glucose they stole from our plasma using a simple and relatively inefficient process known as glycolysis. After all, why would a parasite bother to extract maximum energy from glucose when abundant free glucose is at hand?

On page 1091 of this issue, however, Daily and colleagues[1] show that, in some infections, the parasites behave as if they are starving, cranking up genes involved in energy-harvesting pathways to wring out the maximum burn from the proceeds of their parasitism. Switching on these genes could enable parasites to engage the tricarboxylic acid (TCA) cycle, the cellular motor that burns the leftover fuel from glycolysis to allow energy production to shift into top gear (see Fig. 4 of the paper[1] on page 1093). Intriguingly, the different parasite behaviours might correlate with different disease profiles, potentially explaining why different patients experience radically different symptoms during severe malaria infections.

Without a straightforward, easily accessible animal model for the deadliest malaria species, *Plasmodium falciparum*, lab work on the disease has been a difficult proposition. In 1976, a seminal paper[2] described a method of growing *P. falciparum* in Petri dishes of glucose-rich human blood with reduced oxygen levels. This method, essentially unchanged, is used in all modern malaria labs; it underpins all quests for a cure, whether they involve drug screens, genetic studies, genome sequencing, immunology, biochemistry or cell biology. Post-genomic studies have painstakingly mapped the expression levels of every gene and the quantities of each encoded protein across the orderly 48-hour part of the life cycle that the parasite executes in red blood cells[3–5]. These studies reinforced the view that genes encoding the proteins required for glycolysis are abundantly

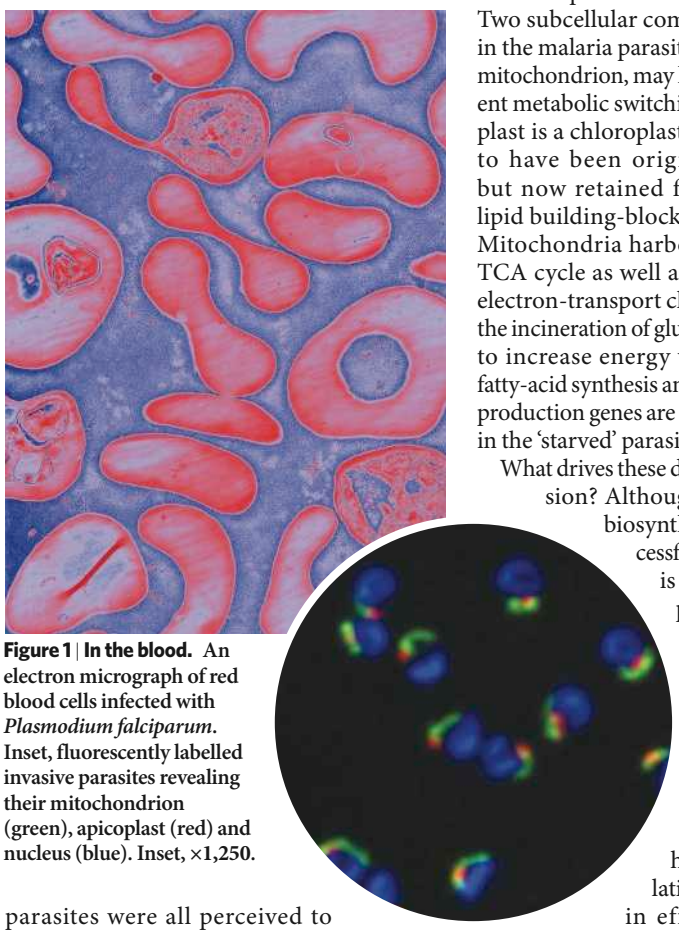

Figure 1 | In the blood. An electron micrograph of red blood cells infected with *Plasmodium falciparum*. Inset, fluorescently labelled invasive parasites revealing their mitochondrion (green), apicoplast (red) and nucleus (blue). Inset, ×1,250.

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parasites were all perceived to be marching to a rigid, yet energy-profligate rhythm, apparently oblivious to the world around them — us.

