Objectives:

IL-1Rs are broadly expressed across cell types and little is known about differences in signaling between cell types and the role of IRAK1 and IRAK4 kinase activity.

Objectives: We have identified a potent and selective IRAK1/4 inhibitor, R835, that substantially suppressed the elevation of LPS (TLR4 agonist)-induced cytokines produced. The ability of R835 to inhibit cytokine production induced by high or low amounts of IL-1β in dermal fibroblasts was assessed.

Results: In human endothelial cells, inhibition of IRAK1/4 kinases with R835 resulted in a block of IL-1β-induced IRAK4 phosphorylation, IRAK1 degradation and downstream NFκB, p38 and JNK activation.

Conclusion: This study has elucidated signaling differences between cell types downstream of the IL-1R. In endothelial cells, as in myeloid cells, the kinase activity of IRAK1 and IRAK4 is required for the activation of all downstream signaling. Unexpectedly, in human fibroblasts, IRAK1/4 kinase activity appears to primarily regulate the JNK pathway, and not the NFκB pathway. Concomitant with that, only the cytokines induced by the additional activation of JNK in fibroblasts are regulated by a dual IRAK1/4 inhibitor. Clinically, an IRAK1/4 inhibitor may show select inhibition of IL-1β-induced cytokines depending on the tissue and cell type involved in inflammation.