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A protective role for sensory nerve denervation in Aldara™-induced mouse dorsal skin inflammation

Psoriasis is a common chronic skin disease, affecting 2-3% of the UK population (1). While clinical studies have shown topical capsaicin and sensory denervation improved lesions, the mechanisms involved are unknown (2). This study used a pharmacological approach to elucidate the role of sensory nerves using a recent murine model of psoriasis (3). We hypothesised that chemical-mediated sensory denervation by repeated resiniferatoxin(RTX) injection would attenuate inflammation in this model, as previously observed in the mouse ear (4).

I*n vivo* procedures were carried out according to the UK Home Office Animals (Scientific Procedures) Act 1986. Male C57BL/6J (n=4-7;6-8 weeks) mice were used in recovery procedures performed under 2% isoflurane. Dorsal skin hair was removed prior to measuring blood flow using Full Field Perfusion Imager. Doublefold skin thickness was measured and epidermal thickness confirmed by H&E staining. 75mg of Aldara™ (5% imiquimod) cream (Meda Pharma, UK) or Vaseline (for control) was applied over a 2x2cm^2 area daily for 4 days. Sensory nerve denervation was performed by *s.c.*300µg/kg of RTX or vehicle (10% DMSO/10% Tween-80 in saline) into the nape of the neck prior to dorsal skin treatment and confirmed by exposing mouse paw to hot plate (55^{o}C) test (5). Skin samples were frozen at -20^{o}C until analysis. Data were analysed using 2-way or repeated measures ANOVA with Bonferonni's *post-hoc* test.

Aldara^{TM} induced skin thickening and inflammation (measured by N-acetyl-β-glucosiminidase, NAG, assay, indicative of mononuclear leukocytes), and blood flow, which was significantly reduced by RTX-mediated denervation (Table 1).

In conclusion, we have developed a feasible murine model with characteristics of psoriasis in C57BL/6J mice, with enhanced inflammation and blood flow in the dorsal skin. We provide evidence that sensory nerve plays an important role in driving skin inflammation in this model. At present, the precise mechanisms are unknown.

Table 1: The effects of sensory nerve denervation in Aldara™-induced skin inflammation. For blood flow and doublefold skin thickness, results are shown for 24-hour post-day 4 treatment. * p<0.05, ** p<0.01, *** p<0.001 between vaseline vs Aldara™ of the same treatment/genotype group. # p<0.05, ## p<0.01, ### p<0.001 between vehicle vs RTX-treated groups.

	Vaseline		Aldara™	
	Vehicle-treated	*RTX-treated*	*Vehicle-treated*	*RTX-treated*
Blood flow (flux units)	397.2 ± 46.2	570.5 ± 26.1	708.2 ± 43.0 *** ###	537.5 ± 26.9
Doublefold skin thickness (mm)	0.10 ± 0.06	0.04 ± 0.09	0.6 ± 0.06*** ###	0.07 ± 0.04
Epidermal thickness (µm)	24.4 ± 5.3	23.1 ± 4.4	89.7 ± 2.6 *** ###	44.5 ± 2.4 ***
Spleen weight/body weight	0.003 ± 0.0004	0.003 ± 0.0003	0.007 ± 0.0003 *** ###	0.004 ± 0.0004
NAG Assay (Unit/mg protein)	0.027 ± 0.013	0.028 ± 0.02	0.178 ± 0.043 * #	0.043 ± 0.015

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