Studying pandas in a zoo is not the same as studying them in the wild. Likewise, these lab-based *in vitro* culture studies might not accurately reflect how the parasites behave in their natural environment. Hence the approach adopted by Daily *et al.*[1], who took blood from patients infected with *P. falciparum* in Senegal, and used microarray DNA chip technology to generate a parasite gene-expression profile for each patient. In many patients, parasite profiles were the same as those observed in lab-cultured parasites — the parasites seemed to be running on energy derived from glycolysis.

But parasites from two other groups of patients exhibited very different, and hitherto unseen, gene-expression profiles. In one group, the parasites had upregulated stress-response genes, probably to cope with host immune pressure. In the other group, they had switched on in lab-cultured parasites, but upregulated genes involved in alternative means of energy generation, a trait seen, for instance, in yeast cells starved of glucose. These results imply that there are physiological differences in the growth of parasite populations in different individuals. In other words, malaria parasites do not always grow in humans as they do in Petri dishes.

The changes in gene expression seen in 'starved' parasites are particularly curious. Two subcellular compartments (organelles) in the malaria parasite, the apicoplast and the mitochondrion, may hold the key to the apparent metabolic switching seen here. The apicoplast is a chloroplast-like organelle thought to have been originally photosynthetic but now retained for the biosynthesis of lipid building-blocks known as fatty acids[6]. Mitochondria harbour the enzymes of the TCA cycle as well as an energy-generating electron-transport chain that together finish the incineration of glucose and other substrates to increase energy yields. Both apicoplast fatty-acid synthesis and mitochondrial energy-production genes are dramatically upregulated in the 'starved' parasites[1].

What drives these differences in gene expression? Although apicoplast fatty-acid biosynthesis is essential for successful infection[7], its exact role is unclear because malaria parasites can scavenge fatty acids from their host. Upregulation of the apicoplast pathway for fatty-acid synthesis may suggest an increased need for fatty acids or a short supply of them from hosts. Similarly, upregulation of pathways involved in efficient mitochondrial energy generation implies either an increased need for energy or a reduced supply of glucose for glycolysis. A recent study[8] on laboratory-grown parasites concluded that mitochondria are not required for energy generation. But Daily and colleagues' discovery of the upregulation of genes involved in these mitochondrial energy-synthesizing pathways suggests that this may not always be the case.

The findings presented here raise various questions. What causes the different parasite gene-expression profiles? Do these profiles reflect distinct temporal stages of *in vivo* parasite development, or are they discrete snapshots of an intense battle between parasite and host? Are parasites initiating these differences, or are they merely reacting to cues from the host? Patient factors such as blood glucose levels, the amount of haemoglobin and the number of parasites in the blood do not seem to be linked to the starvation response. If there

One caveat in interpreting Daily and colleagues' results[1] is that gene upregulation doesn't always translate to metabolic upregulation; biochemical validation of actual metabolic switching is needed, and this will probably require elicitation of the starvation response in laboratory-grown parasites. At a more practical level, it will be important to understand whether different parasite gene-expression profiles are linked to the spectrum of disease experienced by patients with malaria, which, in turn, may point to more effective treatments. For example, drugs targeting fatty-acid biosynthesis and the mitochondrial electron-transport chain[8,9] should be especially effective against parasites in starvation mode.

We have come a long way in understanding malaria and its causes. But the findings presented by Daily *et al.*[1] show that we are just beginning to comprehend the complexity of the metabolic engine that drives these parasites. ■

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ASTRONOMY

Dim view of past clashes

Curtis Struck

Simulations indicate that faint galaxies of a seemingly tranquil class were born in violent cosmic encounters. This would be good news for the prevailing model of how the Universe is constructed.

Giant low-surface-brightness galaxies, or GLSBs, are gentle giants of the cosmos. Their gaseous disks are up to 100 kiloparsecs across, several times the size of our Milky Way, yet rates of star formation within them are very low[1]. This makes them difficult to spot: the prototypical GLSB, Malin 1, was found only in 1986, despite being, at that time, the largest spiral galaxy ever seen[2,3]. But GLSBs are not just troublesome to observe: their existence is also a challenge for the prevailing 'cold dark matter' (CDM) model of the Universe's composition. Writing in *Monthly Notices of the Royal Astronomical Society*, Mapelli *et al.*[4] now propose an origin for these perplexing galaxies that might circumvent that difficulty.

