



Endotheliopathy of Trauma



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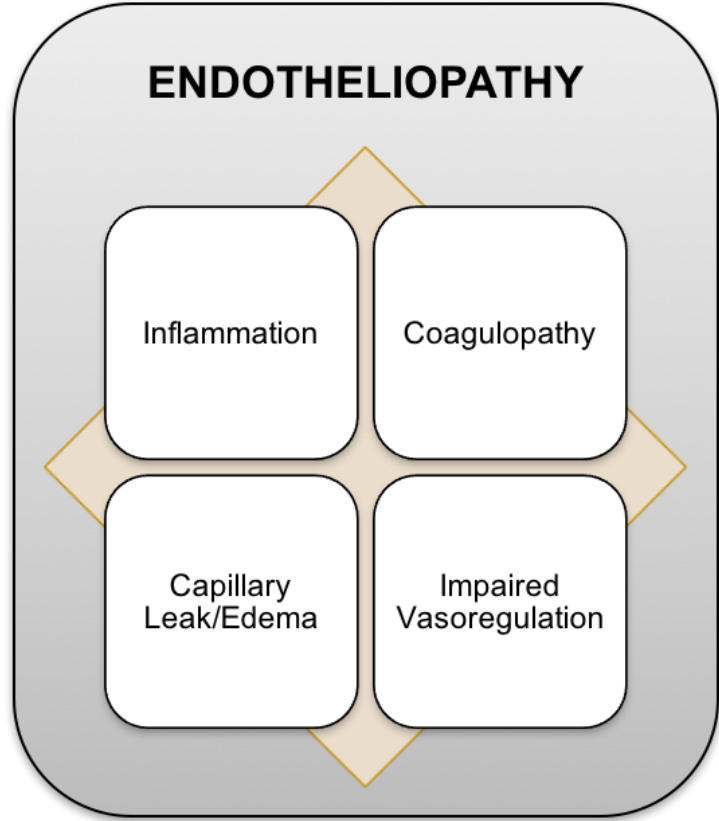
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Disclosures

