Pleiotropic Effects of Statins

Subjects: Infectious Diseases

Contributor: Susan McDowell

An emergent approach to bacterial infection is the use of host rather than bacterial-directed strategies. This approach has the potential to improve efficacy in especially challenging infection settings, including chronic, recurrent infection due to intracellular pathogens. For nearly two decades, the pleiotropic effects of statin drugs have been examined for therapeutic usefulness beyond the treatment of hypercholesterolemia.

ML141 Action Staphylococcus aureus bacteria Pleiotropic Effects Statins

1. Staphylococcus aureus Infection

Epidemiology

Staphylococcus aureus colonizes approximately 30% of the human population, yet colonized individuals typically remain asymptomatic [1][2]. However, *S. aureus* is also an opportunistic pathogen and is the causative agent in life-threatening infections associated with high morbidity and mortality. Wisplinghoff et al. reported *S. aureus* as the second leading cause of bacteremia in hospitals in the United States, exceeded only by coagulase-negative *Staphylococcus* species [3], and Fowler et al. reported *S. aureus* as the leading cause of infective endocarditis worldwide [4]. High mortality rates are associated with *S. aureus* infections. Noskin et al. reported a 5-fold increase in the risk of in-hospital death for *S. aureus* infection compared to non-*S. aureus* infection [5]. Wisplinghoff et al. reported 25% of *S. aureus* bloodstream infections are associated with mortality [3], and De la Calle et al. reported a 30-day mortality rate of 46.9% for *S. aureus* pneumonia [6]. High morbidity and mortality rates are not merely attributable to antibiotic resistance, such as in the reporting of the 19% all-cause in-hospital mortality rate associated with methicillin-susceptible *S. aureus* (MSSA) bloodstream infections [7]. Thus, this opportunistic pathogen inflicts significant morbidity and mortality through infection by resistant strains and by strains susceptible to first-line antimicrobial treatment.

Invasive *S. aureus* strains are an important cause of chronic, relapsing infection, especially notable in cystic fibrosis [8][9]. *S. aureus* is an initial isolate identified in the colonization of the respiratory tract of cystic fibrosis patients, as indicated by Armstrong et al., where 66.6% of infants less than 6 months old with cystic fibrosis had lower respiratory infections caused by *S. aureus* [10]. Evidence that *S. aureus* infection persists includes findings from Schwerdt et al. showing 61% of cystic fibrosis patients chronically infected with *S. aureus* for more than 50% of a 22-year observation period [11]. Persistence by the same strain can continue for extended periods, as evidenced in Branger et al., who found 48% of cystic fibrosis patients persistently infected with a single *S. aureus* strain for 12–28 months [12]. The Cystic Fibrosis Foundation Patient Registry annual report for 2019 detailed an

increase in the percentage of patients infected with *S. aureus* per year from 56.2% in 2002 to 70.2% in 2019 [13]. Of these infections, 55.3% were attributed to MSSA, more than doubling methicillin-resistant *S. aureus* (MRSA) infection (24.6%). Thus, in addition to acute pathogenesis, both MSSA and MRSA represent an important cause of severe, chronic infections associated with high mortality.

2. Emerging Approaches in Treatment Strategies—Statins

Given the propensity of bacteria, especially *S. aureus*, to develop antibiotic resistance, an emerging approach is to target the host rather than promote resistance by targeting the bacterium [14][15]. One such host-directed approach is the use of statins, therapeutics commonly prescribed in the treatment of hypercholesteremia. Increasing evidence suggests patients prescribed statins for cholesterol-lowering indications exhibit a decreased risk of contracting bacterial infections and improved survival during infections [16][17][18][19][20][21][22][23]. This is supported by findings by Smit et al. that statin-users are 27% less likely to contract community-acquired *S. aureus* bloodstream infections than non-statin users [17]. Almog et al. reported patients on a statin regimen had a 16.6% lower risk of developing sepsis during acute bacterial infections [18]. Björkhem-Bergman et al. found statin use was associated with 50% decreased odds of death during bacterial infections [16]. The protective effect raises the possibility statins may function as a host-directed therapeutic for treating bacterial infections.

