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Oral presentation

12.2 Mevalonate kinase deficiency: Impaired isoprenoid synthesis induces IL-1beta production via activation of Rac1

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Mevalonate kinase deficiency is an autosomal recessive disorder characterized by recurring episodes of fever and inflammation. Peripheral blood mononuclear cells from mevalonate kinase deficiency patients secrete high levels of IL-1β when stimulated with lipopolysaccharide (LPS) due to the presence of hyperactive caspase-1. The molecular mechanism of mevalonate kinase deficiency-induced caspase-1 activation remains unclear.

We artificially impaired isoprenoid biosynthesis in the monocytic cells (THP-1) with simvastatin, after which cells were stimulated with LPS. Simvastatin-treated THP-1 cells stimulated with LPS demonstrated enhanced release of IL-1β. LPS enhanced transcription of IL-1β., whereas simvastatin enhanced proteolytic activation of IL-1β. This effect was mediated by phosphatidylinositol 3 kinase (PI3K) and protein kinase B (PKB/c-Akt). In addition, simvastatin-induced IL-1β secretion required the small GTPase Rac1. Simvastatin treatment increased the levels of biologically active GTP-bound Rac1 and inhibition of Rac1 reduced simvastatin-mediated IL-1β secretion. Rac1 functioned upstream of PKB, since Rac1 inhibition abolished the effect of simvastatin on PKB. Simvastatin-mediated activation of the Rac1/PI3K/PKB pathway enhanced IL-1β secretion through activation of caspase-1, since inhibition of both Rac1 and PI3K blocked the release of active caspase-1 subunits. The importance of Rac1 in mevalonate kinase deficiency was confirmed when a specific Rac1 inhibitor was shown to inhibit spontaneous IL-1β release by mononuclear cells from mevalonate kinase deficiency patients.

Together, these results demonstrate that Rac1, PI3K and PKB are involved in simvastatin-induced secretion of IL-1β through regulation of caspase-1 activity and that Rac1 is a potential new therapeutic target in mevalonate kinase deficiency.