Peptide Evolution

Molecular Mimicry by Venom Peptides

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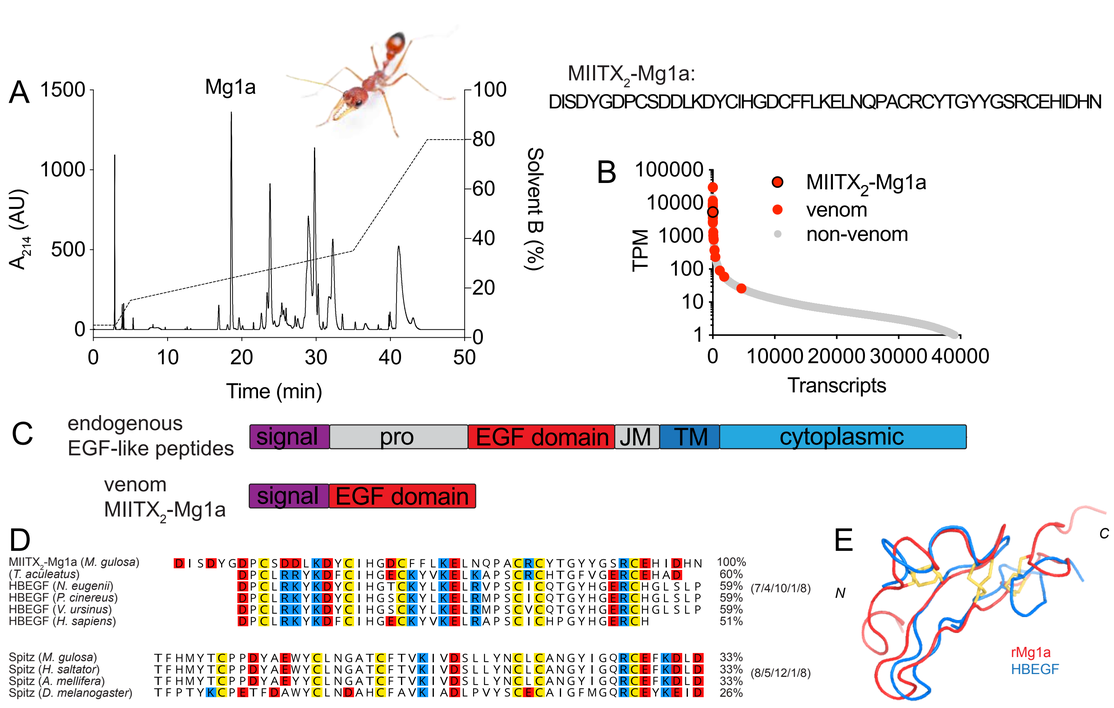
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https://doi.org/10.17952/38EPS.2026.P494

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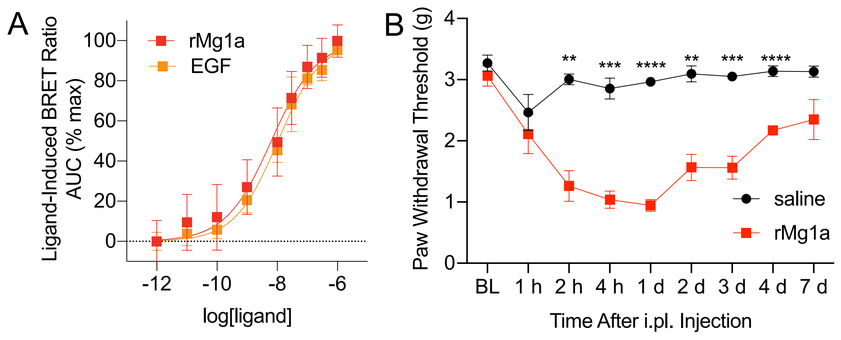


Natural selection can drive the evolution of similar traits through convergent evolution. Peptides identical to certain vertebrate hormones are present as toxins in the venoms of species of ants and wasps (hymenopterans) and the defensive skin secretions of frogs. The genes encoding the hymenopteran and frog peptide toxins do not share common ancestry with those of the vertebrate hormones but instead independently evolved, sometimes multiple times, from other peptide toxin genes.

