Statins and Demyelination

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Abstract Statins are inhibitors of the 3-hydroxy-3-methylglutaryl coenzyme A reductase, which are widely prescribed for their cholesterol-lowering properties in order to reduce atherogenesis and cardiovascular morbidity. Moreover, statins have been shown to exert pleiotropic immunomodulatory effects that might be of therapeutic benefit in autoimmune disorders. Statins appear to alter immune function largely independent of lipid lowering and rather through inhibition of posttranslational protein prenylation of small regulatory GTP-binding proteins. In experimental autoimmune encephalomyelitis (EAE), the murine model for multiple sclerosis (MS), statins were shown to reverse established paralysis and to exert synergistic benefit in combination with agents approved for MS therapy. Based upon these encouraging findings in treatment of EAE, statins are now being tested in clinical trials in patients with MS.

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1 Introduction

Currently, FDA-approved disease-modifying drugs for multiple sclerosis (MS) are only partially effective. Thus, the search for novel therapies and new treatment regimes must continue. Statins inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. The enzyme HMG-CoA reductase catalyzes the conversion of HMG-CoA to L-mevalonate, the key intermediate in the biosynthesis of cholesterol [17]. Over decades, statins have established themselves as generally safe and well-tolerated drugs [1, 2, 22] and are prescribed to more than 25 million people worldwide today. The family of statins includes naturally occurring members (lovastatin, mevastatin, pravastatin, and simvastatin) and synthetic members (fluvastatin, atorvastatin, and rosuvastatin), which differ in their lipophilicity, half-life, and potency.

Statins studied in animal models of autoimmune diseases demonstrate immunomodulatory properties independent of their cholesterol-lowering properties that might be of benefit in treatment of neuroinflammatory disorders. Orally administered statins are particularly attractive candidates for treatment of MS; all currently approved drugs, such as interferon-beta, glatiramer acetate (GA), mitoxantrone, and natalizumab, are administered parenterally and have side effects and potential toxicities.

2 Mechanism of Action

In 1995, the potential impact of statins on immune function surfaced with a study demonstrating that cardiac transplant patients treated with pravastatin had a reduced incidence of hemodynamically significant rejection episodes and showed decreased mortality that did not correlate with cholesterol reduction [25]. Numerous subsequent studies further elaborated the anti-inflammatory properties of statins [43].

Rather recent studies have elucidated the molecular mechanisms that may be responsible for statin-mediated immune modulation. One report suggested that statins directly bind the cellular adhesion molecule leukocyte function antigen 1 (LFA-1), primarily resulting in reduced migration of pro-inflammatory leukocytes [50]. The majority of statin-mediated immunomodulatory effects, however, appear related to the competitive displacement of HMG-CoA from the HMG-CoA reductase, as these effects can be reversed by addition of its downstream product mevalonate. Importantly, mevalonate is the key metabolite, not only for the synthesis of cholesterol, but also for the synthesis of isoprenoid intermediates, such as farnesylpyrophosphate (FPP) and geranylgeranylpyrophosphate (GGPP). These molecules are responsible for the prenylation of GTP-binding proteins [56], such as Ras and Rho, which have important roles in multiple signaling pathways regulating cellular differentiation and proliferation [46]. Posttranslational isoprenylation of these proteins is necessary for their attachment to the cytoplasmic surface of the plasma membrane, where they function. Thus, by inhibiting isoprenylation of Ras and Rho, statins modulate cellular functions that are also required for the activation of immune cells (Fig. 1).