Animal Antimicrobial Peptides: Ancient Players in Innate Immunity

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Outstanding research often begins by asking a simple question. Hans Boman asked two such questions. How do animals survive infections if the division time for bacteria is as low as 20 min and the adaptive immune system that produces Abs and T cells requires a week or longer to expand and come into play? Equally important, how do insects survive infection if their circulating hemolymph contains no Abs and no cells capable of mounting an adaptive immune response? He imagined that these two questions could be closely related. Indeed they were.

The work began in the early 1970s where he had founded a microbiology department in a newly established university at Umeå, just 350 miles south of the Arctic Circle in northern Sweden. In his first publication on insect immunity (1), he turned to the insect that was much studied genetically then and now: Drosophila melanogaster. Infection was induced by injecting several different Gram-negative bacteria into the abdomen. Even at doses as low as a 100 bacteria per fly, all flies died. Some reports had previously appeared that insects could be immunized against bacterial infection with vaccines, i.e., heat-killed cultures. However, these experiments were at odds with the finding that animals lower in evolution than teleost fishes do not produce Abs. Vaccinations showed that after injection of Drosophila with 10^3–10^5 cells of a non-virulent strain of Aeromonas hydrophila followed a few days later by a virulent strain of the same organism, within a few hours the titer of the latter dropped to <5. Clearly Drosophila had an inducible system that resulted in a bactericidal effect of hemolymph. The stage was set.

Boman quickly realized that purification of these materials from the hemolymph of organisms as small as Drosophila would be exceedingly difficult, and his laboratory then turned to the use of the giant silk moth, Hyalophora cecropia, from which ~1 ml of hemolymph could be obtained from each pupa. In a series of papers in the 1970s they showed that this insect also had an inducible antibacterial system and examined many of its properties. The work culminated in 1981 and 1982 with the first inducible antibacterial system and examined many of its properties. The work culminated in 1981 and 1982 with the first inducible antibacterial system and examined many of its properties.

Boman's laboratory isolated a proline-arginine-rich antibacterial peptide, PR-39 (19/39 proline and 10/39 arginine residues), from pig intestine (9), a member of still another family of animal antimicrobial peptides. By now, >700 antimicrobial peptides have been isolated from mammalian tissues (10). Two broad groups are known. They are α- and β-defensins and cathelicidins, all small cationic peptides encoded mostly by separate genes and initially expressed as pro-proteins. They have been shown to have broad functions in the immune system in addition to their antimicrobial activity and are important players in the role of the innate immune system in stimulatingadaptive immunity. For example, the cathelicidin LL37/FALL39, the only known human cathelicidin (a 37-aa peptide of which the first two amino acids are leucines) (11), modulates dendritic cell differentiation (12). FALL39 is a precursor of LL37. Another striking discovery in the late 1980s was the isolation and characterization of antimicrobial peptides (called magainins) from frog skin (13). Their secretion in a creamy liquid was induced by noxious stimuli to frogs (or by keeping frogs in an infected terrarium).

I knew Hans personally, and I remember asking him during a sailing trip: "How do you know that these substances function as antibacterial agents in vivo? You need a mutant to answer the
question.” Mutants were indeed found, both induced in insects in the laboratory and naturally occurring in man.

An initial proof of the hypothesis that antimicrobial peptides are important in vivo was the isolation of mutants of *D. melanogaster* that succumbed to bacterial infection even after vaccination. This pathway is called *imd* (immune deficiency) (14). A second signaling pathway that includes *spätzle, toll, and cactus*, also important in *Drosophila* differentiation, mediates resistance to fungal infection that is abrogated by mutants (15). This pathway leads to the secretion of drosomycin, an antifungal peptide.

Later, a mutation was also found in a human gene essential for the protection of the intestine from bacteria. In the intestine, α-defensins are mainly synthesized by Paneth cells at the bases of crypts of the terminal ileum, and soon Crohn’s disease (regional ileitis) was ascribed to a deficiency of α-defensin secretion by Paneth cells that was linked to a mutation in NOD2, an intracellular receptor of the innate immune system whose ligand is the universal bacterial component muramyl dipeptide (16–19). However, only one-third of patients with this disease carry this mutation. A second mutation that leads to the same phenotype was described in the signaling pathway Wnt/TCF, a regulator of Paneth cell differentiation (20, 21). Both NOD2 and TCF4 deficiencies in mice induced by knockouts have been shown to result in dysregulation of bacteria in the intestinal tract (20, 22). Moreover, it has recently been suggested that reduction in copy number of the genes encoding β-defensins may be related to an important disease of the large colon, ulcerative colitis (19).

Finally, a defect in the synthesis of LL37 has also been linked to a human disease, Kostmann’s disease (23). Rolf Kostmann was a humanist as well as a philosopher. He spent three months each summer sailing with Anita (his wife and research companion) on his boat *Ariana*, mainly between Stockholm and Helsinki, reading and thinking about life and about science. Ann and I had the pleasure of joining him on one such trip. He was as accurate in sailing the channels of the Finnish Archipelago as he was in his science.

**References**


