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

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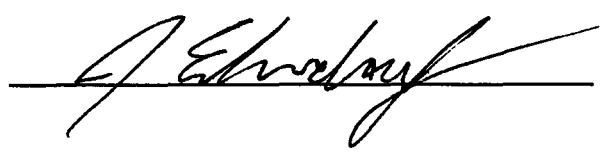

Jeffrey Elmendorf, PhD

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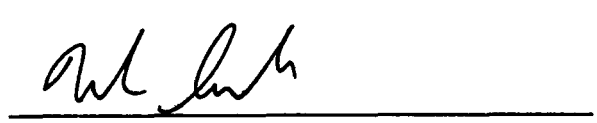

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ABSTRACT

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Coordination of LPS, TNFα and IL-1β 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 (TNFα) followed by interleukin-1 (IL-1). The interleukin-1 receptor associated kinase-1 (IRAK-1) is an integral component of the LPS, TNFα and IL-1 signaling pathways that culminate in expression of NF-κB regulated genes. Genetically LPS, TNFα and IL-1 control different aspects of the immune response, yet IRAK-1 is essential for NF-κB activation in all three signaling pathways. I hypothesized that IRAK-1 coordinates the cellular responses to LPS, TNFα and IL-1. To test my hypothesis I examined simultaneously the effect of LPS, TNFα 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 TNFα 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 TNFα 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-κB 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, TNFα and IL-1 and generates a cell poised to both activate NF-κB controlled gene expression in response to TNFα and to negatively feedback to control the inflammatory response.

Maureen Harrington, PhD, Chair

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