- None



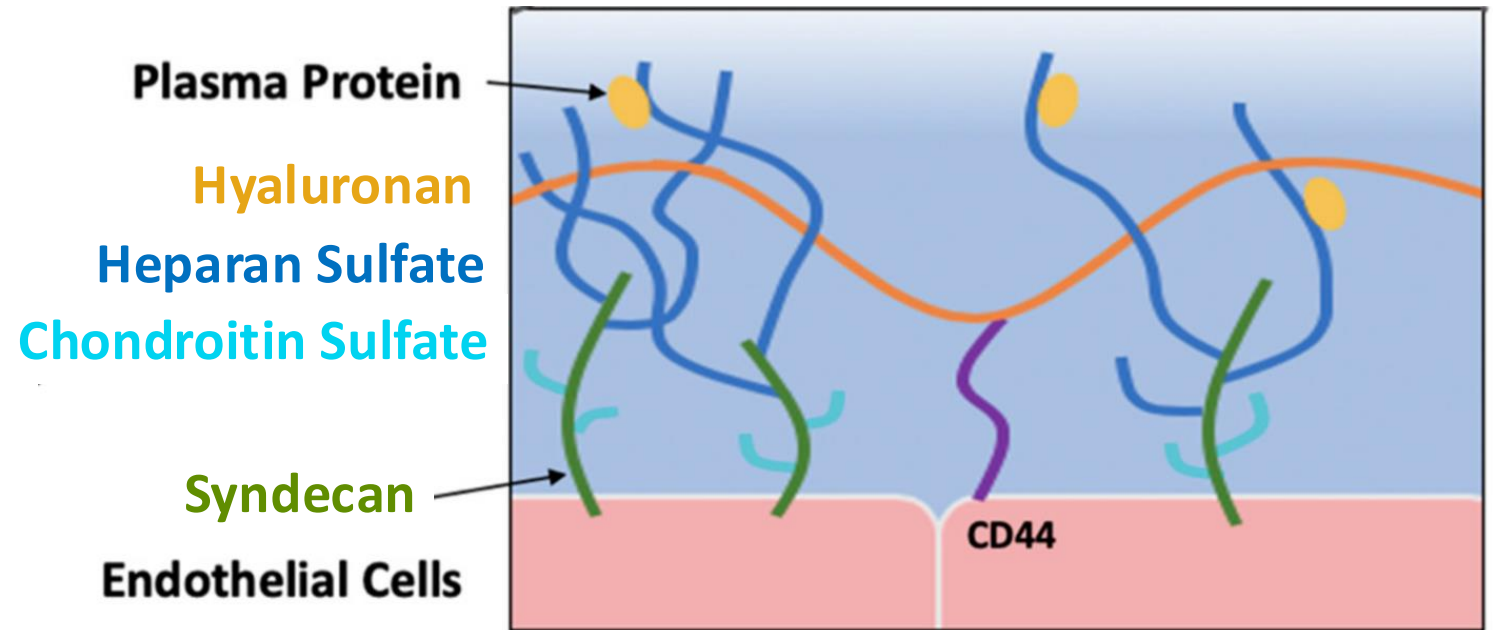
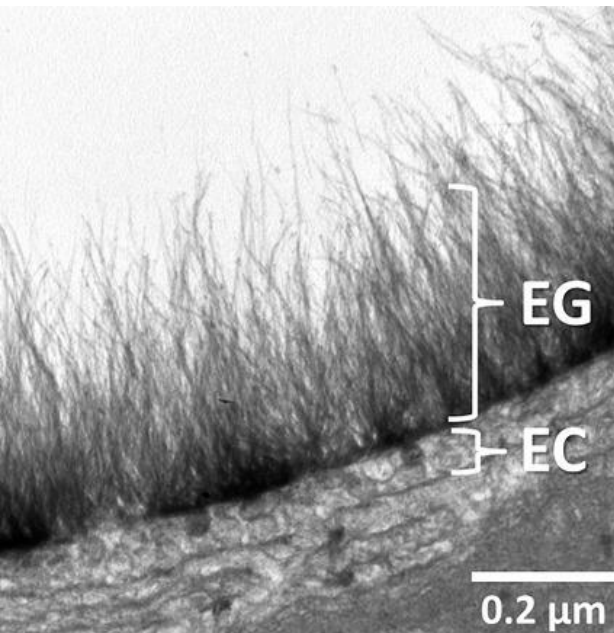
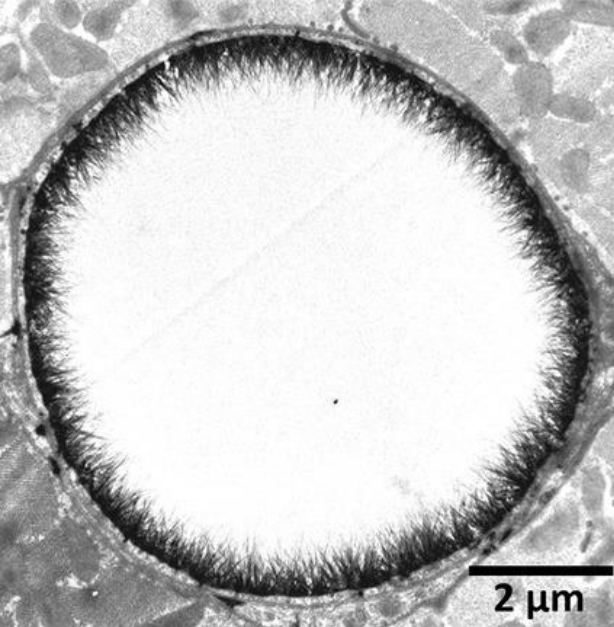


“Endotheliopathy of Trauma” (EoT)

“...systemic endothelial injury and dysfunction that lead to coagulation disturbances, inflammation, vascular leak, edema and tissue injury”

- Holcomb and Pati, 2013

The endothelial glycocalyx (eGCX) is a central regulator of vascular functions



Khan and Reilly. 2021

Van den Berg BM et al. 2007



eGCX Damage + Trauma

SHOCK, Vol. 49, No. 4, pp. 420–428, 2018

ENDOTHELIOPATHY OF TRAUMA IS AN ON-SCENE PHENOMENON, AND IS ASSOCIATED WITH MULTIPLE ORGAN DYSFUNCTION SYNDROME: A PROSPECTIVE OBSERVATIONAL STUDY

David N. Naumann,^{*†‡} Jon Hazeldine,^{†‡} David J. Davies,[‡] Jon Bishop,[‡] Mark J. Midwinter,[§] Antonio Belli,[‡] Paul Harrison,[†] and Janet M. Lord[†]

FEATURE

A High Admission Syndecan-1 Level, A Marker of Endothelial Glycocalyx Degradation, Is Associated With Inflammation, Protein C Depletion, Fibrinolysis, and Increased Mortality in Trauma Patients

