reactivity, can be viewed as decoherence evolving over time. This could also be investigated using the authors' approach. Such experiments may address the role of electronic coherence between different potential-energy surfaces at points where such surfaces intersect (known as conical intersections).

Returning to our optical analogy, conical intersections can be thought of as beam splitters. In optics, when a single beam of light strikes a beam splitter, two beams that have a well-defined phase relationship are produced as output. Now imagine reversing the process, so that two rays are sent to a beam splitter. It takes precise control of the rays' relative phases and amplitudes to obtain a single beam as output — or a well-defined product of a chemical reaction in the molecular context. Similarly, one should expect that the amplitudes and phases of the electronic states that make up a hole's wave packet will affect how this wave packet passes through the conical intersection, and what will appear at the output of such a molecular beam splitter. With charge transfer playing a vital role in many biological and chemical systems, the ability of attosecond transient absorption spectroscopy[1] to characterize attosecond-scale preparation of electronic coherence and its subsequent evolution over tens of femtoseconds opens a route to discovering and characterizing new mechanisms of chemical reactivity. ■

Olga Smirnova is at the Max-Born-Institut für Nichtlineare Optik und Kurzzeitspektroskopie, D-12489 Berlin, Germany.
e-mail: olga.smirnova@mbi-berlin.de

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METABOLISM

Malaria parasite stands out

Hagai Ginsburg

One of the hallmarks of cellular biochemistry is the ability to extract energy efficiently from available substrates. The malaria parasite, however, deviates from the norm, and has come up with its own solution.

All living organisms require energy for growth, maintenance and reproduction. At the cellular level, chemical reactions transform energy from one type to another: the energy stored in chemical bonds is turned into ATP — the cell's energy currency — when certain complex molecules are broken down to simpler ones. One such molecule is glucose, which is broken down through a sequence of pathways that lead to the generation of ATP. In this issue (page 774), Olszewski *et al.*[1] show that the malaria-causing parasite *Plasmodium falciparum* does not follow the usual route to generate ATP.

After glucose has been taken up by a cell, it is broken down to two molecules of pyruvate through the cytoplasmic process of glycolysis (Fig. 1). In eukaryotes (organisms whose cells contain membrane-bounded organelles), pyruvate then moves into the mitochondria — the cell's powerhouses — where it is converted to acetyl-CoA and carbon dioxide. There, acetyl-CoA enters the tricarboxylic-acid (TCA) cycle (also called the citric-acid cycle or the Krebs cycle), the central crossroads of intracellular metabolic pathways.

Indeed, the TCA cycle is involved not only in the production of energy, but also in the synthesis and degradation of biomolecules. For its energy-generating activity, acetyl-CoA reacts with oxaloacetate to form citrate. In a series of enzyme-mediated reactions, citrate is then reconverted to oxaloacetate, while two molecules of CO_2 are produced, completing the cycle. Along the way, the movement of protons and electrons (provided by the cofactor $NADH^+$ and H^+) across the inner mitochondrial membrane and the electron-transport chain, respectively, drives the multiprotein enzyme complex F_OF_1-ATP synthase to produce ATP — a process known as oxidative phosphorylation. In total, for each molecule of glucose that is broken down, 36 molecules of ATP are produced (Fig. 1).

When pyruvate cannot be processed through the TCA cycle, ATP production is much less efficient. Under certain conditions — such as oxygen shortage, an incomplete ATP-synthase complex or lack of mitochondria — pyruvate is fermented into lactate or ethanol, yielding just two ATP molecules for each glucose molecule.

The biochemical properties of the enzymes that participate in the various stages of ATP production have long been known, and the overall activity of the TCA cycle has been extensively studied. Moreover, recent progress in metabolomics (the study of small-molecule metabolite profiles produced by distinct cellular processes) has enabled specific details of metabolism to be elucidated. And recent advances in liquid chromatography and mass spectrometry allow the detection and quantification of metabolites in ever-smaller amounts of biological material. Furthermore, when

