Scutellarein attenuates atopic dermatitis by selectively inhibiting transient receptor potential vanilloid 3 channels

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**Background and Purpose:** Atopic dermatitis (AD) is one of the most common chronic inflammatory cutaneous diseases with unmet clinical needs. As a common ingredient found in several medicinal herbs with efficacy on cutaneous inflammatory diseases, Scutellarein (Scu) has been shown to possess anti-inflammatory and anti-proliferative activities. We aimed to evaluate the therapeutic efficacy of Scu against AD and its underlying molecular mechanism.

**Experimental Approach:** Efficacy of Scu on AD was evaluated in 2,4-dinitrofluorobenzene (DNFB) and carvacrol-induced dermatitis mouse models. Cytokine mRNA and serum IgE levels were examined using qPCR and ELISA, respectively. Voltage clamp recordings were used to measure currents mediated by transient receptor potential (TRP) channels. In silico docking, site-direct mutagenesis, and covalent modification were used to explore the binding pocket of Scu on TRPV3.

**Key Results:** Subcutaneous administration of Scu efficaciously suppresses DNFB and carvacrol-induced pruritus, epidermal hyperplasia and skin inflammation in wild type mice but has no additional benefit in *Trpv3* knockout mice in the carvacrol model. Scu is a potent and selective TRPV3 channel allosteric negative modulator with an apparent affinity of 1.18 μM. Molecular docking coupled with site-direct mutagenesis and covalent modification of incorporated cysteine residues demonstrate that Scu targets the cavity formed between the pore helix and transmembrane helix S6. Moreover, Scu attenuates endogenous TRPV3 activity in human keratinocytes and inhibits carvacrol-induced proliferative and proinflammatory responses.

**Conclusion and Implications:** Collectively, these data demonstrate that Scu ameliorates carvacrol-induced skin inflammation by directly inhibiting TRPV3, and TRPV3 represents a viable therapeutic target for AD treatment.

**Keywords:** atopic dermatitis, keratinocytes, scutellarein, TRPV3

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