239. IL-1β REGULATES THE DECTIN-1 INDUCED CYTOKINE PROFILE IN HUMAN DENDRITIC CELLS

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Background: C-type lectin receptors including dectin-1 are pattern recognition receptors that recognize β-glucans on the surface of fungi, yeasts and bacteria. Immune responses to β-glucans have been implicated both in a murine model of SpA (the SKG mouse) and AS patients have increased levels of antibodies to yeast. Dectin-1 stimulation initiates a plethora of immunological effector mechanisms from human dendritic cells (DCs), including phagocytosis and inflammatory cytokine secretion, required for protective immunity. β-glucan presentation to DCs determines their capacity to generate dectin-1-mediated inflammatory cytokines, and small particulate β-glucans are thought to be poor activators of innate immunity. We investigated β-glucan induction of immune responses in human DCs and the role of IL-1β in their regulation.

Methods: Human DCs were isolated from peripheral blood monocytes and differentiated with IL-4 and GM-CSF. DCs were stimulated with the dectin-1 agonists, curdlan (CUR) or β-1,3 glucan microparticles (MPs).

Results: We show that large particulate β-glucans stimulate the secretion of the inflammatory T helper 17 (Th17)-priming cytokines IL-1β, IL-6 and IL-23 from human DCs. In comparison, smaller β-glucans only stimulate negligible quantities of these cytokines, while stimulating equivalent amounts of the cytokine TSLP and chemokine CCL22. Surprisingly, pro-IL-1β upregulation is unaffected by β-glucan size, suggesting inflammasome activation to process pro-IL-1β is missing. Inhibition of phagocytosis during small β-glucan stimulation induces IL-1β, IL-6 and IL-23 secretion from DCs, suggesting that prolonged dectin-1 signalling from the cell surface is required for their production. In addition, we show that β-glucan induced IL-6, IL-23 and TSLP are regulated by IL-1β production.

Conclusion: These data demonstrate that different β-glucans induce different cytokine profiles from human DCs. Furthermore, IL-1β production regulates the composition of this inflammatory cytokine profile. The DC-derived cytokine milieu is critically important in orchestrating the nature of the adaptive immune responses to fungi. Since fungal infection and subsequent induction of Th17 responses is implicated in the pathogenesis of SpA in the SKG mouse and Th17 responses are critical in human SpA, understanding mechanisms that control this cytokine induction could suggest new therapies.

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