Epidermal SNARE-dependent vesicle release drives itch and inflammation, but not pain in a mouse model of atopic dermatitis

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Epidermal cell-derived inflammatory and excitatory signaling molecules play an important role in both the initiation and progression of atopic dermatitis (AD). However, the molecular signaling mechanisms by which epidermal cells release these molecules are not well understood in AD. Thus, we utilized a genetic mouse model to selectively inhibit canonical SNARE-mediated vesicle release from epidermal cells by expressing tetanus neurotoxin (TeNT) under control of the keratin 14 (K14) promoter (*K14^{Cre};R26$^{TeNT/+}$* mice). Using the MC903 model of AD, we assessed lesion severity, itch and pain behavior, immune cell skin infiltration, and the release of inflammatory mediators into the skin. We found MC903-treated *K14^{cre};R26$^{TeNT/+}$* mice spent significantly less time scratching compared to MC903-treated littermate controls (*R26$^{TeNT/+}$* mice). We also observed a significant decrease in basophil recruitment to skin lesions, despite no significant differences in lesion severity across genotypes. Strikingly, while MC903-treated *K14^{cre};R26$^{TeNT/+}$* mice displayed diminished itch, we observed similar degrees of pain-associated wiping across genotypes. Together, our data suggest that epidermal cells use TeNT-dependent vesicle release to modulate itch and facilitate immune cell recruitment, but not pain, in AD. Our current work is now focused on defining the TeNT-dependent and -independent inflammatory mediators that promote AD-associated itch and pain.