Exploring simvastatin, an antihyperlipidemic drug, as a potential topical antibacterial agent

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Abstract:

The rapid rise of bacterial resistance to traditional antibiotics combined with the decline in discovery of novel antibacterial agents has created a global public health crisis. Repurposing existing drugs presents an alternative strategy to potentially expedite the discovery of new antimicrobial drugs. The present study demonstrates that simvastatin, an antihyperlipidemic drug exhibited broad-spectrum antibacterial activity against important Gram-positive (including methicillin-resistant Staphylococcus aureus (MRSA)) and Gram-negative pathogens (once the barrier imposed by the outer membrane was permeabilized). Proteomics and macromolecular synthesis analyses revealed that simvastatin inhibits multiple biosynthetic pathways and cellular processes in bacteria, including selective interference of bacterial protein synthesis. This property appears to assist in simvastatin's ability to suppress production of key MRSA toxins (α-hemolysin and Panton-Valentine leucocidin) that impair healing of infected skin wounds. A murine MRSA skin infection experiment confirmed that simvastatin significantly reduces the bacterial burden and inflammatory cytokines in the infected wounds. Additionally, simvastatin exhibits excellent anti-biofilm activity against established staphylococcal biofilms and demonstrates the ability to be combined with topical antimicrobials currently used to treat MRSA skin infections. Collectively the present study lays the foundation for further investigation of repurposing simvastatin as a topical antibacterial agent to treat skin infections. The blockbuster statin drugs have revolutionized the treatment of cardiovascular disease, primarily by reducing low-density lipoprotein cholesterol (LDL-C) levels, leading to a decline in the morbidity and mortality associated with coronary artery diseases1. All statins drugs exert their effect by inhibiting the enzyme class I 3-hydroxy-3-methyl-glutaryl-CoenzymeA reductase (HMG-CoA) leading to decreased synthesis of cholesterol and increased removal of low-density lipoprotein (LDL) circulating in the body2,3. These drugs possess a good safety profile with limited side effects thus permitting their frequent use in reducing lipid levels in patients with high cholesterol levels. In addition to their lipid-lowering effect, statins have been found to have potential use for other applications including influencing the host immune response via the drugs' anti-inflammatory and immune-modulatory properties4. Furthermore, multiple reports have investigated the potential role of statins in preventing and treating various infectious diseases and have demonstrated that statins can pre- vent the establishment of infections (by decreasing host cholesterol synthesis5,6 limiting certain bacterial species' ability to invade host cells) and potentially decrease the mortality rate attributed to bacterial infection7,8. Interestingly, several studies have shown that certain statins possess antimicrobial activity.

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