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TLR7/8 agonists stimulate plasmacytoid dendritic cells to initiate a Th17-deviated acute contact dermatitis in humans

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A standardized human model to study early pathogenic events in psoriasis is missing. Activation of Toll-like receptor 7/8 by topical application of imiquimod is the most commonly used mouse model of psoriasis. Here, we investigated the potential of a human imiquimod patch test model to resemble human psoriasis. We demonstrate imiquimod induces a monomorphic and self-limited inflammatory response independent of the disease background. The clinical and histologic phenotype as well as transcriptome of imiquimod-induced inflammation resembles an acute contact dermatitis rather than psoriasis. Nevertheless, the imiquimod model mimics hallmarks of psoriasis. Plasmacytoid dendritic cells (pDC) are primary sensors of imiquimod, responding with stress signals and pro-inflammatory cytokine production. This cascade results in a Th17 immune response with IL-23 as a key driver. In a *proof-of-concept* setting, systemic treatment with ustekinumab dramatically diminished the imiquimod-induced inflammation. Taken together, in humans imiquimod induces contact dermatitis with the unicity that pDC are the primary sensors, leading to an IL-23/Th17 deviation. Despite these shortcomings, the human imiquimod model might be useful to investigate early pathogenic events and prove molecular concepts in psoriasis.