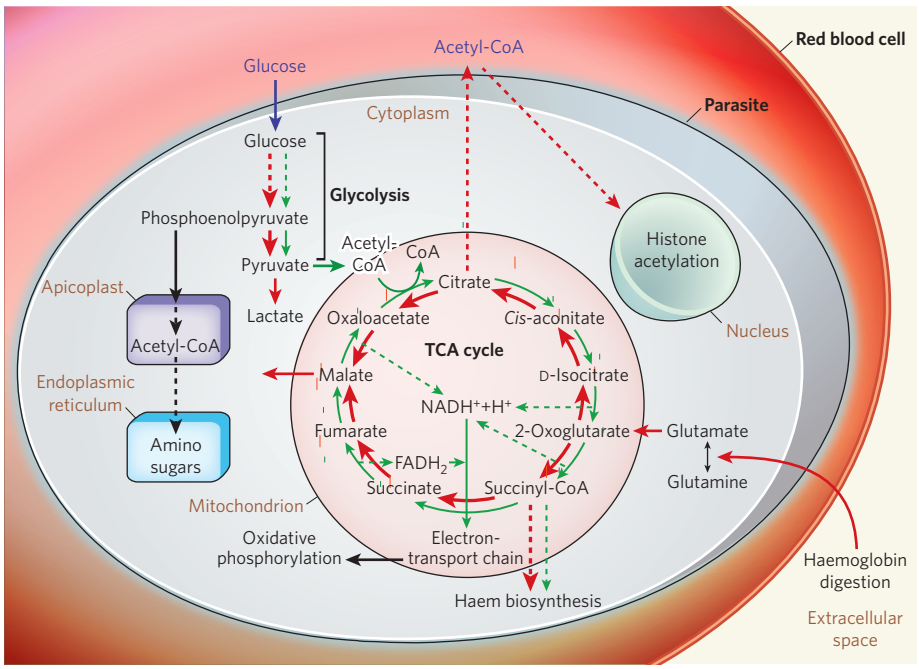

Figure 1 | Canonical intracellular metabolic pathways and those of *Plasmodium falciparum*. A red blood cell infected with a malaria parasite is depicted. The normal tricarboxylic-acid (TCA) cycle is denoted by green arrows, and the branched pathway used by *P. falciparum* is shown in red (with bifurcation starting at 2-oxoglutarate). The main cellular processes that mediate the supply or consumption of metabolites are depicted in black. The host-cell contributions are in blue. Dashed arrows indicate multiple steps.

substrates containing carbon or nitrogen isotopes are fed to cells and the data are collected over time, both the metabolic kinetics and the relative rates of different pathways can be determined accurately.

Olszewski and colleagues[1] use a metabolomic approach to analyse the TCA cycle of blood-stage *P. falciparum*, the most lethal of the four parasite species that cause malaria in humans. Their Herculean effort seems to have been well rewarded. In agreement with previous suggestions[2], they find that — unlike the canonical TCA cycle, which is unidirectional and oxidative — the cycle used by the parasite (which contains the genes encoding all of the known TCA-cycle enzymes) is bifurcated, part of it being oxidative and the other part being reductive (Fig. 1). What's more, as the parasite cannot convert pyruvate into acetyl-CoA in its mitochondrion[3], depriving it of this substrate for the TCA cycle, it instead feeds the amino acids glutamic acid and/or glutamine into the cycle.

The main metabolic roles of the TCA cycle in the malaria parasite seem to be production of succinyl-CoA for haem biosynthesis through the oxidative branch and the synthesis of citrate through the reductive branch. The two branches converge on malate, which, together with citrate, is exported from the mitochondrion, thus driving the process in both directions. It is noteworthy that *P. falciparum* cannot convert citrate to acetyl-CoA[1]. This may be carried out by the appropriate enzyme (ATP-dependent citrate lyase) of the red blood cell in which the parasite resides, with the acetyl-CoA that is generated being shuttled back to the parasite.

Two distinct, compartmentalized routes mediate the synthesis and use of acetyl-CoA in the parasite. The mitochondrial source (derived from the exported citrate) is targeted to the nucleus, where it is involved in the acetylation of histone proteins, which determine the spatial organization of DNA and control the processes of DNA replication and transcription. In addition, acetyl-CoA can be synthesized, in a parasitic and alga-derived organelle called the apicoplast, from phosphoenolpyruvate — an intermediate of the glycolytic pathway[3]. Apicoplast-derived acetyl-CoA is used to synthesize amino sugars, a process that occurs in yet another organelle, the endoplasmic reticulum.

In nature, there is no known precedent either for a non-standard TCA pathway such as that of *P. falciparum* or for the exclusive use of acetyl-CoA originating from different cellular compartments (and then probably mixing in the cytoplasm) in two other distinct compartments.

