When a frog swallows a fly

Vivienne Baillie Gerritsen

When you punch a hole in a tyre, it deflates. Besides being simple, it is a strategy that is used by a number of plants and animals as a means of defence. To this end, they make use of antimicrobial peptides which alter the enemy’s cellular membrane in such a way that the inside leaks out, or the outside leaks in, thus causing cell death. Antimicrobial peptides have been discovered in all kinds of organisms, from fruit flies to horseshoe crabs, and honeybees to humans. It is a rapid immune response to microbes that surround us daily. When a frog swallows a fly, it also ingurgitates an army of microbes, which have to be eliminated or, at least, whose growth rate has to be checked. Magainins, from the Hebrew “maga in” meaning shield, do just this and they were the first antimicrobial peptides to have been described.

Magainins were discovered in 1987 in *Xenopus laevis* whilst Michael Zasloff was working on the frog’s oocyte system. Though his discovery is a fortunate one, associations for the prevention of cruelty to animals may wince. He was accustomed to practising non-sterile surgery on female frogs; the incisions were repaired with sutures and the animals were tossed back into microbe-contaminated tanks… Zasloff, himself, was amazed at the absence of infection and predicted some kind of “sterilising” activity on the frogs’ skin. Indeed, it was not long before he discovered a number of small peptides secreted by the skin, which could kill a host of bacteria and viruses, not to mention fungi and protozoa. When Zasloff rubbed adrenalin onto a frog’s back, within seconds he observed hordes of tiny white spots on the reptile’s skin, which soon merged into a milky film – what Zasloff called “a beautiful bandage”. And that is just what it is.

Though magainins were first extracted from *Xenopus* skin, they are also found in the gastrointestinal tract. They are synthesized both in the skin and the stomach, where they are stored in the granular dermal glands and the granular multinucleated cells, respectively. Magainins do not attack the frog’s cells. How is it that these peptides can recognise an unfriendly membrane from a friendly one? And how do they work? It all has to do with the physicochemical properties of the lipid bilayers, and of course those of the magainins.

Magainins are particularly short (20 to 26 amino acids) and specifically attracted to lipid bilayers. Not all lipid bilayers, however. Eukaryotic cell membranes consist of zwitterionic phospholipids and cholesterol mainly, and only carry a very low electric charge. Bacterial membranes are packed with negatively charged phospholipids and sugars, and thus carry a strong negative charge. In the presence of lipid bilayers, magainins curl up into amphipathic alpha helices and are immediately attracted to the charged microbial membranes. Eukaryotic membranes are ignored because of their low charge, and their cholesterol also acts as a barrier to the antimicrobial peptides.

Magainins are just long enough to span lipid bilayers, and they have been observed to do just...
that. However, over the years it became apparent that magainins also coat the membranes. It is all a question of peptide to lipid ratio... When there are not too many peptides, they curl into their alpha-helix conformation and recline on the bacterial membrane. When they are joined by more, they turn and adopt a transmembrane orientation and, along with a few phospholipids, they form a peptide-lipid supramolecular complex pore.

There is not much the bacteria can do with a punched membrane; resistance mechanisms such as enzymatic degradation or export processes are useless. When the peptide ratio diminishes, the supramolecular pore is disrupted and the magainins rest on the inner phospholipid bilayer. The peptide waltz from the outside phospholipid monolayer to the inner phospholipid monolayer spells death.

Naturally, magainins fast became a pole of therapeutic interest. Their broad anti-viral, anti-bacterial, anti-fungal and even spermicidal activities have therapeutic potential in the treatment of infections in man. Staphylococcus aureus and Pseudomonas aeruginosa are two of the "superbugs" that infest hospitals and are fast becoming antibiotic-resistant. Antimicrobial peptides could take over thanks to their pore-forming mode of action. One particularly interesting development is the use of these peptides as a potent vaginal contraceptive. In a world where there are 250 million new cases per year of sexually transmitted diseases – besides the AIDS virus – a contraceptive with anti-viral, anti-bacterial and anti-fungal activity would be a godsend. There are obstacles, though. Antimicrobial peptides can be digested by the host or even prove to be toxic. Tests have been carried out with more resistant synthetic peptides, which seem to be less prone to enzymatic digestion in their host. However, there is still a long way to go before such drugs are deemed safe for humans.

Cross-references to Swiss-Prot

Magainin, Xenopus laevis (African clawed frog) : P11006

References

1. Berkowitz B.A., Bevins C.L., Zasloff M.A.
   Magainins: a new family of membrane-active host defense peptides
   PMID: 1689576

2. Matsuzaki K.
   Why and how are peptide-lipid interactions utilized for self-defense? Magainins and tachyplesins as archetypes
   PMID: 10590299

3. Reddy V.R.K., Manjramkar D.D.
   Evaluation of the antifertility effect of magainin-A in rabbits: in vitro and in vivo studies
   PMID: 10685543

4. Glausiusz J.
   The frog solution
   Discover magazine, November 1998

5. Coughlan A.
   Bug busters
   The New Scientist magazine, vol. 166, April 8th 2000, page 15