Statins as adjunctive host-directed therapy for TB

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Lipid-laden macrophages in tuberculosis

Lipid droplets in *M. tuberculosis*-infected macrophages *in vitro*
Lipid-laden macrophages in tuberculosis

Metabolism of lipids and lipoproteins in pathway analysis of gene expression in *M. tuberculosis*-infected THP1 cells

Hugh Salamon
Agents that block lipid droplet formation usually inhibit intracellular growth of *M. tuberculosis* – an example is a PPAR\(\gamma\) antagonist.
Simvastatin blocks lipid droplet formation in infected macrophages

Karim Lakehal
Statins: Common clinical use

- Statins are among the best-selling drugs worldwide and used extensively to reduce morbidity and mortality in patients with coronary disorders and hypercholesterolemia.

Endo A. J Lipid Res. 1992;33:1569-82.
Statins: Host-modulating properties

- Statins have pleiotropic effects, including broad-range immunomodulatory and anti-inflammatory properties.

- Statin use reduced mortality in patients with bacteremia\(^1\) and multiple organ dysfunction syndrome.\(^2\)

Statins: Protective effect against intracellular pathogens

• Lovastatin and atorvastatin reduced *Salmonella enterica* growth in a murine macrophage cell line and in mouse spleens/livers, respectively.

• Mice treated with simvastatin had reduced growth of *Chlamydia pneumoniae* in the lungs.

Anti-TB effect of statins

- PBMCs and MDMs from statin-treated FH patients were more resistant to Mtb infection compared to those of healthy donors.

- Statin treatment of Mtb-infected mice increased host protection with reduced lung burden and improved histopathology.

- The effect of statins appears to be mediated by reduction of membrane cholesterol, which promotes phagosomal maturation and autophagy.

Statins mediate increased host protection against Mtb infection in mice

Statins as adjunctive therapy in combination with the standard first-line regimen

Aerosol infection with Mtb H37Rv (10-25 CFU)

Untreated
Antibiotic treatment*
RHZ+Sim

*Antibiotic treatment, H= isoniazid 10mg/kg
R= rifampin 10 mg/kg
Z= pyrazinamide 150 mg/kg
Sim= simvastatin 25 mg/kg†

8 Wks treatment

6 Wks

Wk-6 Wk-0 Wk 2 Wk 4 Wk 8

All antibiotics were given 5 times/week by oral gavage

Simvastatin does not enhance immune-based killing during acute TB infection in mice
Simvastatin accelerates bacterial clearance in combination with RHZ
Simvastatin accelerates bacterial clearance in combination with RHZ
Histopathology: 4 weeks after treatment

RHZ

100X

RHZ + Sim

200X
Lung histology:
Morphometry analysis

Week 4

Week 8

Areas of involvement (%)
A panoply of drugs

Zhenya Nikolaev
Conclusions

- Statins are among the most commonly prescribed drugs and have a very favorable toxicity profile.

- This class of drugs appears to have host-protective properties against various intracellular pathogens.

- Readouts such as lipid droplet formation, intracellular growth of *M. tuberculosis*, and macrophage cytotoxicity can be used to investigate the basis of the antibacterial mechanisms of statins.

- Simvastatin, when added to RHZ, increased *M. tuberculosis* killing in murine lungs.
Unanswered questions

• Does adjunctive use of statins reduce the time required to achieve stable cure (relapse-free state) in mice?

• What is the optimal statin to use for adjunctive anti-TB therapy?

• What is the optimal dosing?

• Are statins as effective in the immunodeficient host?

• Are statins active against MDR-TB?

• Are there additional lipid-lowering drugs that can be evaluated as HDT for TB?