Johansson, Pär I. MD, DMSc, MPA^{*}; Stensballe, Jakob MD, PhD[†]; Rasmussen, Lars S. MD, PhD, DMSc[‡]; Ostrowski, Sisse R. MD, PhD, DMSc^{*}

[Author Information](#) ☺

Annals of Surgery: August 2011 - Volume 254 - Issue 2 - p 194-200

ORIGINAL SCIENTIFIC ARTICLE | VOLUME 225, ISSUE 3, P419-427, SEPTEMBER 01, 2017

PDF [293 KB]

Syndecan-1: A Quantitative Marker for the Endotheliopathy of Trauma

Erika Gonzalez Rodriguez, MD   • Sisse R. Ostrowski, MD, DMSc • Jessica C. Cardenas, PhD
Lisa A. Baer, BSc • Jeffrey S. Tomasek, MD • Hanne H. Henriksen, BSc • Jakob Stensballe, MD, PhD
Bryan A. Cotton, MD, MPH, FACS • John B. Holcomb, MD, FACS • Pär I. Johansson, MD, DMSc •
Charles E. Wade, PhD • [Show less](#)

[Open Access](#) • Published: June 01, 2017 • DOI: <https://doi.org/10.1016/j.jamcollsurg.2017.05.012>



Research Goals:

1. Mitigate

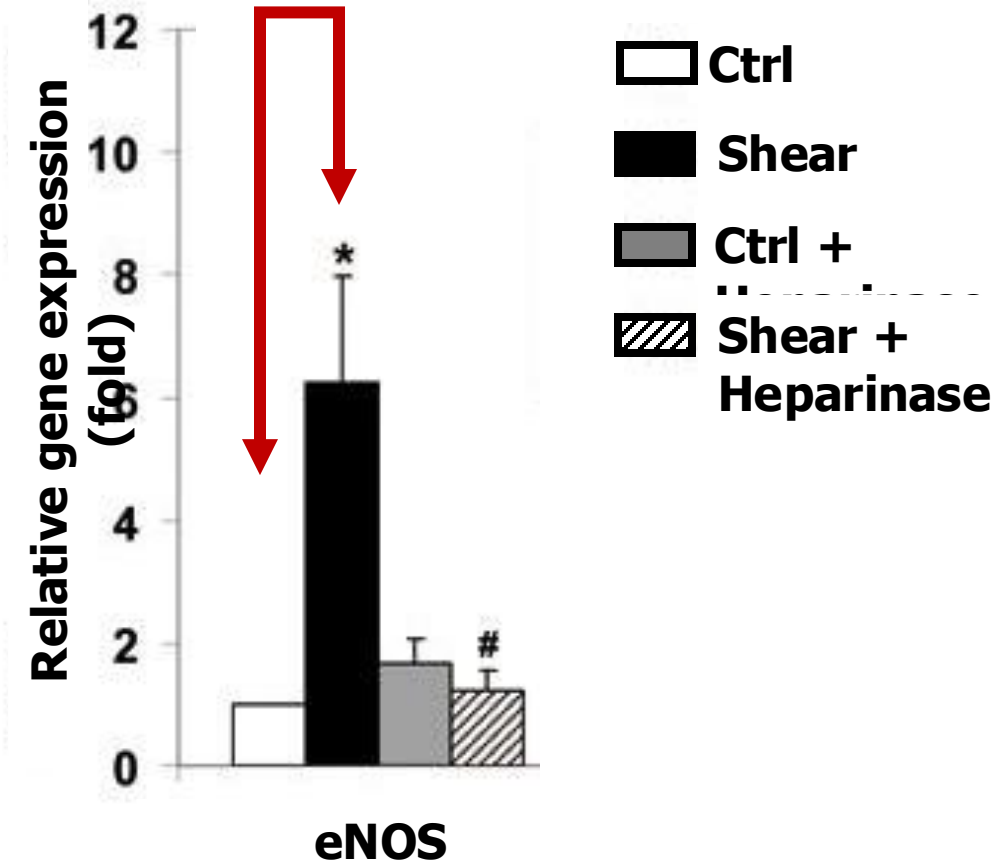
Can we mitigate the consequences of eGCX damage to prevent EoT?

2. Repair

Can we target mechanisms of eGCX synthesis to restore vascular homeostasis?