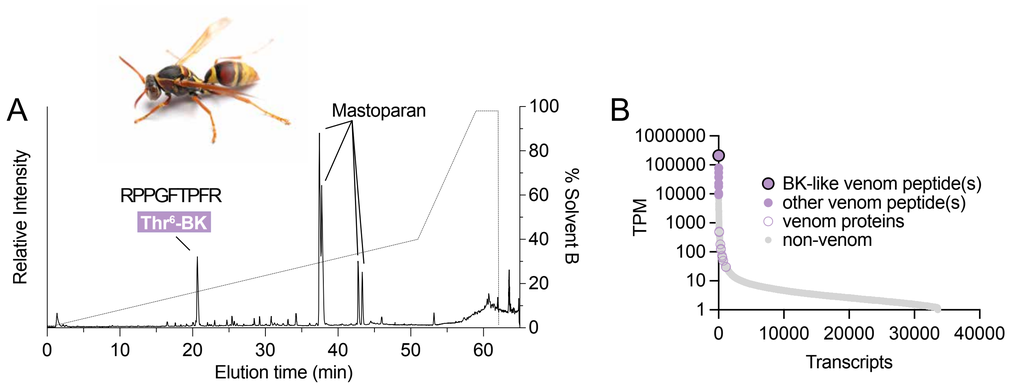
These peptides serve a defensive function against vertebrate predators and their resemblance to vertebrate hormones was driven by selection for efficacy at the predators' receptors. These studies highlight how with a suitable genetic substrate and shared environmental pressure, natural selection can result in repeated convergent evolution of identical peptides even across distantly related species.[1,2]



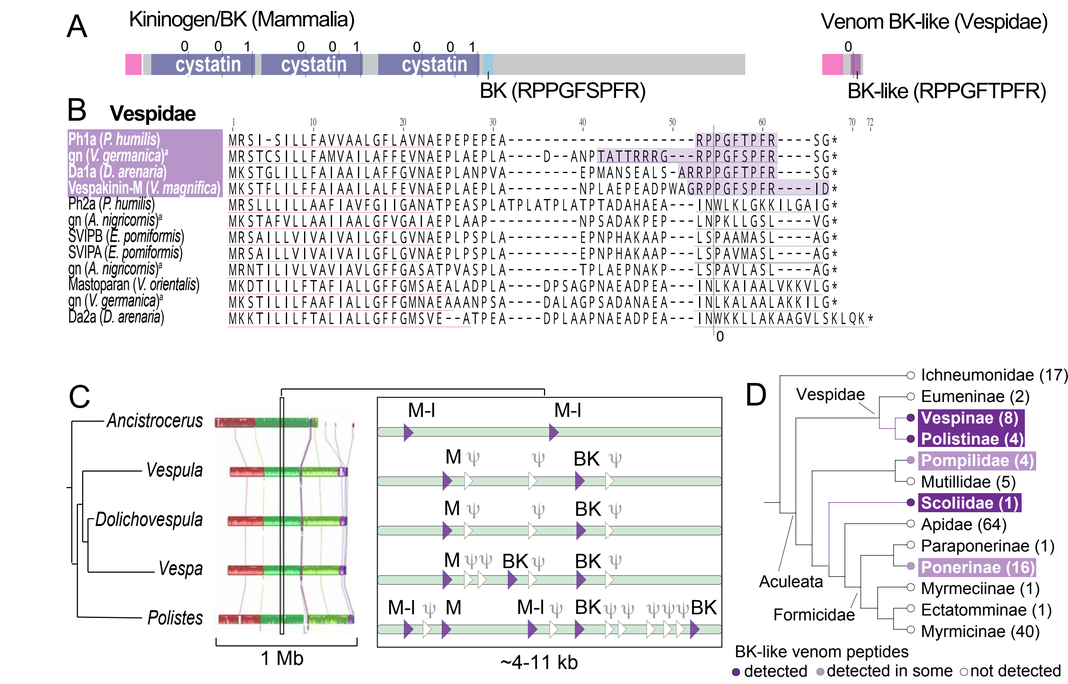
1 Mg1a, a major component of the venom of the Giant red bull ant (*Myrmecia gulosa*), is an analog of vertebrate EGF-like peptide hormones. (A) An RP-HPLC chromatogram of *M. gulosa* venom. The peak corresponding to Mg1a is labeled. (B) The Mg1a-encoding transcript is found in the highly expressed portion of the venom-apparatus transcriptome (highlighted in red). TPM, transcripts per million. (C) The precursor structures of endogenous EGF-like peptide hormones and Mg1a. JM, juxtamembrane domain; pro, propeptide; TM, transmembrane domain. (D) Sequence alignment of Mg1a (mature peptide) with the EGF-like domain of the short-beaked echidna (*T. aculeatus*) peptide and HBEGF of other mammals. Alignment of Spitz sequences from *M. gulosa* and other insects. Percentage sequence identity with Mg1a is indicated (Right). The intercysteine loop length of each group is indicated (Far Right). (E) Alignment of the closest-to-average structures of Mg1a (red) and HBEGF (blue).



