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ANTIMICROBIAL PEPTIDES FROM FROG SKIN SECRETIONS: ISOLATION AND ACTIVITY SPECTRUM

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1. INTRODUCTION

Frogs live in damp, microbe-rich places and rely on skin that is thin, permeable and constantly wet. They do not have the thick keratin of reptiles or the fur of mammals, yet infected skin wounds in many species heal remarkably well. The explanation began to emerge in 1987, when Michael Zasloff described two small cationic peptides, which he named magainins, in the skin of the African clawed frog *Xenopus laevis* [1]. He had noticed that surgical incisions in frogs kept in unclean water seldom became infected. Skin extracts proved to kill bacteria

Abstract

Skin secretions of frogs are a rich natural source of cationic antimicrobial peptides, first described in the magainins of *Xenopus laevis* in 1987. This narrative review summarises published work on the isolation of these peptides and the spectrum of activity they display. It describes the main peptide families, the usual workflow from non-lethal secretion collection to chromatographic purification, mass spectrometric sequencing and synthesis, and the assays used to define activity against bacteria, fungi and the chytrid pathogen. It also reviews mechanisms and selectivity. The review reports no new data. Peptides are potent in vitro, but toxicity, protease instability and inconsistent reporting have limited clinical progress.

and fungi, and the active material turned out to be a pair of 23-residue peptides that fold into amphipathic helices on contact with membranes [1, 2]. The observation was simple, but it changed how biologists thought

about innate immunity, because it showed that a vertebrate could defend a barrier surface with small, rapidly deployed peptides rather than only with antibodies and cells.

Since then, hundreds of related peptides have been isolated from the dermal granular glands of frogs belonging to more than a dozen families, and amphibian skin has become one of the richest natural sources of host-defence peptides known [3, 4]. Their value for medicinal chemistry lies in three features: a mode of action based on membrane disruption that differs from most conventional antibiotics, activity against bacteria that have become resistant to those drugs, and a small size that makes synthesis and modification straightforward [5, 6]. Their drawbacks, including toxicity to host cells and instability in the body, have so far limited clinical progress. The numbers keep rising as new species are sampled, and public databases of antimicrobial peptides now hold a very large number of entries of amphibian origin.

This review addresses how antimicrobial peptides are obtained from frog skin secretions and what range of microorganisms they affect. It covers the main peptide families, the usual isolation workflow, the antimicrobial assays used to define an activity spectrum, the link between structure and selectivity, and the reasons these molecules have not yet become routine medicines. The review draws on published work and reports no new data, and quantities are described qualitatively unless a figure is widely reported [6, 7]. Particular attention is given to the questions a reader would ask before relying on a reported activity: how the peptide was obtained, how pure it was, what organisms were tested, under what conditions, and how toxic it proved to be for host cells.

2. SKIN SECRETIONS AND PEPTIDE FAMILIES

The skin of a frog contains granular, or serous, glands that store defensive chemicals in secretory granules. When the animal is stressed or attacked, muscular contraction around the gland expels the contents onto the surface as a mucus-rich secretion. That secretion contains biogenic amines, alkaloids,

protease inhibitors and a diverse set of peptides, many with antimicrobial activity [6, 7]. The peptides are synthesised as prepropeptides, with an N-terminal signal sequence, an acidic spacer region and a C-terminal mature peptide, and are cleaved before release. The conserved prepro region has made it possible to clone precursors from skin cDNA libraries and infer the mature sequence [3, 8]. The release is holocrine in character, so the gland must regenerate its stores over days or weeks, which is one reason that repeated collection from the same animal has to be spaced out.

Peptides are usually grouped into families by sequence similarity, and the families tend to follow the taxonomy of the frogs that make them. Magainins come from *Xenopus*; dermaseptins and phylloseptins from leaf frogs of the genus *Phyllomedusa*; brevinins, esculentins and temporins from ranid frogs such as *Rana esculenta* and *Rana temporaria*; and aureins from Australian tree frogs of the genus *Litoria* [3, 9, 10]. Because families map onto evolutionary lineages, peptide profiles have been used as taxonomic markers, and they help in separating cryptic species. Within a species, each individual may express a dozen or more related peptides, which probably gives a broader and more robust defence than any single molecule [9, 11]. Naming conventions are not uniform, and the same peptide sometimes carries different names in papers from different laboratories, which complicates literature searching.

