Molecular Microbiology and Statins Frontier

Hayder M Al-kuraishy*

Department Of Pharmacology, Toxicology and Medicine, College of Medicine, Almustansiriya University, Baghdad, Iraq

*Corresponding author: Hayder M Al-kuraishy, Assistant Professor in Department Of Pharmacology, Toxicology and Medicine, College of Medicine, Almustansiriya University, Baghdad, Iraq, Tel: +96407906230487; E-mail: Hayderm36@Yahoo.Com

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Editorial

There is an unremitting and basic need to find novel antimicrobial compounds with different synthetic structures and novel components of activity since; there has been a surprising increase in the rate of antibiotic resistances [1].

One of the major recognized clinical achievements of the twentieth century was the discovery of the statin family. These compounds are prestigious for their capacity to bring down cholesterol levels and are utilized to treat roughly 40 million people with elevated cholesterol around the world. Since; the disclosure of mevastatin as a metabolic result of *Penicillium citrinum* in 1976 [2] a sum of nine statins have been portrayed, seven of which are affirmed by the FDA to treat patients with elevated cholesterol, structurally, statins are described by the presence of a conserved lactone ring [3]. This structure is available as a hydrolyzed (active) form in all statins aside from mevastatin, lovastatin and simvastatin, where the lactone ring is hydrolyzed in the liver [4]. Statins can be partitioned into two classes; Type 1 statins are lipophilic, as mevastatin, lovastatin, pravastatin and simvastatin. Type 2 statins are traditionally lipophobic, similar to atorvastatin, cerivastatin, fluvastatin, pitavastatin and rosuvastatin are Type 2 statins [5].

Statins are a potent antihyperlipidemic drug group that is broadly utilized for the management of hyperlipidemia. The 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCoA reductase) is the enzyme responsible for the rate-limiting step in the cholesterol synthesis mevalonate pathway [6]. 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors are recognized to have effects away from their lipid lowering effects, known as pleiotropic effects [7]. Statins have also been investigated for their antibacterial action apart from antibacterial action it also has immune-modulatory and anti-oxidative actions [8]. Statins act via inhibition of HMG-CoA reductase, in bacteria HMG-CoA reductase is essential for the biosynthesis of isoprenes. However, bacterial HMG-CoA reductase is of a dissimilar structural with an affinity for statins that is 10000 times less than the enzyme found in human [9]. Consequently, it is improbable that antibacterial activity of statins can be ascribed to the inhibition of HMGCoA reductase. Additional likely components might be identified with the pleiotropic properties of statins, since atorvastatin and simvastatin subdue cells development and empower apoptosis [10]. New proof has proposed that statins have coordinate antimicrobial impact including gram-positive and gram-negative microorganisms, discovering proof that distinctive statins had changing antimicrobial effects [11]. Despite the fact that atorvastatin and simvastatin are more powerful than rosuvastatin with adoration to Gram-positive agents however Gram-negative organisms are more sensitive to atorvastatin than either simvastatin or rosuvastatin [12]. Lovastatin is a metabolic product of *Penicillium citrinum*, Pravastatin and simvastatin are semi-synthetic forms that are derivatives of lovastatin [13] and atorvastatin is the pure synthetic form. Pravastatin has hydrophilic properties but simvastatin and atorvastatin are lipophilic, [14]. Along these lines, simvastatin presumably crosses the cell membrane all the more effortlessly, causing bacterial inhibition in a dose dependent way. Although lipophilic, atorvastatin has no critical antimicrobial action. These discrete impacts could be identified with the distinctions in compound structure among statins, as simvastatin is natural result of fungal fermentation, whereas atorvastatin is a chemically synthesized derivative, thus satins have different intrinsic activities [15]. Moreover, the statins effect the intracellular growth of pathogens has been studied on drug concentrations nearer to physiological levels; they have been shown to decrease the growth of several obligate intracellular bacterial pathogens [16] and both atorvastatin and simvastatin, in a dose-dependent manner reduce the growth of *Mycobacterium leprae* by up to 90%, suggesting an indirect impact on cholesterol levels as because the intracellular growth of those pathogens requires cholesterol [17].

Surprisingly, simvastatin, at a physiological concentration (0.5 mg/kg), but not pravastatin significantly reduce the levels of the pulmonary pathogen *Chlamydiae pneumonia* in lung cells of infected mice [18]. This discovery indicates an indirect effect due to cholesterol inhibition.

Additionally, inhibition of the non-obligate intracellular growth of *M. tuberculosis* in peripheral blood macrophages and mononuclear cells was extensively reduced in humans, when the patient is treated with atorvastatin [19]. Indeed, simvastatin treatment effectively reduce the function of *Listeria monocytogenes* to grow inside mouse and primary macrophages, in a cholesterol dependent manner and significantly decrease the bacterial growth and dissemination

to the liver and spleen in infected mice [20]. Moreover, simvastatin- decrease bacterial growth is reversed by mevalonate pathway suggested that statins control microbial infection by phagolysosomal arrest of *Mycobacterium tuberculosis* [21].

The intracellular growth of *Salmonella Typhimurium* was decreased more than 10-fold, when it is treated with lovastatin of murine macrophages, in any event partially because of attenuation of the mevalonate pathway [22].

Thus, bacteria influence the lipid rafts to invade and survive within cells, lipid rafts are glycoprotein domains present in the cell membrane, which is formed as a result of cholesterol interacting with sphingoglycolipids, and a key mechanism appears to be the statin-mediated inhibition of lipid raft formation [23]. Though, statins inhibit the formation of lipid rafts due to inhibition of cholesterol biosynthesis. Two studies investigating the effects of statins on the intracellular growth of *L. monocytogenes* and plaque formation of *R. conorii* suggest their findings were due to the inhibition of lipid raft formation, hence there was no direct effect on bacterial viability but that statins promoted bacterial killing by inducing the formation of phagocyte extracellular traps [24].

These statins have an unexpected antimicrobial effect *in vitro* but require concentrations that are far higher than are probably achieved *in vivo* with traditional indications for statins. Therefore, statins most likely don't exert a major antimicrobial impact in patients, however these knowledge have unconcealed the unanticipated class effect and further testing of statins and their metabolites is warranted.

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