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Identification of intracellular signaling pathways activated in ESP-treated dendritic cells.

The murine nematode *Heligmosomoides polygyrus* serves as a model for studying human gastrointestinal helminth infections, which are highly endemic in areas of poor sanitation worldwide. *H. polygyrus* is recognized for its potent modulatory effects on host immune responses to unrelated antigens. Excretory-secretory products (ESP) released from adult *H. polygyrus* worms have been shown to be responsible for the immunosuppressive effects. Our previous studies showed that *H. polygyrus*-derived ESP modulates immune responses to unrelated antigens by inhibiting dendritic cell (DC) maturation and cytokine production in response to potent TLR ligands, but the intracellular signaling pathway(s) by which ESP modulates DC function are unknown. To identify the signaling pathways involved, bone marrow-derived dendritic cells (BMDC) were stimulated in vitro with medium, CpG-ODN, ESP, or ESP prior to CpG-ODN. Following overnight culture, BMDC lysates were prepared and analyzed by Western blotting for differential signaling cascades, namely, the MAPK and spleen tyrosine kinase (Syk) pathways. Neither p38 MAPK, Erk 1/2, nor pSAPK/JNK were differentially regulated as a result of DC stimulation with ESP. However, we observed increased PLC-γ1 expression, indicating activation of the Syk pathway known to be involved in response to C-type lectins. Collectively, our data suggest that DC may recognize ESP in a TLR-independent manner but that *H. polygyrus*-derived ESP may induce signaling in DC via the Syk pathway. In conclusion, these observations provide novel information that may be useful in identifying *H.* polygyrus-derived ESP proteins involved in modulating DC function.