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Pleiotropic Effects of Statins on Embryonic Stem Cells

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Statins, potent inhibitors of cholesterol synthesis, act by inhibiting 3-hydroxy-3-methylglutaryl CoA (HMG-CoA) reductase which catalyzes the conversion of HMG-CoA to mevalonate. In addition to cholesterol lowering property, many biological effects of statins can be derived from cholesterol-independent (pleiotropic) mechanisms which are likely a consequence of blocking intracellular signaling through inhibition of protein isoprenylation. However, the molecular mechanisms of statin action on embryonic stem cells (ESCs) are largely unknown. Therefore, we examined statin's actions and their interference with downstream metabolites of HMG-CoA reductase including mevalonate, FPP and GGPP in three different ESC lines derived from 129 strains of mice (J1, D3, and RW.4). Treatment of ESCs with simvastatin, mevastatin, atorvastatin, or pravastatin induced morphological change, decreased cell proliferation, and loss of ESC self-renewal. Those effects were selectively reversed by either mevalonate or its metabolite GGPP, but not by cholesterol or FPP. In addition, we confirmed that down-regulation of ESC self-renewal by statin is significantly related to its inhibitory effect on RhoA geranylgeranylation while other Rho family members including cdc42 and Ras had no effect. Our data suggest that statin, independently of its choresterol-lowering properties, impairs the ESC self-renewal by modulating RhoA-dependent cell-signaling.

Key Words: mouse embryonic stem cells, self-renewal, simvastatin, GGPP, RhoA