However, in a series of randomized clinical trials, statin's efficacy in treating sepsis or acute respiratory distress syndromes was not supported [24][25][26], calling into question the influence of bias in the earlier retrospective studies [27][28]. Countering this, Kruger et al. [29] demonstrated improved outcomes in patient populations when statin therapy was initiated prior to infection onset. Thus, the timing of statin therapy appears to influence the clinical outcome. The contradiction may signal protection is mediated not only through cholesterol-lowering capacity of statins, but also through pleiotropic effects of statins.

3. Statins' Mechanism of Action

Statins inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate limiting enzyme in cholesterol biosynthesis [30][31][32]. During cholesterol biosynthesis, acetyl-CoA is converted into HMG-CoA by HMG-CoA synthetase [31]. Next, during the rate-limiting step, HMG-CoA reductase converts HMG-CoA into mevalonate, which, through a series of additional steps, is converted into geranyl pyrophosphate and farnesyl pyrophosphate (Fpp). Cholesterol is synthesized from Fpp through numerous additional conversion steps.

4. Pleiotropic Effects of Statins

In addition to cholesterol lowering, statins yield cholesterol-independent effects, also known as pleiotropic effects. Statin inhibition of HMG-CoA reductase diminishes synthesis not only of cholesterol, but also of hydrophobic isoprenoid intermediates Fpp and geranylgeranyl pyrophosphate (GGpp) that form from Fpp. Statin pleiotropic effects in part are due to decreased synthesis of these intermediates. These long hydrophobic molecules are

modified and attached covalently through the process of post-translational prenylation of proteins containing the conserved CaaX domain [33]. In this domain, “C” is the prenylated cysteine and “X” is the amino acid that determines which isoprenoid, Fpp or GGpp, will become covalently attached to the protein through post-translational prenylation. Thus, when Fpp and GGpp synthesis is reduced through inhibition of the cholesterol biosynthesis pathway by simvastatin, post-translational protein prenylation is likewise reduced [31]. Numerous pleiotropic effects of statins are due to this diminished availability of isoprenoid intermediates.

5. Pleotropic Effects of Statins—Inhibition of Infection

Statins interrupt specific stages of host cell invasion through non-cholesterol-dependent pleiotropic effects. The centrality of isoprenoid depletion in these effects is evidenced by the restoration of invasion during simvastatin treatment if Fpp or GGpp are replenished. Invasion was not restored by replenishing cholesterol [14] with this concentration of simvastatin, a lower concentration than that of early work showing apoptotic responses to simvastatin [34]. Multiple effects are rendered through small GTPases, including CDC42, a CaaX domain-containing host cell protein that relies on post-translational prenylation for membrane localization [35][36]. As prenylation decreases following treatment with simvastatin, CDC42 becomes sequestered in the cytoplasm, no longer anchored at the host cell membrane [14]. This loss of membrane localization appears central to several downstream effects.

Although CDC42 remains sequestered within the cytosol, simvastatin stimulates GTP-loading within the CDC42 activation site [37]. In the active, GTP-bound state, mislocated CDC42 is available for coupling with cytosolic PI3Kp85α. Coupled to GTP-bound CDC42 in its cytosolic location, PI3Kp85α is sequestered away from the host cell membrane [14]. The loss of membrane localization of PI3Kp85α potentially results in loss of membrane anchoring for the PI3K110 catalytic subunits that rely on PI3Kp85α for membrane localization. The loss of PI3K110 catalytic subunit access to membrane-bound phosphoinositide would have a resultant loss of formation of the cell-signaling molecule PIP_3. Evidence of this disruption is that simvastatin treatment limits actin stress fiber disassembly, the endocytic process dependent on PIP_3 binding α-actinin.

