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Editorial

From Venom to Medicine: Reptile Toxins as a Source of Therapeutic Innovation

Od strupa do zdravila: plazilski toksini kot vir terapevtskih inovacij

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Natural toxins have for centuries evoked fear, fascination, and scientific curiosity. Today, it is well recognized that reptile venoms are not merely weapons for predation or defense, but also an exceptionally rich source of bioactive molecules with significant potential for drug development. Over millions of years of evolution, complex mixtures of peptides, enzymes, and proteins have emerged that precisely target key physiological pathways, including blood coagulation, neural signaling, metabolism, and cellular communication (1, 2). This remarkable specificity positions venoms among the most important sources of inspiration for modern translational medicine and emphasizes the importance and power of comparative research (3–7).

One of the earliest and most paradigmatic examples of successful translation from nature to clinical practice is the development of angiotensin-converting enzyme (ACE) inhibitors. Research on peptides from the venom of the Brazilian pit viper (*Bothrops jararaca*) led to the discovery of bradykinin-potentiating factors, which were instrumental in the development of captopril, the first ACE inhibitor. This drug profoundly transformed the treatment of arterial hypertension and heart failure (4, 5). A similar translational breakthrough is represented by glucagon-like peptide-1 (GLP-1) receptor agonists, such as exenatide (Byetta) and semaglutide (Ozempic), whose development is based on the peptide exendin-4 from the venom of the Gila monster (*Heloderma suspectum*) (8, 9). These therapies are now reshaping the management of type 2 diabetes and obesity and exemplify how research on animal toxins can lead to therapeutics with substantial societal impact.

Naravni toksini že stoletja vzbujajo strah, fascinacijo in znanstveno radovednost. Danes vemo, da strupi plazilcev niso zgolj orožje za lov ali obrambo, temveč predstavljajo izjemno bogat vir bioaktivnih molekul z velikim potencialom za razvoj novih zdravil. Evolucija je skozi milijone let oblikovala kompleksne mešanice peptidov, encimov in proteinov, ki natančno ciljajo ključne fiziološke poti, vključno s strjevanjem krvi, živčnim signaliziranjem, presnovo in celično komunikacijo (1, 2). Prav ta visoka specifičnost omogoča, da strupi predstavljajo enega najpomembnejših virov navdiha za sodobno translacijsko medicino ter poudarjajo pomen in moč primerjalnih raziskav (3–7).

Eden najzgodnejših in najbolj paradigmatskih primerov prenosa znanja iz narave v klinično prakso je razvoj zaviralcev angiotenzin-konvertirajočega encima (ACE). Raziskave peptidov iz strupa brazilske jararake (*Bothrops jararaca*) so vodile do odkritja bradikinin-potencirajočih dejavnikov, ki so bili ključni za razvoj kaptoprila, prvega ACE inhibitorja. Ta je bistveno spremenil zdravljenje arterijske hipertenzije in srčnega popuščanja (4, 5). Podoben translacijski preboj predstavljajo agonisti receptorja GLP-1, kot sta eksenatid (Byetta) in semaglutid (Ozempic), katerih razvoj temelji na peptidu exendin-4 iz strupa kuščarja Gila (*Heloderma suspectum*) (8, 9). Danes ta zdravila pomembno preoblikujejo zdravljenje sladkorne bolezni tipa 2 in debelosti ter ponazarjajo, kako lahko raziskave živalskih toksinov vodijo do terapevtskih rešitev z izrazitim družbenim vplivom.

In recent years, interest in venom research has been further strengthened by rapid advances in computational and structural biology, artificial intelligence, and protein modeling, which now enable increasingly efficient deconvolution of complex toxin mixtures and identification of functional motifs. At the same time, the growing emphasis on the 3Rs principles and the reduction of animal use in biomedical research has fostered interest in naturally evolved molecular libraries as efficient sources of bioactive scaffolds. Together with the increasing clinical demand for safer and more selective therapeutics, particularly in anticoagulant therapy, these developments have once again placed venom research at the forefront of drug discovery.

Snake venoms are also particularly important in the context of hemostasis and thrombosis, as they contain numerous proteins that precisely modulate coagulation pathways. As highlighted by Kini (1) and Sajevic et al. (2), these molecules represent powerful tools for understanding blood coagulation mechanisms while simultaneously providing a rich resource for the development of novel antithrombotic agents.

