In vitro differentiated human pathogenic Th2 cells as a new model for studying signaling requirements and transcriptional mechanisms driving T cell pathogenicity in allergic inflammation

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Abstract text
Text: Pathogenic Th2 cells (pTh2) are key drivers of allergic diseases, including allergic asthma. Chronic antigen exposure, co-stimulatory signals, and the cytokine milieu in the tissues promote their differentiation. As a result, Th2 cells undergo changes in their chromatin architecture and metabolism, driving pathogenic effector function through upregulated expression of IL-5 and IL-13. These type 2 cytokines further induce features of allergic lung inflammation, such as eosinophil expansion and airway hyperresponsiveness. Studying human pTh2 cells in detail is challenging, primarily due to the lack of a standardized protocol for their *in vitro* differentiation and their low abundance in the peripheral blood of allergic patients. Therefore, we established an *in vitro* differentiation protocol for generating pTh2 cells from human naïve $CD4^+$ T cells, considering the inflammatory conditions present in the lungs of allergic patients and a recently developed mouse pTh2 differentiation protocol. Culture conditions were optimized, and cells were characterized extracellularly and intracellularly by spectral flow cytometry. This approach aimed to bridge the translational gap between animal studies and human applications. The differentiated cells closely resembled the extracellular phenotype (CD27 downregulation, CD25 upregulation) and cytokine profile ($IL\text{-}5^+$/$IL\text{-}13^+$) of pathogenic Th2 cells found in allergic patients and in lungs from sensitized mice, as described in the literature. Our *in vitro* model thus provides the basis for further studies to investigate transcriptional and epigenetic regulations as well as specific signaling pathways induced in these cells. Gaining novel insights into the characteristics and regulatory mechanisms of pTh2 cells across species will facilitate the identification of therapeutic targets and the development of new treatment approaches.

Conflict of Interest statement
Do you have any conflict of interest to declare?: No

Affirmation
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2. Consent to publication publication: Yes
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