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INFECTIOUS DISEASE

Glutamine analogue reverses cerebral malaria

Despite effective antimalarial treatment, cerebral malaria (CM) can be a deadly complication of *Plasmodium falciparum* infection, and there are no adjunctive treatments available. Now, Pierce, Powell and their colleagues demonstrate that a glutamine (Gln) analogue rescues mice infected with *Plasmodium berghei* ANKA (PbA) from experimental CM (ECM).

Although the pathological mechanisms leading to CM remain incompletely understood, it is believed to be in part immune mediated.

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Indeed, degranulation and release of perforin by parasite-specific $CD8^+$ T cells that accumulate in the brains of PbA-infected mice has been shown to play a crucial part in ECM development. Upon activation, $CD8^+$ T cells undergo a shift from oxidative metabolism to aerobic glycolysis and glutaminolysis and import large quantities of Gln, a process necessary for T cell expansion and effector function. Therefore, the authors set out to investigate the potential therapeutic effect of blocking Gln metabolism in ECM.

To do this, they infected mice with PbA to induce ECM and treated them intraperitoneally with the Gln analogue 6-diazo-5-oxo-L-norleucine (DON), which inhibits Gln metabolism by blocking Gln transport and inhibiting glutaminase. Whereas untreated PbA-infected mice died by day 7 post-infection (p.i.), the majority of mice treated with DON beginning at 7am or 11pm on day 5 p.i. (day 5a p.i. and day 5p p.i. respectively) survived for the duration of the study (day 12 p.i). Furthermore, nearly 50% of mice treated as late as day 6a p.i. survived.

DON treatment beginning on day 5a p.i. prevented the development of neurological symptoms in all PbA-infected mice. In addition, signs of ECM were rapidly resolved by DON treatment begun on day 5p p.i; the compound restored blood–brain barrier integrity and reduced cerebral oedema after just 1 day, with petechial haemorrhages being no longer apparent by day 15 p.i.

Next, the authors determined the effect of DON on T cells in the brains of PbA-infected mice. Although DON treatment (beginning day 5p p.i.) did not inhibit the expansion of parasite-specific $CD8^+$ T cells, it did appear to block their effector function as indicated by degranulation.

DON also markedly affected brain metabolism during ECM. Metabolic profiling of mouse brains identified more than 81 PbA-induced metabolic changes (including those in pathways involved in citrulline metabolism, the urea cycle and nitric oxide biosynthesis) that were either reversed or blocked by DON, revealing a potentially selective metabolic signature for ECM and subsequent disease reversal.

In summary, this study demonstrates the potential of targeting glutamine metabolism to arrest disease and promote survival in late-stage ECM, identifying DON as a promising candidate for an adjunctive CM therapy.

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ORIGINAL RESEARCH PAPER Gordon, E.B. *et al.* Targeting glutamine metabolism rescues mice from late-stage cerebral malaria. *Proc. Natl. Acad. Sci.* **112**, 13075–13080 (2015)