

Little Rafts Battle Anthrax

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Whether as a bioweapon or as a “mere” animal epidemic, anthrax is a serious threat. A team of Canadian and American researchers has now developed a method to increase the effectiveness of an anthrax toxin inhibitor.

As they describe in the journal *Angewandte Chemie*, the scientists led by Jeremy Mogridge (University of Toronto) and Ravi S. Kane (Rensselaer Polytechnic Institute) introduce their drug molecules into liposomes so that they aggregate into separate domains that “float” on the liposome surface like tiny rafts.

The fatal effect of the anthrax organism stems from three different toxins that work together: EF (edema factor), LF (lethal factor), and PA (protective antigen). PA ushers the two other toxins into cells, LF destroys the white blood cells of the afflicted organism. If LF is prevented from binding to PA, it can no longer enter cells and progress of the disease is stopped.

Some time ago, a peptide that binds to PA and blocks binding of LF was developed. To be effective, multiple copies of the protein must bind to PA. In order to “bundle” the peptides, they are attached to a lipid (a fat molecule), which is incorporated into a liposome, a tiny fat bubble. The concentration of peptide within each liposome must be above a certain threshold, because the peptide molecules must be no further apart than the distance between the individual peptide binding sites on the PA.

The team led by Mogridge and Kane wanted to allow the peptides to get

even closer together to further raise the concentration. Like a natural cell membrane, the shell of a liposome consists of a kind of two-dimensional liquid made of fat molecules. The composition of natural cell membranes is not uniform; they have tiny domains with different structures, which play an important role in various physiological processes. This is also true of liposomes, if they are made of saturated and unsaturated fats in addition to 20 % cholesterol. This results in two different phases. The peptide accumulates in one or the other of these fats, and the peptide molecules aggregate and “float” on the surface of the liposome like a tiny “raft”. This could significantly increase the anthrax-inhibiting activity of the peptides.

Alternatively, the microdomains can also be triggered by an external stimulus, such as a change in ion concentration, temperature, light, or enzymes. As an example, liposomes containing the lipid phosphatidylserine (PS) form PS-enriched domains as soon as calcium ions are added. This may make it possible to “switch on” inhibitors only once they have reached their target.

Citation: Ravi S. Kane, Raftlike Polyvalent Inhibitors of the Anthrax Toxin: Modulating Inhibitory Potency by Formation of Lipid Microdomains, *Angewandte Chemie International Edition* 2007, 46, No. 13, 2207–2209, doi: 10.1002/anie.200604317

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