Novel human EAG1 channel antagonists from spider venoms

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hEAG1 (Kv10.1) is a member of the large family of voltage-gated potassium channels. Functional channels are homotetramers, with each monomer comprised of six transmembrane segments. hEAG channels are distinctive in that they are almost exclusively expressed in the central nervous system in healthy people, with gain-of-function mutations leading to epilepsy. Remarkably, however, hEAG is overexpressed in 70% of human tumors of various tissue origin, and this overexpression has been demonstrated to be causative for tumorigenesis. Thus, selective antagonists of the channel are much sought after both as pharmacological tools for studying channel function and as potential leads for anti-cancer and anti-epileptic drugs. We recently identified and purified two hEAG inhibitors from the venoms of tarantula spiders. As revealed by a combination of MALDI-TOF mass spectrometry, Edman sequencing and carboxypeptidase Y digestion, both toxins are C-terminally amidated peptides composed of 36 amino acid residues. Their structures solved by NMR spectroscopy revealed classical inhibitor cystine knot folds in which the peptides are cross-braced by three disulfide bonds. These hEAG inhibitors do not block the channel pore; rather, they act as gating modifiers that affect channel activation and inactivation, presumably by interacting with the channel's voltage-sensor domain. We show that these peptides specifically inhibit the proliferation of certain cancer cell lines, but not others.