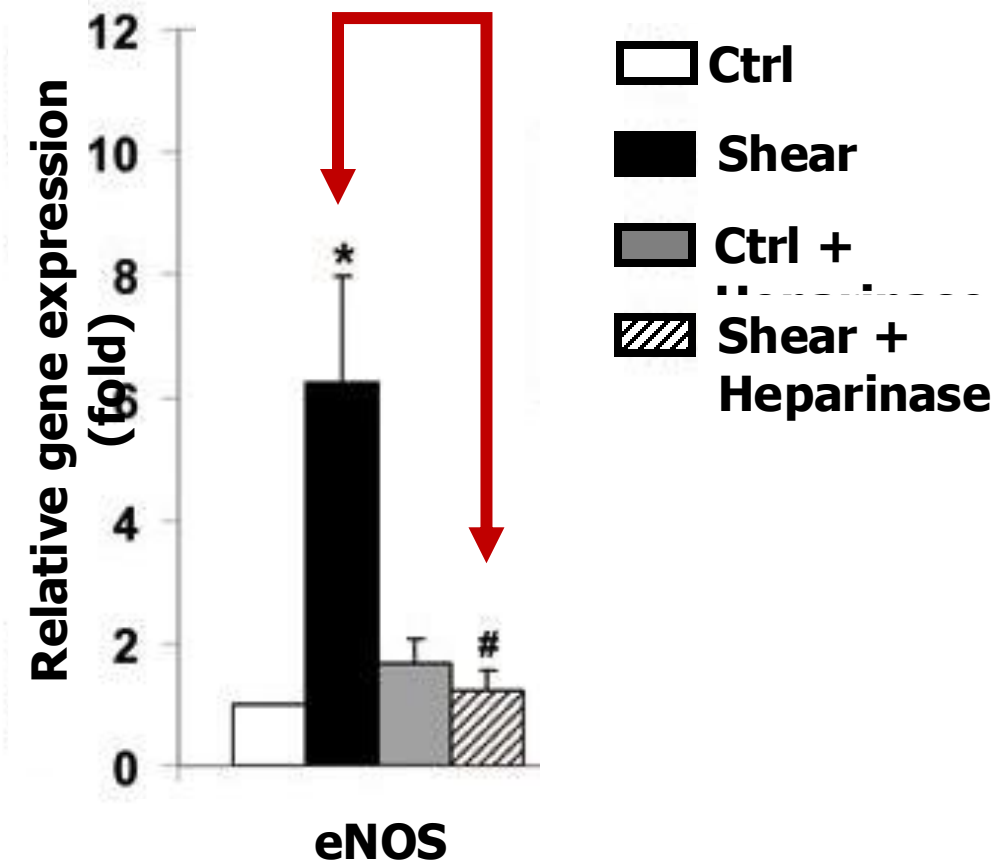


Heparan Sulfate (HS)



