0737. Statins protect the vasculature from excessive angpt-2 production in sepsis

The Harvard community has made this article openly available. Please share how this access benefits you. Your story matters.

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Published Version</td>
<td>doi:10.1186/2197-425X-2-S1-P59</td>
</tr>
<tr>
<td>Accessed</td>
<td>February 8, 2018 10:20:18 PM EST</td>
</tr>
<tr>
<td>Citable Link</td>
<td><a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:27822260">http://nrs.harvard.edu/urn-3:HUL.InstRepos:27822260</a></td>
</tr>
<tr>
<td>Terms of Use</td>
<td>This article was downloaded from Harvard University's DASH repository, and is made available under the terms and conditions applicable to Other Posted Material, as set forth at <a href="http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA">http://nrs.harvard.edu/urn-3:HUL.InstRepos:dash.current.terms-of-use#LAA</a></td>
</tr>
</tbody>
</table>

(Article begins on next page)
0737. Statins protect the vasculature from excessive Angpt-2 production in sepsis

K Thamm1, C Ghosh2, JT Kielstein1, WC Aird2, A Santel3, SM Parikh2, S David1*

From ESICM LIVES 2014
Barcelona, Spain. 27 September - 1 October 2014

Introduction
Sepsis is a syndrome of systemic inflammation arising from infection that constitutes a top-ten cause of adult mortality. The recent withdrawal of a specific sepsis therapeutic has diminished pharmaceutical enthusiasm for developing novel drugs in this domain. Angiopoietin-2 (Angpt-2) is an endothelial-derived protein that potentiates vascular inflammation and permeability and may be involved in sepsis pathogenesis.

Objectives
We set out to screen well-established drugs for their Angpt-2 lowering potential to ameliorate sepsis morbidity and to analyse the underlying molecular mechanism.

Methods
In vitro
FDA-approved library screening in human umbilical vein endothelial cells (HUVECs) and confirmation via Angpt-2 ELISA and quantitative RT-PCR.

In vivo
Murine experimental sepsis was induced both by endotoxin (LPS) and cecal ligation and puncture (CLP). Mice were either treated with an Angpt-2 specific siRNA, simvastatin, or both and survival as well as the direct effect on Angpt-2 production was assessed by RT-PCR. In men: We analyzed circulating Angpt-2 levels in a retrospective matched case-control study in individuals with septic shock.

Results
We found that simvastatin reduced endothelial Angpt-2 release and transcription in a time- and dose dependent manner in HUVECs. This effect required Simvastatin’s HMG-CoA reductase activity. Similarly, in vivo simvastatin reduced the transcription of Angpt-2 murine lungs. In septic mice, specific inhibition of Angpt-2 in the pulmonary endothelium via an RNAi approach improved survival by 50% (p=0.002). Simvastatin equally improved survival, but the combination of Angpt-2 siRNA and simvastatin showed no additive benefit indicating that simvastatin might act via Angpt-2 inhibition. To investigate a potential link between statins and Angpt-2 in humans, we performed a matched case-control study in critically ill subjects and found that prior statin use was associated with lower circulating Angpt-2.

Conclusions
In an unbiased approach Simvastatin was found to inhibit Angpt-2 production in vitro. This observation could be confirmed in vivo in different murine models of the disease. Our data indicate that a potential beneficial effect of prior statin use in septic humans might be promoted via the Angpt-2/Tie2 axis. Therefore, ‘point of care’ screening for circulating Angpt-2 in candidates for a clinical sepsis trial might help to identify those individuals that benefit from a statin treatment.

Grant acknowledgment
SD is supported by the DFG (DA 1209/4-1).

Authors’ details
1 Hannover Medical School, Hannover, Germany. 2 Harvard Medical School, Center for Vascular Biology Research, Boston, USA. 3 Silence Therapeutics AG, Berlin, Germany.

Published: 26 September 2014

Cite this article as: Thamm et al. 0737. Statins protect the vasculature from excessive Angpt-2 production in sepsis. Intensive Care Medicine Experimental 2014 2(Suppl 1):P59.