MICROBIAL PATHOGENESIS

Mtb takes a Trp

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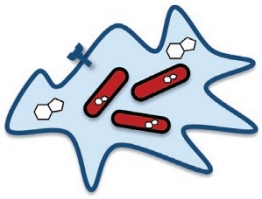

The intracellular pathogen *Mycobacterium tuberculosis* (Mtb) has numerous strategies to subvert human host bactericidal mechanisms. For instance, CD4$^+$ T cells of the host's immune system limit the growth of Mtb. To gain more insight into the anti-pathogen effector mechanisms used by CD4$^+$ T cells and the Mtb evasion mechanisms, Zhang *et al.* profiled the Mtb genome for mutants with growth defects that are rescued when CD4$^+$ T cells are absent (in MHCII knockout mice). Growth during Mtb infection required 576 genes known as the 'counteractome', in which two biochemical pathways were highly represented, including tryptophan (Trp) biosynthesis. Experiments with Mtb mutants deleted for *trpE*, which catalyzes the first committed step of Trp biosynthesis, showed that Trp starvation leads to killing by the immune system and suggested that CD4$^+$ T cells induce the requirement for Mtb Trp biosynthesis. The authors found that CD4$^+$ T cells most likely act through IFN-γ to stimulate Trp depletion, forcing Mtb to synthesize its own Trp. They identified the fluorinated anthranilates 5-FABA and 6-FABA as inhibitors of TrpE, which were toxic to Mtb *in vitro*. In a mouse model of infection, a 6-FABA ester derivative effectively inhibited the growth of Mtb. These results suggest a therapeutic potential in harnessing the ability of CD4$^+$ T cells to target Trp metabolism. *MB*

METABOLISM

Brucei's next top model

PLoS Comput. Biol. **9**, e1003371 (2013)

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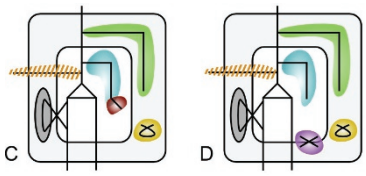

Existing metabolic models of *Trypanosoma brucei* have aided in the search for new drug targets in this parasite but provide only a limited picture of cellular metabolism. Kerkhoven *et al.* now expand the existing, glycolytic-focused model to include the pentose phosphate pathway (PPP), which generates NADPH and thus links to oxidative stress. With these reactions in place, the authors discovered that phosphorylated compounds were 'leaking' from glycolysis into the PPP, disrupting the conservation of the glycolytic reactions. To resolve this, the authors tried two separate amendments: in model C (see picture), ribokinase was introduced to enzymatically restore phosphates. Experimental tests ruled out ribokinase as capable of single-handedly fixing the leak but suggested that a larger network of enzymes could provide a solution to the problem. In model D, an ATP-ADP antiporter was added to transport phosphorylated metabolites into the system; however, this mathematically complete solution could not be tested directly as the relevant transporters are not yet known. By combining these models, which explicitly incorporate uncertainty, with cellular assays, the authors were able to test a prior prediction that the enzyme 6PGDH would be a good drug target; they observed that 6PGDH inhibition was lethal, but this was unexpectedly related to the loss of the oxidative branch of the PPP rather than anticipated feedback mechanisms. *CG*

NEUROTRANSMITTERS

Glutamate gets fat

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The activity of melanocortin receptor 4 (Mc4r) in Single-minded homolog 1 (Sim1)-expressing neurons in the paraventricular nucleus of the hypothalamus (PVH) is important for body weight homeostasis, but the neurotransmitter that mediates Mc4r function in these neurons is not known. In the mouse PVH, Xu *et al.* noted that the vesicular glutamate transporter 2 (Vglut2), which loads the neurotransmitter glutamate into vesicles for presynaptic release, was coexpressed with Mcr4. In sections from mice with genetic deletion of *Vglut2* in Sim1-expressing neurons of the PVH, glutamate release was decreased compared with sections from wild-type mice. In obese *Mc4r*-null mice, selective restoration of *Mc4r* expression in Sim1 neurons decreased body weight. Restoration of *Mc4r* in combination with selective *Vglut2* deletion in the same neurons countered the effect of *Mc4r* expression, indicating that Mc4r's impact on body weight depends on glutamate. In the mice lacking *Mc4r* expression or in those expressing *Mc4r* but not *Vglut2*, O_2 consumption was decreased compared with wild-type mice, indicating that a change in energy expenditure might be responsible for changes in body weight. Consistent with this notion in wild-type mice, a synthetic Mc4r agonist led to increased O_2 consumption compared with vehicle. Taken together, these data indicate that Mc4r alters energy expenditure to control body weight, and the activity of Mc4r in Sim1 positive neurons depends on glutamate release from the neurons. *AD*

DRUG REPURPOSING

Down goes Ikaros

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The use of thalidomide was discontinued as a sedative for pregnant women owing to its teratogenic properties. However, thalidomide and other derivatives such as lenalidomide have recently been shown to be highly effective for the treatment of multiple myeloma and other B-cell malignancies. Thalidomide has been shown to interact with cereblon (CBRN), a substrate recognition component of a Cul4 ubiquitin E3 ligase complex, but the basis for anti-myeloma activity downstream of CRBN remains unknown. Krönke *et al.* used a quantitative proteomic MS approach to perform ubiquitination profiling in lenalidomide-treated myeloma cells, and Lu *et al.* used a cell-based assay relying on an ORF library to detect proteins with lenalidomide-dependent changes in stability. Both studies found that lenalidomide promoted the binding of CBRN to two members of the Ikaros family of transcription factors, IKZF1 and IKZF3, which are required for B- and T-cell development. The CBRN-Ikaros interaction resulted in the ubiquitination and degradation of IKZF1 and IKZF3. Both groups identified unique residues on IKZF3 (Q147) and IKZF1 (Q146) that are necessary and sufficient for lenalidomide responsiveness. Knockdown of IKZF1 or IKZF3 reduced growth of lenalidomide-sensitive cell lines, whereas overexpression of a stabilized form of IKZF1 or IKZF3 conferred resistance to lenalidomide, suggesting that decreased IKZF1 and IKZF3 expression mediates the antimyeloma effects of lenalidomide. *GM*