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PIM2 induced MMP-9 expression in macrophages requires PI3K and Notch1 signaling

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Introduction

Granuloma formation during *Mycobacterium tuberculosis* infection represents pathological attributes of the host immunity to infection and is required for the containment of infection. Granuloma formation is a complex process involving initiation and development of organized multicellular structures comprised of components of extracellular matrix [1]. Activation of inflammatory immune responses during granuloma formation upon infection with mycobacteria is often associated with tissue remodeling and breakdown of the extracellular matrix. In these complex processes, Cyclooxygenase-2 plays a major role in chronic inflammation and regulates matrix metalloproteinase-9 expression significantly in tissue remodeling but the molecular mechanisms involved remain elusive.

Aim

To investigate the molecular mechanisms underlying Phosphatidyl-myo-inositol dimannosides triggered MMP-9 expression in macrophages.

Methods

We show possible implications of Notch signaling on immunological parameters associated with interaction of macrophages with novel cell wall antigen of Mycobacteria.

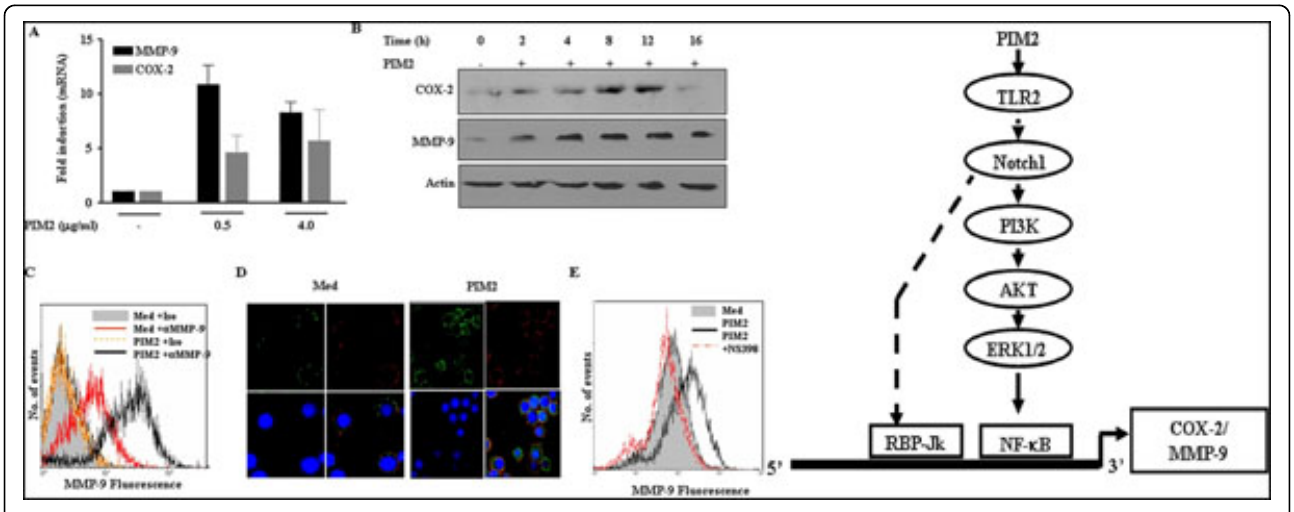

Figure 1 PIM2 induced COX-2 and MMP-9 expression and a model depicting signaling cascades regulating their expression: PIM2 treated macrophages shows upregulated COX-2 and MMP-9 expression both at mRNA and protein levels as analyzed by qRT-PCR, immunoblotting, FACS and confocal microscopy. Immunoflourescent staining of NS-398 treated macrophages shows decreased MMP-9 expression.

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We present evidences that PIM2 triggered expression of MMP-9 involves the activation of PI3K and Notch1 signaling in TLR2- MyD88 dependent manner.

Results

PIM2 triggers the activation of PI3K and Notch1 signaling leading to MMP-9 expression. Notch1 signaling perturbations demonstrate the involvement of a cross-talk with members of PI3K and MAPK pathway. PIM2 triggered significant p65 NF-κB nuclear translocation that was dependent on activation of PI3K or Notch1 signaling. MMP-9 expression requires Notch1 mediated recruitment of Suppressor of Hairless (CSL) and NF-κB to respective promoters.

Conclusions

PI3K and Notch1 signaling are obligatory early proximal signaling events during PIM2 induced MMP-9 expression in macrophages.

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