Peptide size varies widely. Temporins are among the smallest natural antimicrobial peptides, with only 10 to 14 residues, whereas esculentin-1 has 46 and the dermaseptins about 30 to 34 [10, 12]. Most are cationic at neutral pH, with net charges of +2 to +6, and about half of their residues are hydrophobic. In water they are largely unstructured, but in the presence of lipid membranes or membrane-mimetic solvents they adopt an alpha-helical conformation with one face polar and the other nonpolar [13, 14]. Some, notably the brevinins and esculentins, also contain a disulfide-bridged loop at the C-terminus, the so-called Rana box, that contributes to stability and sometimes to selectivity [10, 12]. The balance of charge

and hydrophobicity is the key to function: too little charge and the peptide fails to bind bacterial surfaces, too much hydrophobicity and it attacks host cells as readily as microbes.

3. ISOLATION AND CHARACTERISATION

The first step is collection of the secretion. Older methods relied on killing the animal and extracting skin in acid or organic solvent, but modern studies prefer non-lethal approaches. Mild electrical stimulation of the skin, or injection of noradrenaline into the dorsal lymph sac, causes release of granular gland contents, which are washed off the frog with water or buffer, then immediately acidified and frozen [15]. The animals are returned to their enclosure and recover. Ethical approval and, in many countries, collection permits are required, and wild-caught frogs must be handled with disease control in mind to avoid spreading chytrid or other pathogens [15, 16]. Collection should be scheduled so that frogs are not stressed repeatedly, and weight and skin condition should be monitored afterwards.

Purification generally proceeds in stages. The acidified secretion is passed through a reversed-phase cartridge to remove salts and polar contaminants, and the retained peptides are eluted with acetonitrile. The fraction is then separated by reversed-phase high performance liquid chromatography on a C18 column using a gradient of acetonitrile in 0.1% trifluoroacetic acid, and fractions are collected and tested for antimicrobial activity [5, 6]. Active fractions are rechromatographed on columns of different selectivity until a single symmetrical peak is obtained. This activity-guided approach has the advantage of finding what is actually active, rather than what might be predicted. Typically three or four chromatographic steps are needed to move from a crude secretion to a homogeneous peptide, and yield at the end is often a few micrograms.

Structure determination relies on mass spectrometry and, increasingly, on sequence information from the precursor. Matrix-assisted laser desorption ionisation or

electrospray mass spectrometry gives the molecular mass and detects post-translational modifications such as C-terminal amidation, which is common in frog peptides and affects charge and activity [6, 11]. Tandem mass spectrometry or Edman degradation provides sequence, and cloning of skin cDNA identifies the precursor so that the mature peptide can be predicted and confirmed [3, 8]. Once the sequence is known, the peptide is made by solid-phase synthesis, which gives the amounts needed for testing and permits the preparation of analogues. Where a species has not been sequenced, de novo interpretation of fragmentation spectra can be laborious, and cloning is usually the quicker way to confirm a sequence.

Secondary structure is checked by circular dichroism in water and in trifluoroethanol or in lipid vesicles, and sometimes by nuclear magnetic resonance for a detailed picture [13, 14]. Helical content in a membrane-like environment correlates with activity for many peptides, though not perfectly. Purity and identity of synthetic material must be confirmed by chromatography and mass spectrometry, because truncated or oxidised by-products can bias activity data. Reports that use crude or unverified preparations make it harder to compare peptides across studies [5, 16]. These checks are routine in specialist laboratories but are sometimes skipped in broader pharmacological studies that simply buy a synthetic peptide.