Simvastatin reduces host cell binding to fibronectin [38]. Moreover, simvastatin decreases uptake of the β1 integrin complex from the cell surface and decreases nascent formation of these complexes by limiting recycling of the β1 component to the host cell membrane [37]. Thus, pleiotropic effects of simvastatin, as a host-directed therapeutic, limits *S. aureus* invasion into host cells through decreased synthesis of isoprenoid intermediates, sequestration of RAC, RHO, and CDC42 in the cytosol, decreased membrane localization of these small-GTPases coupled to PI3Kp85α, reduced actin stress fiber depolymerization, decreased host cell binding to fibronectin, and decreased internalization and recycling of β1-integrin receptor complexes to the host cell surface.

In vivo, simvastatin treatment aids in clearing pulmonary infection by invasive *S. aureus* [39]. Similar to findings by Merx et al. in the host response to the endogenous murine microbiome [40][41], simvastatin decreases lung bacterial burden by exogenously administered *S. aureus* and decreases lethality. Simvastatin blunts pulmonary pathogenesis and the inflammatory response to infection, in addition to lowering markers of the inflammatory

response both within lung tissue and systemically. Thus, in vivo evidence supports the potential efficacy of statin use for limiting pulmonary infection.

Although pleiotropic effects of statins include inhibition of infection, the use of statins in the critically ill has been challenged due to altered pharmacokinetics within this patient population that renders statins more toxic [42][43][44][45][46]. The usefulness of statins in the treatment of infection has also been questioned following clinical trials demonstrating their limited efficacy [24][25] and concerns that observational studies may have overestimated their therapeutic benefit [27][28]. However, benefit is in evidence in patient populations undergoing statin therapy prior to the onset of infection [21][29][47]. This finding speaks to a potential underlying mechanism of statin efficacy reliant on pleiotropic effects following a reduction in the levels of isoprenoid intermediates that would require a prior statin regimen for efficacy to be achieved.

6. Emerging Approaches in Treatment Strategies—ML141

Alternative small molecule inhibitors have been examined that might limit host cell invasion yet circumvent adverse effects and limitations associated with statins. In characterizing the underlying mechanism of simvastatin, RAC, RHO, and CDC42 had emerged as potential molecular targets central to host cell invasion by *S. aureus* [14]. Earlier work had shown CDC42 is activated during *S. aureus* invasion [15] and CDC42 acting upstream of both RAC and RHO [35]. We therefore examined the role of CDC42 by using site-directed mutagenesis to encode valine in place of cysteine within the canonical CAAX prenylation site of CDC42. This inhibition of prenylation within this single host protein diminished invasion by more than 90%, suggesting a central role for CDC42 in invasion [14]. To examine this possibility, we used ML141, a small molecule inhibitor with specificity for hCDC42 [48].

7. ML141’s Mechanism of Action

ML141 differs from simvastatin in its target and mechanism of action. While simvastatin demonstrates specificity for HMG-CoA reductase at the early, rate limiting step of cholesterol/isoprenoid biosynthesis and thereby indirectly decreases the prenylation of CDC42, RAC, and RHO [14][49][50], ML141 demonstrates specificity for CDC42 [35][48]. Acting as an allosteric inhibitor, ML141 dissociates GTP and GDP from the CDC42 active site through rapid, reversible inhibition. Longer-term treatment elicits cellular responses similar to those observed previously in $CDC42^{-/-}$ mouse embryonic fibroblasts (MEF) [51][52]. These downstream effects may be mediated in part through the impaired coupling of GTP-bound CDC42 with downstream effector proteins such as members of the WASp and PI3K families [53][54][14][55][37].

8. ML141 Inhibition of Infection

ML141 decreases host cell invasion by MSSA and MRSA strains [15] and by *Streptococcus pyogenes*, a Gram-positive invasive bacterium that shares the fibronectin/integrin invasion mechanism used by *S. aureus* [38]. Similar to simvastatin, the underlying mechanism of inhibition by ML141 includes disruption of α5β1 adhesion complexes

at the host cell membrane and decreasing host cell binding to fibronectin. Also similar to simvastatin, ML141 treatment decreases the reordering of actin necessary for endocytic uptake [15]. Thus, although the target and mechanism of action differ between simvastatin and ML141, host cellular responses are similar, contributing to an overall reduction in the establishment of an intracellular bacterial population.

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