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RESEARCH NEWS

# A scorpion toxin takes the sting out of T cell activation

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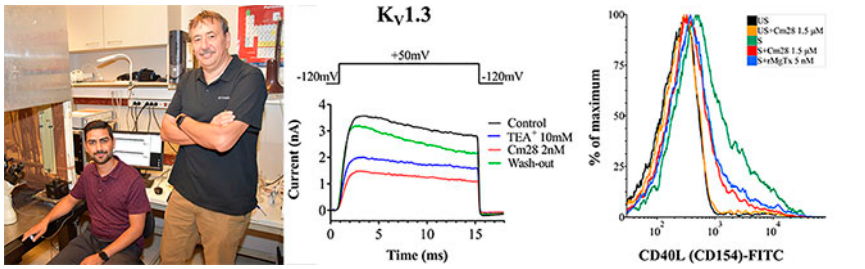
***JGP* study identifies a novel peptide in scorpion venom that inhibits $K_V1.2$ and $K_V1.3$ channels and could form the basis for new treatments for autoimmune diseases.**

Scorpions produce hundreds of biomolecules, many of which target voltage-gated potassium ($K_V$) channels. In this issue of *JGP*, Naseem et al. (1) characterize a novel scorpion toxin that blocks $K_V1.2$ and $K_V1.3$ channels and inhibits T cell activation, a property that could be exploited to develop new treatments for neuroinflammatory diseases and autoimmune disorders.

$K_V1.3$ channels are expressed in peripheral immune cells and are implicated in T cell activation, when an efflux of $K^+$ is required to balance the influx of $Ca^{2+}$ that drives T cell proliferation and cytokine production (2). $K_V1.3$ inhibitors therefore have the potential to suppress the immune system and treat a variety of autoimmune diseases such as multiple sclerosis and rheumatoid arthritis. $K_V1.3$ channels are also expressed in brain-resident immune cells called microglia, and are therefore also considered potential targets for neuroinflammatory disorders like Parkinson's disease.

"My lab's long-term goal is to find high-affinity, selective inhibitors of $K_V1.3$ channels," explains Gyorgy Panyi of the University of Debrecen in Hungary. Such inhibitors might be found in scorpion venom: Researchers have so far identified nearly 200 scorpion toxins that target $K_V$ channels (3). This includes the α-KTx family of toxic peptides that are typically 30–40 amino acids in length, form an α/β scaffold structure stabilized by 3–4 disulfide bridges, and contain a functional lysine–tyrosine dyad that is crucial for blocking the channel pore and determining the toxin's selectivity.




Muhammad Umair Naseem (seated), Gyorgy Panyi (standing), and colleagues identify a novel scorpion toxin, Cm28, that has a unique primary structure and selectively inhibits $K_V1.3$ channels with high affinity. Electrophysiology (center) shows that Cm28 inhibits $K_V1.3$ currents in human T cells, and, accordingly, flow cytometry (right) shows that it reduces expression of the early activation marker CD40L upon T cell stimulation.

Panyi and colleagues, including Muhammad Umair Naseem, a graduate student who received a Stipendium Hungaricum Scholarship from the Tempus Public Foundation, set out to characterize a novel peptide isolated from the Columbian scorpion *Centruroides margaritatus* by Lourival Possani's group at the Universidad Nacional Autónoma de México (4). Phylogenetic analysis of this peptide, named Cm28, shows that it clusters with the α-KTx family, and structural modeling suggests that it adopts a similar α/β structure with three disulfide bonds (1). "However, Cm28's primary structure is unique," says Panyi. "It is only 27 amino acids in length, and it lacks the functional dyad typical of α-KTxs."

Cm28 may therefore be the first member of a new subfamily of α-KTxs. Naseem et al. (1) found that it reversibly inhibits $K_V1.2$ and $K_V1.3$ channels with high affinity, showing $K_d$ values of 0.96 and 1.3 nM, respectively. The peptide shows an ∼400-fold lower affinity for $K_V1.1$ channels, and has no effect on a variety of other $K^+$, $Na^+$, and $H^+$ channels at a concentration of 150 nM.

Most toxins known to inhibit $K_V$ channels do so by either blocking the channel pore or by binding to the voltage-sensing domain and modulating channel gating. The researchers determined that Cm28 has no effect on the voltage dependence of channel activation, suggesting that it isn't a gating modifier. Instead, and despite its lack of the typical lysine–tyrosine dyad, Cm28 likely functions as a pore blocker, since the toxin's binding kinetics were consistent with a simple, bimolecular interaction between the peptide and $K_V1.2/K_V1.3$ channels.

In keeping with $K_V1.3$'s role in T cells, Naseem et al. found that Cm28 inhibited the activation of human effector memory T lymphocytes. Without affecting cell viability,

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Cm28 reduced the expression of two key early activation markers following T cell stimulation. This suggests that the toxin could form the basis of new treatments for autoimmune diseases. However, Panyi cautions, much work remains to be done, beginning with the production of functional recombinant Cm28 to supplement the meager amounts of toxin that can be purified from scorpion venom.

"Then, we can determine how Cm28 binds and inhibits $K_V1.3$ channels," Panyi says. "After that, we can engineer the toxin to improve its channel selectivity and pharmacokinetics and begin testing it in animal models."

## References


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