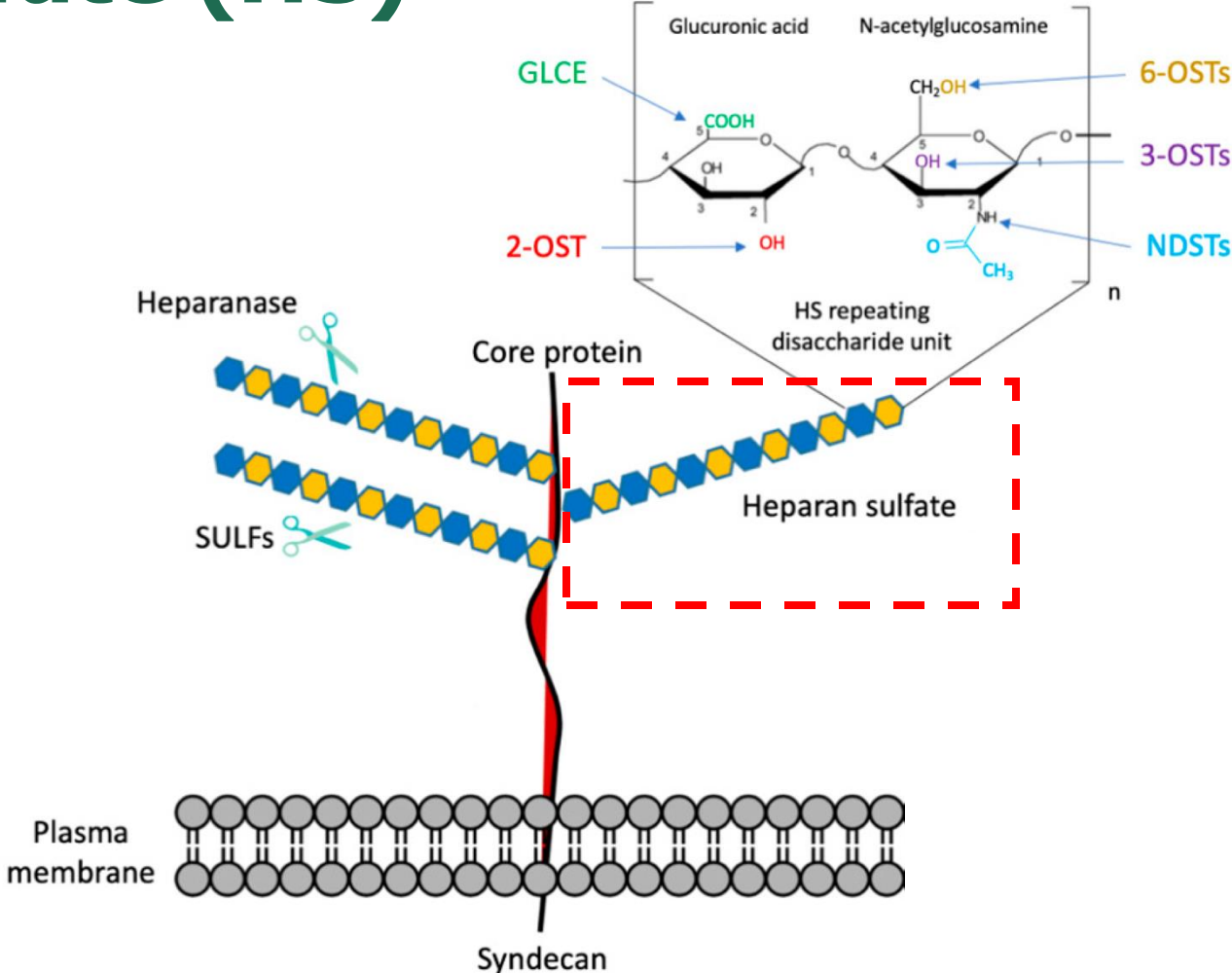
Nikmanesh M. et al. 2012

Heparan Sulfate (HS)



Nikmanesh M. et al. 2012

Heparan Sulfate (HS)



De Pasquale. 2021

Alterations in heparan sulfate proteoglycan synthesis and sulfation and the impact on vascular endothelial function.

Pretorius D ¹, Richter RP ², Anand T ³, Cardenas JC ⁴, Richter JR ¹

Author information ▶

Matrix Biology Plus, 07 Sep 2022, 16:100121

DOI: [10.1016/j.mbplus.2022.100121](https://doi.org/10.1016/j.mbplus.2022.100121) PMID: 36160687 PMCID: PMC9494232



Trauma/Shock

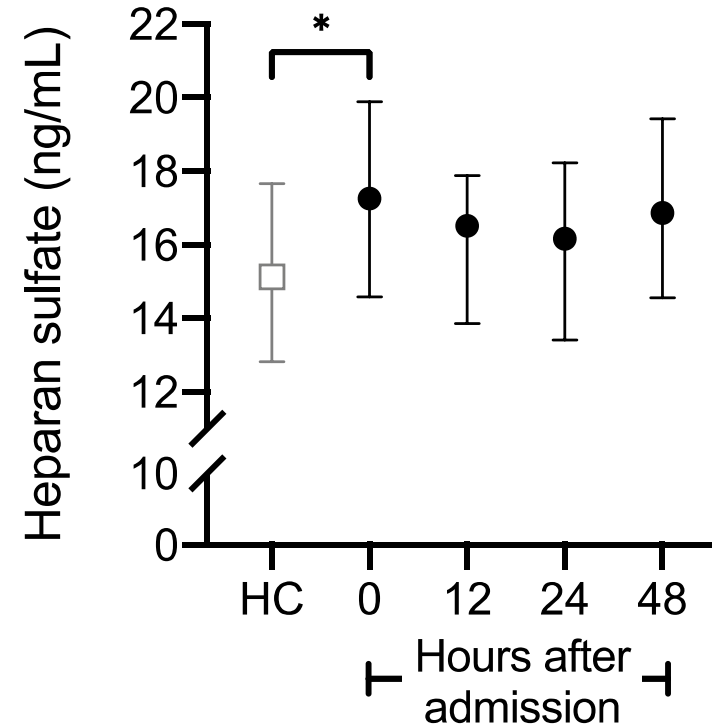
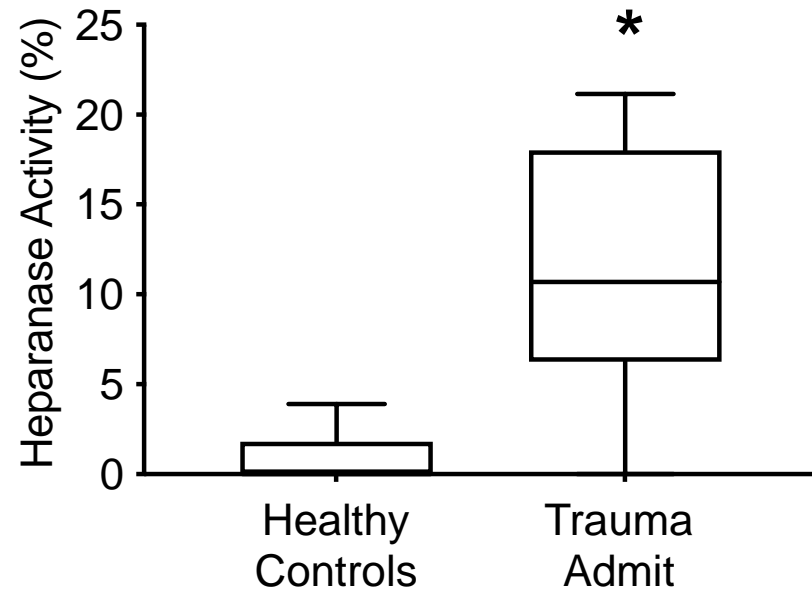


