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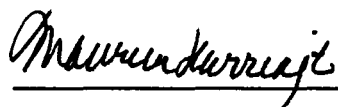
COORDINATION OF LPS, TNF α AND IL-1 β SIGNALING
BY IRAK-1 POSTTRANSLATIONAL MODIFICATION

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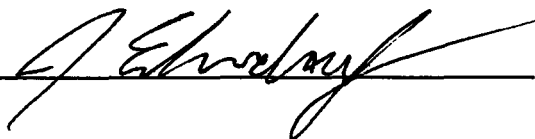


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ABSTRACT

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Coordination of LPS, TNF α and IL-1 β signaling by IRAK-1 posttranslational modification

Chronic activation of the innate immune response is implicated in the pathophysiology associated with many illnesses including cardiovascular and autoimmune diseases and severe sepsis. Bacterial derived lipopolysaccharide (LPS) activates the innate immune response through the induction of a cascade of pro-inflammatory cytokines that includes tumor necrosis factor-alpha (TNF α) followed by interleukin-1 (IL-1). The interleukin-1 receptor associated kinase-1 (IRAK-1) is an integral component of the LPS, TNF α and IL-1 signaling pathways that culminate in expression of NF- κ B regulated genes. Genetically LPS, TNF α and IL-1 control different aspects of the immune response, yet IRAK-1 is essential for NF- κ B activation in all three signaling pathways. I hypothesized that IRAK-1 coordinates the cellular responses to LPS, TNF α and IL-1. To test my hypothesis I examined simultaneously the effect of LPS, TNF α and IL-1 treatment on IRAK-1. Under steady-state conditions IRAK-1 is localized in the cytoplasm and the plasma membrane. In contrast to TNF α where IRAK-1 subcellular localization does not change, in response to LPS or IL-1 there is a time dependent loss in cytoplasmic IRAK-1 with a coordinate increase in modified IRAK-1 in the plasma membrane. The change in IRAK-1 subcellular localization and its post-translational modification occurs rapidly in response to

IL-1, and is detected 1 hour after LPS treatment. Furthermore, in response to LPS, membrane localized, modified IRAK-1 co-immunoprecipitates with the type I TNF α receptor (TNF RI). In MEFs that lack TNF RI, LPS and IL-1 modification and degradation of IRAK-1 is altered. Additionally, TNF R1 deficiency dramatically enhances LPS and IL-1 induction of NF- κ B regulated genes. The data presented herein suggest a model whereby LPS or IL-1 trigger the membrane localization of IRAK-1 where it is modified and degraded in a TNF RI dependent manner. The interaction between IRAK-1 and TNF RI integrates the cellular response to LPS, TNF α and IL-1 and generates a cell poised to both activate NF- κ B controlled gene expression in response to TNF α and to negatively feedback to control the inflammatory response.

Maureen Harrington, PhD, Chair

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