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Tocotrienol and the Mevalonate Pathway in Adipogenesis

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Abstract

Obesity has become a serious public health issue in the U.S. and globally. Adipocyte differentiation and adipocyte obesigenic expansion lead to hypertrophy, hypoxia, macrophage recruitment and chronic inflammation that underlies several associated chronic diseases. One of the key regulators of adipocyte differentiation, peroxisome proliferator-activated receptor γ (PPARγ), is activated by the insulin-RAS signaling pathway. The mevalonate pathway provides an essential intermediate, farnesyl pyrophosphate (FPP), required for the post-translational modification, membrane anchorage and biological activity of RAS. The statins competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, the rate-limiting enzyme in the mevalonate pathway, and block adipocyte differentiation. Mevalonate reverses the statin effect on differentiation while *t,t*-farnesol and its phosphorylation product, FPP, induce adipocyte differentiation and the expression of adipogenic genes including PPARγ and fatty acid binding protein 4. Tocotrienols, vitamin E molecules with an unsaturated side chain, downregulate HMG CoA reductase by suppressing its transcription and accelerating its proteasome-mediated degradation. *d*-δ-Tocotrienol reduces the intracellular triacylglycerol content of murine 3T3-F442A preadipocytes, an effect reversed by the PPARγ agonist rosiglitazone. Dietary *d*-δ-tocotrienol (60 mg/kg body weight for 14 weeks) reduced high-fat diet-induced weight gain in mice and improved intraperitoneal glucose tolerance test results. Modulators of the mevalonate pathway may have potential in the prevention of obesity and inflammation related diseases.

****All are Welcome****