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The role of sphingosine kinase 1 in endosomal TLR mediated innate immune response

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Statement of the Problem: The body protects itself against the invading pathogens by mounting different strategies, collectively called as the immune responses. Toll like receptors (TLRs) recognize pathogens and are vital for innate immune response. The regulation of TLRs is not fully understood, the dysregulation of which can lead to autoimmune conditions. Sphingosine kinase 1 is an enigmatic enzyme that is involved in a myriad of cellular processes. The role of sphingosine kinase 1 is speculated in TLR regulation.

Methodology: The effect of sphingosine kinase 1 in innate immune response is studied *in vitro* using CAL1 cell, a plasmacytoid dendritic cell line, primary cells and *in vivo* in C57Bl/6 mice. SphK1 is pharmacologically inhibited using SK1I. The response in the form of interferon and pro-inflammatory cytokine production is measured in the mRNA and protein level by Real Time qPCR and ELISA. The effect of the inhibition on signalling components was studied by immunofluorescence and western blotting. The interaction between TLR and SphK1 was checked by immunofluorescence and western blotting.

Findings: The inhibition of SphK1 was found to affect the innate immune response as measured by interferon and proinflammatory cytokine production. The effect of the inhibition on innate immune response was not mediated through cell death, but through the modulation of key cellular signaling pathways. SphK1 was found to co-localize with the endosomal TLRs.

Conclusion & Significance: The study brings out the role of SphK1 in innate immune response from a plasmacytoid dendritic cell perspective. These points towards the potential of developing therapeutics based on SphK1 for treatment of autoimmune diseases, where there is aberrant TLR regulation.

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