The CDM model predicts that structure in the Universe is built up hierarchically from smaller units, powered by the gravitational force of 'dark matter' that cannot be seen at any wavelength. With the addition of a cosmological constant or other driver of accelerating cosmic expansion, the CDM model can account for a wide range of cosmological observations[5]. The impressive resolution of recent CDM-based simulations of the formation of structure in the Universe, such as the Millennium Simulation[6], is testament to the model's success.

But some problems remain. One is that CDM simulations tend to produce galaxy disks that are more compact and have less net angular momentum than those of real galaxies. With sufficient numerical resolution, and adequate treatment of feedback effects, the models do produce normal disks in some environments[7], and future models will possibly do better. But the existence of the hugely extended GLSB disks is an extreme challenge to this optimism. Mapelli *et al.*[4] first review several suggestions for the formation mechanism of GLSBs beyond standard CDM processes, and find them wanting. But they provide a new and rather surprising possible solution to the dilemma: that GLSBs are in fact the descendants of another cosmic curiosity, ring galaxies.

In the classic theory, the characteristic bright circle of a ring galaxy is produced when a secondary companion galaxy passes through the centre of a primary disk of stars[8] (Fig. 1). The stars and gas clouds in the primary disk are drawn inwards by the passing galaxy's gravity, but rebound when the companion moves away and the gravitational pull is reduced. The timescale for these effects increases with radius, so when particles farther in are on the rebound, those farther out are still falling in. The result is a circular wave of compression that propagates outwards, triggering the formation of spectacular clusters of bright stars as it passes. As these clusters flare up and slowly fade away again, they form a bejewelled ring that moves slowly outwards over hundreds of millions of years.

Many aspects of this standard theory of ring galaxies have been confirmed by

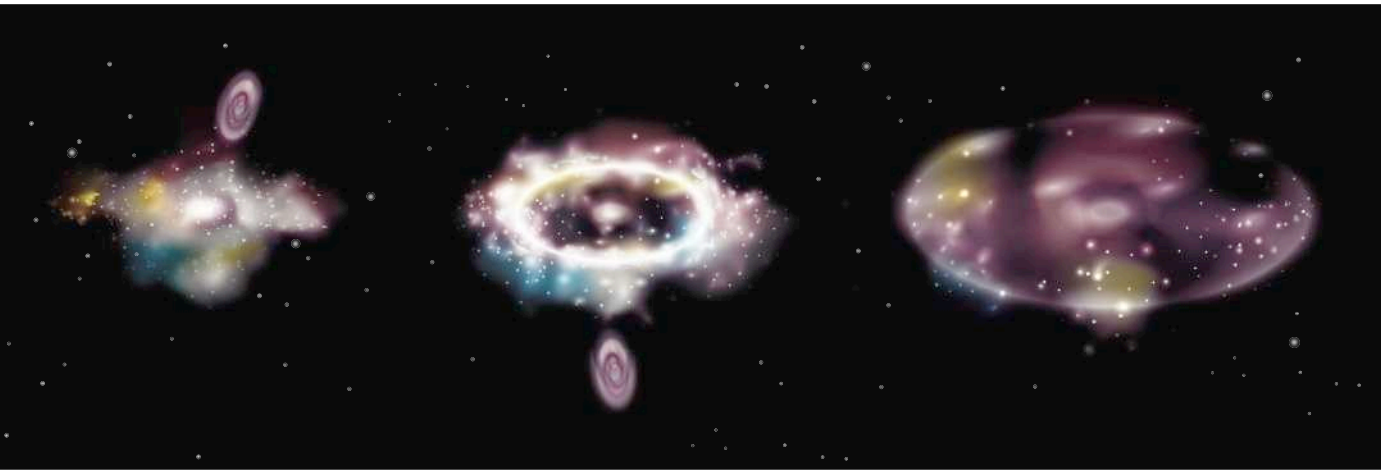

Figure 1 | The twilight of the ring. According to Mapelli and colleagues' simulations[4], the anomalous giant low-surface-brightness galaxies (GLSBs), whose formation is such a problem for the cold-dark-matter model of the Universe's structure, are the embers of cataclysmic galactic collisions.