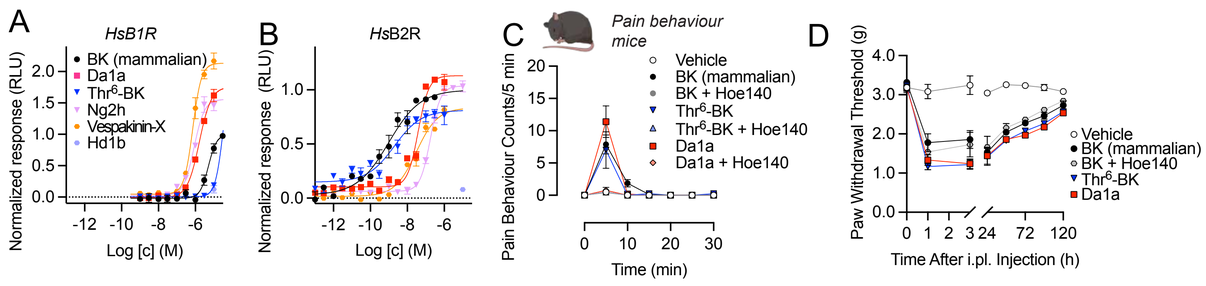
2 Mg1a is a potent ligand of mammalian ErbB1 and intraplantar injection of Mg1a in mice caused long-lasting hypersensitivity. (A) Concentration–response curves of ligand-induced BRET ratio for HEK293T cells transiently expressing hErbB1/Rluc8 and Grb2/Venus following stimulation with rMg1a or hEGF. Data are mean ± SEM (n = 3). (B) Paw-withdrawal threshold to mechanical stimulus. Data are mean ± SEM (n = 6 per group). **P < 0.01, ***P < 0.001, ****P < 0.0001, two-way ANOVA, Sıdak's multiple comparisons. Note: The x axis is nonlinear.



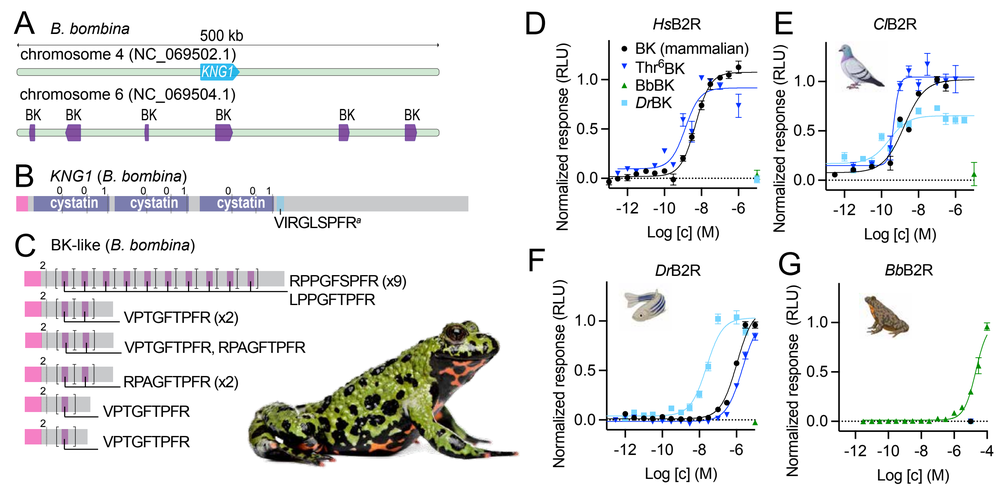
3 Bradykinin (BK) is a vertebrate hormone but is present in wasp venoms. (A) Total ion chromatogram from liquid chromatography–tandem mass spectrometry analysis of Australian paper wasp (*P. humilis*) venom, with peaks corresponding to major venom peptides labeled and that corresponding to Thr^6-BK highlighted. (B) The Thr^6-BK–encoding transcript was the single most highly expressed transcript in the *P. humilis* venom gland transcriptome. Bradykinin-like peptides are major components of the venoms of diverse hymenopteran species.



