STRUCTURE-BASED DRUG DESIGN

Anthrax attacked!

Even when antibiotics are administered, inhalation of anthrax can be fatal because the causative bacterium, *Bacillus anthracis*, releases a large amount of lethal toxin that is not neutralized by antibiotics. Now, two papers in the January issue of *Nature Structural and Molecular Biology* report the identification of small molecule inhibitors of anthrax toxin.

The toxin consists of three proteins: lethal factor (LF), protective antigen (PA) and oedema factor (EF), all of which work together to inactivate host cells. PA binds to a cell surface receptor and forms an oligomeric pore that translocates both EF and LF into the cytosol of target cells. The combination of PA and LF is known as lethal toxin (LeTx), and intravenous delivery of LeTx alone causes death in rodents. LF is a zinc-dependent metalloproteinase that cleaves most mitogen-activated protein kinase kinase (MEK) enzymes at sites near their N-termini, impairing the ability of the MEK to interact with and phosphorylate its downstream signalling proteins. Through a mechanism that is not well understood, this results in the death of the host cell.

On the basis of current understanding, antitoxin therapies that block the interaction of PA and LF, or prevent the translocation of LF and EF across the cell membrane, are expected to be potent inhibitors of the toxin *in vitro* and in animal models. However, a more direct approach would be to identify inhibitors that inactivate the lethal action of anthrax toxin.

In one study, Benjamin Turk, Lewis Cantley, Robert Liddington and colleagues identified peptide analogues that inhibited LF *in vitro* and protected cultured macrophages from LF-mediated cytolysis. Crystal structures of LF bound to an optimized peptide substrate, as well as to peptide-based inhibitors, had several common features that provided a rationale for the observed selectivity. The crystal structures showed that the main determinants for high target affinity were the long, hydrophobic substrate-binding groove and deep pocket adjacent to the catalytic binding site.

In the other study, Rekha Panchal, Rick Gussio, Sinal Bavari and colleagues identified small-molecule non-peptidic inhibitors of LF. The LF inhibitors identified in the preliminary screen were used to develop a pharmacophore model. In combination with X-ray crystallographic data, molecular docking studies and three-dimensional database mining from the chemical repository of the National Cancer Institute, the authors identified additional compounds with LF inhibitory properties. Three of the compounds have K_i values in the 0.5–5 μM range, exhibit competitive inhibition and will be used as the basis for developing therapeutically viable inhibitors of LF.

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References and links

ORIGINAL RESEARCH PAPERS Turk, B. E. *et al.* The structural basis for substrate and inhibitor selectivity of the anthrax lethal factor. *Nature Struct. Mol. Biol.* **11**, 60–66 (2004) | Panchal, R. G. *et al.* Identification of small molecule inhibitors of anthrax lethal factor. *Nature Struct. Mol. Biol.* **11**, 67–72 (2004)

FURTHER READING
Collier, R. J. & Young, J. A. Anthrax toxin. *Annu. Rev. Cell. Dev. Biol.* **19**, 45–70 (2003)