In this issue of Slovenian Veterinary Research, Križaj and Požek present original research on the protein VaaSPH-1 from the venom of the nose-horned viper (*Vipera ammodytes*), which selectively inhibits the intrinsic coagulation pathway and therefore represents a promising starting point for the development of safer anticoagulants for the treatment of venous thromboembolism. The authors emphasize that current therapies are still associated with a significant risk of bleeding, underscoring the urgent need for new therapeutic approaches. The structural and functional properties of VaaSPH-1 enable the design of innovative low-molecular-weight candidates, which are already progressing toward patent protection. This work elegantly illustrates how in-depth understanding of natural toxins, evolutionarily optimized for precise modulation of physiological systems, can drive breakthroughs in translational medicine. Such approaches complement existing therapeutic strategies and highlight the importance of integrating veterinary, biological, and biomedical sciences in the discovery of new drug candidates (6).

Research on animal venoms thus represents a unique intersection of evolutionary biology, veterinary medicine, and pharmacology. It also reminds us that nature remains one of the richest sources of molecular solutions to contemporary medical challenges. Continued progress in this field will be essential not only for the development of new therapeutics, but also for a deeper understanding of fundamental biological processes that connect animal and human health.

V zadnjih letih je zanimanje za raziskave živalskih strupov dodatno okrepil hiter napredek na področju računalniške in strukturne biologije, strukturnega modeliranja in umetne inteligence, ki omogočajo vse učinkovitejšo analizo kompleksnih mešanic toksinov ter identifikacijo njihovih funkcionalnih motivov. Hkrati vse večji poudarek na načelih 3R in zmanjševanju uporabe živali v biomedicinskih raziskavah spodbuja razvoj alternativnih pristopov, pri katerih naravne molekularne knjižnice predstavljajo izjemno učinkovite vire bioaktivnih struktur. V kombinaciji z naraščajočimi kliničnimi potrebami po varnejših in bolj selektivnih terapevtikih, zlasti na področju antikoagulantne terapije, so ti trendi ponovno postavili raziskave strupov v ospredje sodobnega odkrivanja zdravil.

Strupi kač so še posebej pomembni tudi v kontekstu hemostaze in tromboze, saj vsebujejo številne proteine, ki natančno modulirajo koagulacijske poti. Kot poudarjata Kini (1) in Sajevic s sodelavci (2), predstavljajo te molekule izjemno orodje za razumevanje mehanizmov strjevanja krvi ter hkrati bogat vir za razvoj novih antitrombotičnih učinkovin.

V tej številki revije Slovenian Veterinary Research Križaj in Požek predstavljata izvirno raziskavo o proteinu VaaSPH-1 iz strupa modrasa (*Vipera ammodytes*), ki selektivno zavira intrinzično pot koagulacije in tako predstavlja obetavno izhodišče za razvoj varnejših antikoagulantov pri zdravljenju venske trombembolije. Avtorja izpostavljata, da obstoječe terapije še vedno spremlja pomembno tveganje za krvavitve, kar poudarja potrebo po novih pristopih. Strukturne in funkcionalne lastnosti VaaSPH-1 omogočajo razvoj inovativnih nizkomolekularnih kandidatov, ki že napredujejo v smeri patentne zaščite. Prispevek lepo ponazarja, kako lahko poglobljeno razumevanje naravnih toksinov, ki so evolucijsko optimizirani za natančno modulacijo fizioloških sistemov, vodi do prebojev v translacijski medicini. Takšni pristopi dopolnjujejo obstoječe terapevtske strategije ter poudarjajo pomen povezovanja veterinarske, biološke in biomedicinske znanosti pri odkrivanju novih zdravilnih učinkovin (6).

Raziskave živalskih strupov tako predstavljajo edinstveno stičišče evolucijske biologije, veterinarske medicine in farmakologije. Ob tem nas opominjajo, da narava ostaja eden najbogatejših virov molekularnih rešitev za sodobne medicinske izzive. Nadaljnji napredek na tem področju bo pomemben ne le za razvoj novih terapevtikov, temveč tudi za poglobljeno razumevanje temeljnih bioloških procesov, ki povezujejo zdravje živali in ljudi.

Ključne besede: strupi plazilcev; kačji strupi; translacijska medicina; hemostaza; tromboza; razvoj zdravil; GLP-1; antikoagulanti

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