Scavengers beware!

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An analysis of the *Cryptosporidium parvum* genome shows that these parasites rely on nucleosides scavenged from their hosts for survival, report US bioinformatics experts. The pathways involved could be exploited to develop treatments for cryptosporidiosis, they say.

Public health threat

Cryptosporidiosis is often viewed as a public health problem for the developing world, but large outbreaks do occur the US and other Western countries, notes Boris Striepen, of the University of Georgia's Center for Tropical and Emerging Global Diseases in Athens, Georgia (http://www.ctegd.uga.edu/). The chronic severe diarrhea caused by the infection can be life threatening for immunocompromized patients, and currently there is no effective drug to combat the parasites, he says.

Progress towards a treatment has been held back because it is not yet possible to culture *C. parvum* continuously, says Striepen. So, the newly complete genome sequence for the organism is a crucial resource.

Comparing the *C. parvum* sequence with those of several closely related species, Striepen and his colleagues were surprised to find that the parasite seems to have lost a set of genes that, in other species, are involved in pyrimidine synthesis. '*C. parvum* appears to have lost the capacity to perform *de novo* pyrimidine synthesis because we were unable to find any of the genes encoding the six enzymes involved in this pathway,' they conclude in their paper, published in the *Proceedings of the National Academy of Sciences* [1].

Pyrimidine nucleotides

Pyrimidine nucleotides are the basic building blocks of DNA and RNA, and crucial components of other metabolic processes, says Striepen. So to compensate for not being able to produce the nucleotides itself, the parasite seems to have picked up genes that encode 'salvage' enzymes, capable of converting nucleosides stolen from the host cell to match its own needs.

Like several related parasites, *Cryptosporidium* also scavenges purine nucleotides from its host, but even this pathway looks unusual. 'Both the purine and pyrimidine synthesis pathways are unlike those in related parasites that have been studied in the past,' says Striepen. 'These divergent pathways might be exploited to develop antiparasitic drugs,' he suggests.

Striepen's team's findings are 'important and striking', according to Giovanni Widmer, associate professor in the Department of Biomedical Sciences at Tufts University in Boston, Massachusetts (http://www.tufts.edu/), who is involved in the *Cryptosporidium* genome sequencing project. '[They] have some potential for exploiting this for chemotherapy,' he said.

He is slightly sceptical, however, because of the number of promising drug candidates that have failed to treat cryptosporidiosis in the past. 'We have known for a long time that these organisms are dependent on purine salvage, but that has not translated into a magic bullet in terms of a drug,' he said. 'It has been a very frustrating pursuit.'

Therapeutic targets

Striepen, however, holds out more hope. 'The nucleoside biosynthetic pathways are a rich source of therapeutic targets,' he says. And he reports that two inhibitors of a purine-scavenging enzyme inhibited the development of *Cryptosporidium* in infected epithelial cell cultures. 'There is toxicity for the parasite that is dose-dependant,' he said.

This *in vitro* result is only a first step, he notes, but initial experiments in animals are promising. 'We are not saying that these two compounds are the final solution,' he said. 'What we have shown from the genome analysis and the experiments is that [nucleotide scavenging] is a target, and if you hit it, then the parasite is dead.'

Reference

1 Striepen, B. *et al.* (2004) Gene transfer in the evolution of parasite nucleotide biosynthesis. *Proc. Natl. Acad. Sci. U. S. A.* 101, 3154–3159

Suppressing the suppressors

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California-based virologists have uncovered a novel viral mechanism that actively suppresses, rather than simply evades, host immunity. Surprisingly, they report, the virus misappropriates a host protein that is generated by the