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Author(s)	Yim, HCH; Li, JCB; Lau, ASY
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DUAL-SPECIFICITY PROTEIN PHOSPHATASE-1 POSITIVELY REGULATES THE ANTI-MYCOBACTERIAL RESPONSES

H. C.H. Yim, J. C.B. Li, A. S.Y. Lau

Cytokine Biology Group, Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong

Tuberculosis is still prevalent around world. It is caused by *Mycobacterium tuberculosis* (Mtb). This microbe stimulates monocytes/macrophages leading to the production of specific cytokines for initiating immune responses. Of these cytokines, tumour necrosis factor-alpha (TNF-α) is crucial for inducing the granuloma formation for restricting Mtb dissemination. Using Bacillus Calmette Guerin (BCG) as a model, we showed mycobacteria activated mitogen-activated protein kinases (MAPK) for inducing TNF-α expression. Since dual-specificity protein phosphatase-1 (DUSP1) has been shown to negatively regulate the MAPK activation induced by Gram-negative bacterial infection, we hypothesize the proteins of DUSP family regulate mycobacteria-stimulated immune responses. To investigate whether BCG induces DUSPs, primary human blood monocytes (PBMo) were treated with BCG and the expressions of DUSP genes were examined. As assayed by quantitative RT-PCR and Western Blot, we showed BCG stimulated the expression of DUSP1 in a time-dependent manner. This DUSP1 expression was activated by extracellular-signal-regulated kinase-1 and -2 (ERK1/2) and p38 kinase. When the cellular level of DUSP1 protein was knocked down by DUSP1-specific siRNA, we demonstrated the expression level of TNF-α induced by BCG was reduced, but its induction by lipopolysaccharide (LPS) was further augmented. Moreover, the phosphorylation levels of BCG-activated ERK1/2 and p38 kinase decreased after DUSP1 was knocked down. In addition, our preliminary results showed the expression of DUSP5, another member of DUSP family, was induced after mycobacterial infection. Experiments on the biological consequences of DUSP5 activity on cytokine regulation are in progress. To conclude, our results suggested that apart from its well-known negative role in regulating LPS-induced responses, DUSP1 acts as a positive regulator in controlling the BCG-induced activation of ERK1/2 and p38 MAPK, and consequently the induced TNF-α production. These results provide new insights into the role of DUSP family in the regulation of proinflammatory cytokine responses in the pathogenesis of mycobacterial infections.