Title of Abstract: Defensin Signaling in psoriatic inflammation and itch

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Abstract: β-defensins are among the top up-regulated genes in psoriatic skin but the functions of these highly abundant peptides in psoriasis pathogenesis remain unclear, mostly due to lack of genetic models. The mouse genome contains >50 functionally redundant *Def* genes, making genetic analyses difficult. In this study, we used a *Defensin* cluster knockout mouse to evaluate the potential roles of defensins as neuroimmune modulators in psoriasis. Deletion of the *Defensin* gene cluster (*Def* cKO) in keratinocytes significantly attenuated imiquimod (IMQ)-induced psoriatic inflammation, with reduced hyperkeratosis, erythema and scaling. Flow cytometry analyses revealed that defensins amplify neutrophil infiltration and NETosis through the Mrgpra2 receptor, and promote IL-17+ TCRγδ T cell differentiation through activation of epidermal Langerhans' cells. These findings reveal critical roles of defensins in amplifying Th17 immunity. Behavioral analysis further revealed that loss of defensins reduced psoriatic itch, and we showed that human β-defensin 2 directly activated small-diameter Mrgpra3+ (NP2 type) neurons to elicit robust scratching. Overall, our study shows that keratinocyte-derived β-defensins play important roles in mediating psoriatic inflammation and itch by activating neutrophils, type 17 immune response, and pruriceptive sensory neurons. These finds fill a critical knowledge gap about the functions of these highly abundant peptides in psoriasis, and suggest defensin receptors as potential targets for treatment.