4. ACTIVITY SPECTRUM

Activity is usually defined by the minimum inhibitory concentration (MIC), measured by broth microdilution under standardised conditions such as those in the EUCAST broth dilution document for aerobic bacteria, together with published comparisons of broth microdilution methods adapted for cationic peptides [17, 18]. Cationic peptides need modifications of these methods: low-binding polypropylene plates, a non-cationic-adsorbing medium, and care with salts, because ions weaken peptide binding to the bacterial surface [19]. A peptide's activity spectrum is the list of organisms it inhibits at concentrations that are not toxic to host cells, and table 1 gives examples of the main frog peptide families,

arranged by the pattern of activity, with fig. 1 counting the entries per group. Most laboratories report MICs for panels that include reference strains from culture collections, which allows some comparison, although clinical isolates give a more realistic picture.

Table 1: Representative frog skin antimicrobial peptides and the activity patterns reported for them

Peptide source	Reported activity pattern	Ref.
Magainin 2 Xenopus laevis	Inhibits Gram-positive and Gram-negative bacteria and fungi	[1, 2]
Dermaseptin S1 Phyllomedusa sauvagei	Acts on bacteria and filamentous fungi; 34 residues	[20]
Esculentin-1 Rana esculenta	Potent against both bacterial groups, including <i>Pseudomonas aeruginosa</i>	[10, 21]
Temporin A Rana temporaria	Mainly Gram-positive bacteria; very short peptide	[12]
Aurein 1.2 Litoria aurea	Short peptide active mainly against Gram-positive bacteria	[22]
Temporin family chytrid fungus	Several members inhibit <i>Batrachochytrium dendrobatidis</i> in culture	[23]
Temporin L Rana temporaria	Broad antibacterial action but also haemolytic	[24, 25]
Temporin and esculentin analogues	Retained activity against multidrug-resistant hospital isolates	[21]
Pexiganan magainin analogue	Broad in vitro activity against diabetic foot pathogens; late-stage trials, not approved	[26, 27, 28]

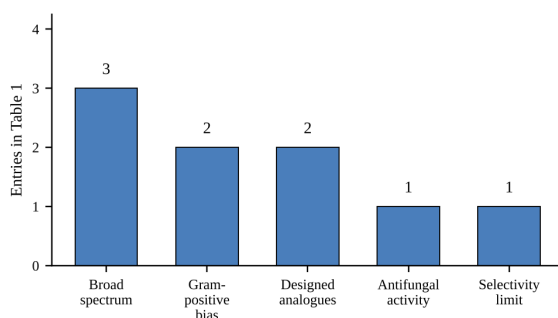


Fig. 1: Number of entries in table 1 by activity pattern

Some frog peptides are broad-spectrum. Magainin 2 inhibits Gram-positive and Gram-negative bacteria, fungi and protozoa in

the original report [1], and dermaseptin S1 from the leaf frog *Phyllomedusa sauvagei* acts on bacteria and filamentous fungi [20]. Esculentin-1 and the brevinins from *Rana esculenta* are potent against both groups of bacteria, with esculentin-1 notably active against *Pseudomonas aeruginosa*, a pathogen that is difficult to treat [10, 21]. Typical MIC values for the more active peptides lie in the low micromolar range, but they are strongly dependent on conditions and strain, and numbers from different laboratories should not be compared directly [17, 18]. Reported values should also be read against the inoculum size, since a heavy bacterial load can overwhelm a limited amount of peptide. Differences in cation content of the medium alone can shift an MIC several-fold, which is one reason that the same peptide appears more or less potent depending on the laboratory [17, 18].

Others are narrower. Temporin A and several of its relatives act mainly on Gram-positive bacteria, including *Staphylococcus aureus*, with much weaker action on Gram-negative species, a pattern attributed to the peptide's inability to cross the outer membrane efficiently [12]. Temporin L is an exception, being active against Gram-negative bacteria as well, but it is also haemolytic, which illustrates the common compromise between potency and selectivity [24, 25]. Aurein 1.2 and related *Litoria* peptides are short, mostly active against Gram-positive organisms and in some cases against tumour cells [22]. The spectrum thus differs from family to family and even among close relatives. It also serves as a reminder that natural peptides have been tuned by evolution for the frog's own pathogens and not for human infections.