4 Wasp venom BK-like peptides evolved multiple times from ancestral venom peptide precursors, independently of vertebrate BK. (A) Transcript structure of mammalian BK and, at the same scale for comparison, that of a representative vespid venom BK- like peptide (Ph1a). Signal peptides are colored pink. Exon/intron boundaries are indicated by a dashed line and labeled with phase. (B) Alignment of the precursor sequences of BK-like peptide precursors of Vespidae with related wasp venom peptide precursors. Signal peptides and mature peptides are underlined in pink and gray, respectively. BK-like peptides are highlighted in purple. (C) Alignment of 1-Mb genomic region containing BK-like peptide genes of representative Vespidae. (Inset) Alignment of local genomic region. M- I, mastoparan-like genes; M, mastoparan genes; BK, BK genes; ψ, pseudogenes. (D) Cladogram of selected hymenopteran families and subfamilies showing presence or absence of BK- like venom peptides. The number of genomic or transcriptomic datasets used for each lineage is indicated in parentheses.



5 Wasp venom BK-like peptides functionally mimic mammalian BK. Venom BK-like peptides are agonists of mammalian BK receptors. Concentration-response relationships for venom BK-like peptides at (A) *Hs*B1R and (B) *Hs*B2R. (C) Spontaneous pain behaviors in mice after shallow intraplantar injection of BK (200 pmol), Thr^6-BK (200 pmol), or Da1a (200 pmol) with and without coapplication of Hoe140 (400 pmol). P values are derived from a one-way ANOVA with Dunnett's multiple comparison test (n = 4 to 8 mice per group). (D) Shallow intraplantar injection of Thr^6-BK (20 pmol) or Da1a (20 pmol) caused mechanical allodynia in mice equivalent to BK (20 pmol). The effect of BK was not inhibited by coapplication with Hoe140 (200 pmol).



6 Frog skin BK-like peptides do not share common ancestry with the endogenous frog BK but evolved independently to mimic specific vertebrate BKs. (A) Fire-bellied toad (*B. bombina*) KNG1 ortholog and BK-like peptide genes are present at distinct genetic loci. (B) Transcript structure of *B. bombina* kininogen. (C) Transcript structure of *B. bombina* BK-like peptides (at the same scale). (D) Concentration-response relationships for BKs at *Hs*B2R andequivalent data for (E) *Cf*B2R, (F) *Dr*B2R, and (G) *Bb*B2R.

These studies highlight the importance of EGF and BK receptor signalling in vertebrate physiology (including in pain) and the importance of vertebrate predation in Hyemnoptera and frog evolution. They illustrate how natural selection can mold the gene product of one organism to resemble that of another (in this case, the gene product of the prey resembles that of the predator). They are examples of both convergent evolution and molecular mimicry that brings to mind the ancient proverb "To know your enemy, you must become your enemy."

[1]Eagles, D. A., ... S. D. Robinson (2022). A peptide toxin in ant venom mimics vertebrate EGF-like hormones to cause long-lasting hypersensitivity in mammals. *Proceedings of the National Academy of Sciences of the United States of America* 119(7).
[2]Shi, N., ... S. D. Robinson (2026). Repeated convergent evolution of bradykinin mimics as defensive toxins. *Science* 391(6789): 1046-1052.

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