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Development of an *in vitro* immunocompetent human skin equivalent

Abstract

Current murine experimental models that are available for inflammatory skin diseases, such as atopic dermatitis, can show markedly different responses to drug treatments that may contribute to the high failure rate of drug development. Therefore, new pre-clinical human immunocompetent skin models are required to aid drug screening. The aim of this work was to generate tissue-engineered human skin equivalents containing functional immune cells to study epidermal responses to topically applied drugs.

Purified peripheral blood human monocytes were differentiated into monocyte-derived dendritic cells (mo-DC) using GM-CSF and IL-4. Purified naïve CD4 T cells were CD3/CD28 activated, stimulated with IL-2 and polarised into Th2 cells using IL-4 and anti-IFNγ. Cell phenotypes were assessed by qPCR, flow cytometry and ELISA for key cell-specific markers. To generate *in vitro* tissue-engineered skin models, a type 1 collagen scaffold containing primary dermal fibroblasts was seeded with immortalised N/TERT skin keratinocytes and Mo-DC, and cultured at an air-to-liquid interface before analysis. Th2 cells were incorporated into the dermal component.

Mo-DC showed successful differentiation from monocytes by expression of cell-specific markers including increased CD1a, CD11c, CD207 and HLA-DR. Th2 cells displayed increased CCR4, CD119, CD154 and CD4, and secreted increased levels of IL-4, IL-5, IL-6, IL-13 and thymic stromal lymphopoietin (TSLP). Tissue-engineered skin equivalents displayed a keratinised, stratified squamous epidermis on top of a well-populated fibroblast containing dermis that histologically mimicked human skin. MoDC were successfully incorporated into the epidermis and Th2 cells into the dermal component as determined by flow cytometric and immunohistochemical analysis. The next aim is to show immune cell functionality in response to stimuli including well-characterised human allergens.