Antifungal and antiviral activity is reported less often but matters. Several temporin family peptides inhibit growth of the chytrid fungus *Batrachochytrium dendrobatidis*, while others act on *Candida* species [11, 23]. Some frog peptides have also been reported to inhibit enveloped viruses and tumour cells at concentrations that spare normal cells, and a more general argument has been made that frog skin peptides are multifunctional, with immunomodulatory and metabolic effects as well [5, 6]. These observations widen the

possible uses of the peptides, though most of them come from cell-based experiments and lack in vivo confirmation. The chytrid work has a conservation rationale as well, since peptide profiles of wild populations may indicate resilience to the disease [23, 29].

Analogues have been designed to improve the therapeutic index. Pexiganan, an analogue of magainin 2, retained a broad antibacterial spectrum in vitro, including activity against bacteria isolated from diabetic foot infections, and it reached late-stage clinical trials as a topical treatment for infected diabetic foot ulcers [26, 27, 28]. It was not approved after the first round of regulatory review, partly because it did not show a clear advantage over existing oral therapy. Other work has shown that analogues of temporin and esculentin remain active against multidrug-resistant hospital isolates, which supports the case for further work [21]. The episode is often cited as a lesson that in vitro potency and a favourable safety profile are not enough, because a new drug also has to beat the existing standard of care.

5. MECHANISM AND SELECTIVITY

Bacterial membranes carry a net negative charge because of anionic phospholipids such as phosphatidylglycerol and cardiolipin, and Gram-negative bacteria add lipopolysaccharide on the outer surface. Cationic peptides are therefore attracted electrostatically to microbial surfaces, whereas the outer leaflet of mammalian plasma membranes is dominated by neutral zwitterionic lipids and cholesterol, which weakens binding [13, 30]. This charge difference is the main basis of selectivity. After binding, the hydrophobic face inserts into the lipid bilayer and the peptide perturbs it, leading to leakage of ions and metabolites and loss of the proton gradient [14, 31]. Cholesterol in mammalian membranes further stiffens the bilayer and makes insertion less favourable. The bacterial cell wall of Gram-positive species is also rich in anionic teichoic acids, which draw cationic peptides toward the membrane beneath [13, 30].

Several models describe how that perturbation arises. In the barrel-stave model, peptides assemble into a bundle that spans the

membrane and forms a pore; in the toroidal pore model, the lipids bend inward along with the peptides; in the carpet model, peptides cover the surface and disrupt the bilayer in a detergent-like manner once a threshold concentration is reached [13, 31]. Magainin is usually described by the toroidal model, and temporin L has been shown to permeabilise the membrane of *Escherichia coli* and to alter cell morphology [14, 25]. Evidence also shows that some peptides enter cells and act on intracellular targets, so membrane disruption is not the only mechanism [30, 31]. The models are idealised, and real peptides probably switch between modes depending on concentration, lipid composition and temperature.

Resistance to these peptides develops less readily than to conventional antibiotics, since changing the basic composition of the membrane is a costly adaptation for bacteria. It does happen, however. Bacteria can lower their surface charge by modifying lipid A or teichoic acids, export peptides with efflux pumps, or secrete proteases that degrade them [32]. Pathogens that colonise mucosal surfaces and are constantly exposed to host peptides seem especially well equipped. Resistance to a therapeutic peptide could also compromise innate immune defence if it provides cross-resistance to the body's own peptides, a theoretical risk that deserves more attention [32, 33]. For this reason, any programme to develop frog-derived peptides as drugs has to monitor for cross-resistance.

