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Apremilast is protective in pemphigus by a Plakoglobin-dependent stabilization of keratinocyte adhesion.

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Abstract: Desmosomes provide adhesive strength to tissues constantly exposed to mechanical stress such as the heart and the epidermis. The importance of desmosomes is reflected by several severe diseases, in which desmosomal adhesion is compromised. Among them, pemphigus vulgaris, a bullous autoimmune disease, in which autoantibodies directed against the desmosomal cadherins desmoglein (Dsg) 1 and 3 cause loss of intercellular adhesion clinically manifested as flaccid blisters of the skin and mucous membranes. At present, therapies focus on suppression of autoantibody formation. However, especially for the acute phase of the disease an additional treatment paradigm directly stabilizing keratinocyte adhesion would fulfill an unmet medical need. We here demonstrate that apremilast, a phosphodiesterase 4 inhibitor used in psoriasis, is protective against pemphigus autoantibody-induced loss of intercellular adhesion in human keratinocytes *in vitro*. In addition, apremilast abrogates pemphigus autoantibody-induced blistering in *ex-vivo* human epidermis and *in vivo* in mice. In parallel, apremilast inhibits keratin retraction as well as desmosome splitting. Further, apremilast induces phosphorylation of plakoglobin at serine 665 - a mechanisms which is known to stabilize cardiomyocyte cohesion. Thus, we established a plakoglobin phospho-deficient mouse model. Phospho-deficient mice reveal a fragile epidermis with altered organization of keratin filaments and desmosomal cadherins. In keratinocytes derived from these mice, intercellular adhesion is impaired and not rescued by apremilast. These data identify an unreported mechanism of desmosome regulation and propose that apremilast stabilizes keratinocyte adhesion via keratin anchorage in pemphigus. Thus, Apremilast may serve as treatment option during the acute phase in pemphigus.

Keywords: Pemphigus vulgaris; apremilast, desmosome, plakoglobin; desmoglein