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The role of Inositol 1,4,5 triphosphate kinase C in the pathogenesis of Kawasaki disease

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Background

Kawasaki disease (KD) is a childhood multisystemic vasculitis resulting in the development of coronary aneurysms. Functional polymorphism in *Inositol 1,4,5-triphosphate kinase C* (*ITPKC*) has recently been identified and linked to KD susceptibility and severity. ITPKC acts as a negative regulator of T-cell activation through the inhibition of Ca^{2+}/Nuclear factor of activated T-cells (NFAT) signalling pathway. *Lactobacillus casei* cell wall extract induced coronary arteritis is an animal model of KD dependent on superantigenic activity.

Objective

To determine the role of ITPKC in the pathogenesis of KD.

Methods

To assess the role of ITPKC in lymphocyte activation, mouse splenocytes were stimulated with superantigen and T-cell proliferation, cytokines production, Ca^{2+} flux and ITPKC protein expression were measured by ^{3}H thymidine, ELISA, flow cytometry, and Western blot, respectively. To confirm the results in a human system, lymphocyte activation was determined in a human cell line after siRNA knockdown.

Results

ITPKC was upregulated at both mRNA and protein levels by mouse splenocytes following superantigen stimulation. Cyclosporin A inhibition of Ca^{2+}/NFAT signalling abolished T-cell proliferation and cytokine production following superantigen activation. *ITPKC* knockdown in superantigen activated human lymphocyte cell line could not completely inhibit cytokine production or Ca^{2+} flux.

Conclusion

Although ITPKC and the Ca^{2+}/NFAT signalling pathway were activated in lymphocytes following superantigen stimulation, inhibition of ITPKC was not able to alter lymphocyte activation or Ca^{2+} flux pointing to overlapping or compensatory pathways. These findings may account for the conflicting reports on the association between *ITPKC* polymorphisms and KD in different ethnicities.

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