6. LIMITATIONS AND FUTURE DIRECTIONS

The leading obstacle to clinical use is the gap between in vitro and in vivo performance. Activity measured in a low-salt medium can vanish in the presence of physiological salt, divalent cations and serum, and peptides are rapidly cleaved by proteases in blood and tissue, giving short half-lives [34, 35]. Systemic toxicity is another concern, so the most realistic uses are topical, for instance on infected wounds, or local, as coatings for devices. Manufacturing cost adds to the problem, since synthesis of peptides is more expensive per gram than that of small molecules [19, 35]. Few host-defence peptides have so far reached the market for

these reasons [28, 34]. Local delivery and formulation in gels or dressings may avoid some of these problems. Clinical trials of earlier peptides have also been hampered by the choice of comparator and by the modest size of the patient groups available for infections of the skin.

Evidence quality is another limitation. Many papers report a single assay on one or two strains, with no clinical isolates, no replicate numbers and no standard comparator antibiotic. Different media and inoculum sizes make results difficult to compare, and haemolysis testing uses blood from different species. Wild collection raises conservation questions in a time when amphibians are among the most threatened vertebrates [15, 36]. Consistent reporting would improve the value of what is already known and allow a proper synthesis of peptide activities across studies [17, 18]. Open sharing of raw MIC data and sequences would be a practical help.

Looking forward, genome and transcriptome sequencing of frog skin should speed up discovery by identifying precursors without having to sacrifice or stress animals, and machine learning could help design analogues with better selectivity from the sequence data that already exist [5, 8]. Combination of peptides with conventional antibiotics, which may restore susceptibility in resistant bacteria, deserves systematic study. Frog peptides are also useful as templates, even if the natural sequences themselves never reach patients, because they have taught medicinal chemists a great deal about how to design membrane-active antimicrobials [19, 35]. Success will depend as much on dull matters such as stability testing and manufacturing as on the discovery of new sequences. Peptidomimetics that copy the amphipathic shape of a helix without the peptide backbone offer one route around protease degradation, and several such compounds are being studied [19, 35].

A last practical point concerns the way results from frog peptides are communicated. Press coverage of natural antibiotics tends to exaggerate near-term prospects. Careful phrasing, which separates a laboratory activity spectrum from a demonstrated treatment, is a service to readers and to the

field [34, 35]. Clear statements of limitations in abstracts, titles that do not promise cures, and publication of negative results all contribute to a more realistic picture of the field. Authors and journals share that responsibility, and the topic of frog peptides, which attracts keen public interest, is a good place to practise it [34, 35].

7. CONCLUSION

Frog skin secretions have yielded one of the largest natural collections of cationic antimicrobial peptides, from the magainins of *Xenopus* to the dermaseptins, esculentins, temporins and aureins of other genera [1, 10, 12, 20, 22]. Non-lethal collection, reversed-phase chromatography, mass spectrometry and synthetic confirmation form a well-established route from secretion to characterised peptide [6, 15, 16]. Activity spectra range from broad action against bacteria and fungi to narrow, Gram-positive-biased action, and a few peptides also inhibit the chytrid fungus that threatens amphibians. Together these features explain why the group of peptides has attracted so much sustained attention. Those who work on them need to remember that a good activity spectrum in the laboratory is only a first step.

Clinical use has lagged far behind the laboratory findings. Salt and serum sensitivity, protease degradation, haemolysis and cost have defeated most candidates, and even the best-studied analogue, pexiganan, was not approved [19, 26, 34]. The more realistic contributions of the field are templates for design, topical applications, and insight into membrane-active antimicrobials. Standardised assays, honest reporting of selectivity and better in vivo evidence would make the next phase of work more productive [17, 35]. Until those points are met, frog peptides will remain a source of ideas more than of medicines.

8. ABBREVIATIONS

cDNA-Complementary DNA, CLSI-Clinical and Laboratory Standards Institute, HPLC-High performance liquid chromatography, MIC-Minimum inhibitory concentration, MRSA-Meticillin-resistant *Staphylococcus aureus*, TFA-Trifluoroacetic acid,

Bd-Batrachochytrium dendrobatidis

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10. AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

11. CONFLICT OF INTERESTS

Declared none

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