Although *P. falciparum* can be admired for the ingenuity of its altered metabolic architecture, the physiological rationale for this is far from clear. Why, for example, would the parasite relinquish oxidative phosphorylation for lactate production, which is fermentative, given that the former is 18 times more efficient at producing ATP than the latter? The physiological consequences of this choice are costly for the infected host. In individuals with severe malaria, the increase in glucose consumption and lactate production that is driven by the parasites causes life-threatening hypoglycaemia (low levels of blood glucose) and lactic acidosis (low blood and tissue pH)[4]. One could argue that if the activity of the electron-transport chain were instead enhanced, this would exacerbate the oxidative stress that the parasite already places on its host cell (through digesting the oxygen carrier haemoglobin), thereby disrupting the infected red blood cells before the parasite could mature[5] — killing the host would obviously destroy the parasite's habitat. By contrast, mice infected with *Plasmodium berghei* or *Plasmodium yoelii*, two other species of the parasite that cause malaria in rodents, carry out active oxidative phosphorylation[6].

Another puzzle is why the parasite's genome contains the genes encoding eight of the subunits of F_OF_1-ATP synthase but the complex is biochemically inactive in these organisms. It is hoped that future investigations will solve these mysteries.

What's clear is that Olszewski *et al.*[1] seem to have resolved a long-standing problem by providing a functional answer to why the TCA-cycle enzymes are present in *P. falciparum* when oxidative phosphorylation is absent. Demonstrating even that the cycle is essential for the parasite remains an obvious challenge. ■

Hagai Ginsburg is in the Department of Biological Chemistry, Institute of Life Sciences, The Hebrew University of Jerusalem, Jerusalem 91904, Israel.
e-mail: hagai.ginsburg@gmail.com

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GENOMICS

Variations in blood lipids

Alan R. Shuldiner and Toni I. Pollin

What is the new gold standard for genome-wide association studies? As exemplified by analyses of blood lipids, it is collaboration to amass huge sample sizes and functional studies of the genes identified.

Cardiovascular disease is a leading cause of death. In the United States, for example, it accounted for 1 in every 2.8 deaths in 2005 (ref. 1). Disruptions in the amounts of blood lipids greatly increase the risk of this disease. On page 707 of this issue, Teslovich *et al.*[2] report on one of the largest meta-analyses of genome-wide association studies so far, involving 46 cohorts and more than 100,000 human subjects. They identify 95 distinct gene variants and/or chromosomal locations — 59 of them new — associated with lipid traits in the blood. What's more, the authors go a step further to validate the biological relevance of three of the novel genes in mice.

Cells need cholesterol and triglycerides — derived from dietary sources and the liver — for membrane synthesis and energy. These lipids circulate in the blood as part of lipoprotein particles, which are made of various proportions of cholesterol, triglycerides, phospholipids and proteins. Low-density lipoproteins (LDLs), for example, shuttle cholesterol from the liver to other tissues, whereas high-density lipoproteins (HDLs) scavenge cholesterol from blood vessels and other tissues, returning it to the liver.

Much of what we know about lipid metabolism and the treatment of dyslipidaemia (disruptions in blood-lipid levels) comes from the ongoing discovery and characterization of numerous, relatively rare genetic variants with large effects on lipid levels (reviewed in ref. 3). Brown and Goldstein's landmark studies identifying mutations in the LDL receptor pioneered such work[4]. More recently, however, researchers have focused on identifying genetic variants that influence the more common causes of increased blood-lipid levels, apparently resulting from the interaction of multiple small genetic effects with environmental and life-style factors such as diet and physical activity[3].

An earlier meta-analysis of genome-wide association studies (GWAS) involving more than 8,000 individuals[5], for instance, implicated 36 genes and chromosomal loci in common variation in the levels of blood lipids. But to detect smaller effects of genetic variants, even larger sample sizes are needed in GWAS that evaluate the association of lipid levels with millions of single nucleotide polymorphisms (SNPs) distributed throughout the genome. Pooling several GWAS in a larger meta-analysis enables detection of yet smaller effects.

This is exactly the approach Teslovich *et al.*[2] took — a strategy that led to several insights. Many of the variants the authors discovered are in, or near, genes known to mediate lipid metabolism. They include common variants in