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Karl Drlica
Public Health Research Institute
455 First Avenue
New York
NY 10016 USA

Bacterial fatty-acid biosynthesis: an antibacterial drug target waiting to be exploited ▼

Fatty-acid biosynthesis has been validated as a target for antimicrobial agents through extensive work in *Escherichia coli*[1]. This has demonstrated that fatty-acid biosynthesis is essential to the survival of the organism, is distinct from the mammalian pathway and is generally highly conserved among bacteria. Thus, there exists the potential for the generation of a broad spectrum of novel antibacterial drugs. To date, triclosan, isoniazid, cerulenin, thiolactomycin and diazaborines are known fatty-acid-synthase inhibitors with proven efficacy.

New leads described recently in *Drug Discovery Today*[2], target the enoyl-acyl carrier protein (ACP) reductase step. The FabI reductases of Gram-negative and Gram-positive bacteria are inhibited by the consumer antimicrobial, triclosan, whereas the protein from Mycobacteria is inhibited by isoniazid. However, the enoyl-ACP reductase step has some drawbacks that limit enthusiasm for further developments. Two novel isoforms of this enzyme have been discovered: FabL, identified in *Bacillus subtilis* by its weak homology to FabI, has overlapping, redundant functions *in vivo* with FabI; and FabK, which was identified as the sole enoyl-ACP reductase in *Streptococcus pneumoniae* as a triclosan-resistant flavoprotein with no homology to FabI (Refs 3,4). The existence of these enzymes will limit the activity spectrum of drugs targeted against FabI.

Triclosan had been thought to kill bacteria by disruption of the cell membrane, an effect that has now been disproved for Gram-negative bacteria. Overexpression of either the FabK or FabL isoforms renders *E. coli* refractive to triclosan inhibition[3,4]. Expression of these isoforms in Gram-positive bacteria, however, merely increases triclosan resistance by approximately eightfold. Payne and co-authors[2] conject that this remaining sensitivity is a result of membrane-perturbing effects in Gram-positive bacteria. However, inhibition of a second, undefined target in Gram-positive bacteria remains a plausible hypothesis.

Bacterial fatty-acid-synthase inhibitors have a potentially wider usage, as antimalarial chemotherapeutics. *Plasmodium falciparum*, a unicellular eukaryotic parasite, contains a bacterial-like fatty-acid synthase system in a vestigial chloroplast. Thiolactomycin and triclosan have been demonstrated to have antimalarial activity *in vitro*[5,6], and thus new inhibitors of the bacterial pathway could also be effective against this organism.

Two targets in particular stand out as potential candidates for further development. The condensing enzymes, FabH, FabB and FabF, are essential, highly conserved and inhibited by thiolactomycin and cerulenin[7]. Despite different substrate specificities, their similar active-site architecture makes them ideal candidates for the design of new drugs that can inhibit both isoform activities. Thus, the bacteria would need to mutate two loci to become resistant. The second possibility lies with the FabG β-ketoacyl-ACP reductase[8]. From a bioinformatic analysis, it is observed that this enzyme is highly conserved in all bacteria, has no known isoforms and is probably essential. Thus, inhibitors of FabG should possess broad-spectrum activity.

Bacterial fatty-acid synthesis is a pathway with a high potential for the discovery of new antimicrobial drugs. The time is now ripe for further exploitation by the pharmaceutical industries, which will hopefully result in much needed new chemotherapeutics.

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Richard J. Heath
Protein Production Facility
St Jude Children's Hospital
Memphis
TN, USA
tel: +1 901 495 3602/3460
fax: +1 901 523 2622

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