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Title: The effect of γ -tocotrienol on human airway smooth muscle cell proliferation and migration

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Body: Background Vitamin E is known to have antioxidant activity and there are eight different forms of Vitamin E (α, β, γ and δ tocopherol and tocotrienol). Clinical trials using tocopherol supplementation for patients with asthma to assess impact of antioxidant activity have yielded equivocal results. Of note, the tocotrienol form of vitamin E has greater antioxidant activity than tocopherol, this manifest through several biological effects in vivo and in vitro. Therefore, we tested the effect of tocotrienol on human airway smooth muscle (ASM) cell growth and migration, which play an important role in airway remodeling in asthma. Methods: We measured PDGF-BB-induced ASM cell proliferation using colorimetric assay by Cell counting kit-8 and ASM cell migration by transwell migration assay. We also assessed the effect of γ -tocotrienol (an isoform of tocotrienol), on ASM cell proliferation and migration. Results: PDGF-BB-induced ASM cell proliferation and migration was significantly inhibited by γ -tocotrienol. This effect was associated with an inhibition of RhoA activation, but had no impact on activation of p42/p44 mitogen-activated protein kinase (MAPK) or Akt1. In follow up studies we confirmed that pharmacological inhibition of Rho kinase activity was sufficient to inhibit ASM cell proliferation and migration induced by PDGF-BB. Conclusion: These results indicate that γ -tocotrienol could have therapeutic effects related to airway remodeling in asthma by inhibiting human ASM cell proliferation and migration.