

Fungal modulation of toll like receptor-induced activation in dendritic cells.

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Initiation of protective defenses against pathogens require appropriate recognition of microbe-associated molecular patterns by pattern recognition receptors, like toll-like receptors (TLR) displayed by innate immune cells. TLR-mediated recognition by dendritic cells (DC) is a key element for appropriate activation of adaptive immune responses, and modification of TLR-induced responses may result in reduced ability to clear of pathogenic microbes. The impact on DC of concurrent presence of TLR ligands and response modifiers in pathogenic microbes is an area that is yet incompletely defined, but of relevance in relation to the mechanistic basis for development of persistent infections. In the present study, we looked into the specific immune regulation in DC by fungal-derived response modifiers when present alone or in conjunction with TLR-ligands. We tested the effect of fungal-derived components on DC's ability to produce cytokines, to induce surface marker expression, and to activate naive CD4+ T cell subsets (Th1, Th17, Th2, and Treg). Moreover, we studied the involvement of several receptors and kinases in the negative regulation of DCs.

Fungal-derived compounds were found to suppress TLR-induced IL-12p70 and IL-23, while synergistically enhancing IL-10 and IL-2 production from DC. The response modifiers *per se* induced up-regulation of CD40, CD80, CD86 and MHC class II on DC, but in presence of TLR-ligands, the display of CD40 was down-regulated, whereas CD86 was enhanced. Activation of naive CD4+ T cell subsets was significantly reduced by the fungal components in presence of TLR-ligands. While the dectin-1 receptor was found to be partly involved in the synergistic induction of IL-10 and IL-2 in DC in presence of TLR-ligands and response modifiers, the TLR-modulating effect of response modifiers was independent of CD11b and DCAL-2 receptors. The regulatory activity was also independent of MAPK (ERK1/2, JNK, p38), Akt, Raf-1 as well as Syk activation, some of which was previously shown to be involved in fungal-induced activation of DC.

Collectively, we here demonstrate that fungal-derived components modulate the TLR-induced immune response in DC by yet unrecognised receptors and signal modifiers leading to weak IL-12, IL-23, and CD40 expressing cells with reduced capacity to activate naive CD4+ T cells. These data indicate that fungal-derived compounds induce a non-effective phenotype in DC that may reduce the potency of host immune responses.