Heparan Sulfate:
1. Cleavage
2. Sulfation
3. Synthesis

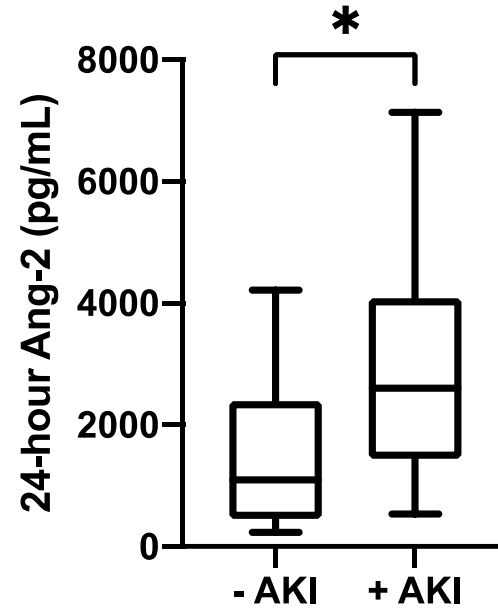
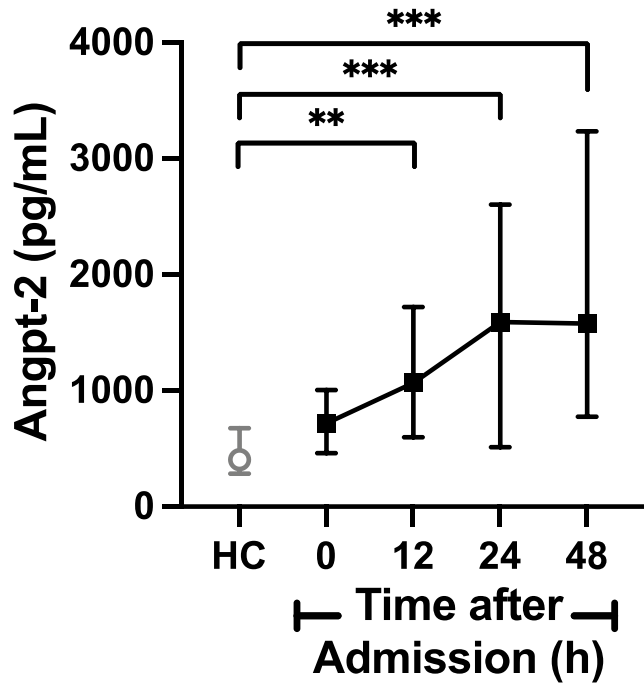


Endotheliopathy

Heparanase activity increases following injury:



Trauma-induced Angiopoietin-2 (Angpt-2) release is associated with poor clinical outcomes:



Spearman's rank correlation between 24-hour Angpt-2 levels and clinical outcomes.

	rho	p-value
MV Duration	0.410	0.004
ICU Length of Stay	0.610	<0.0001
Hospital Length of Stay	0.527	<0.0001

Uhlich RM et al. *Shock*. 2020.

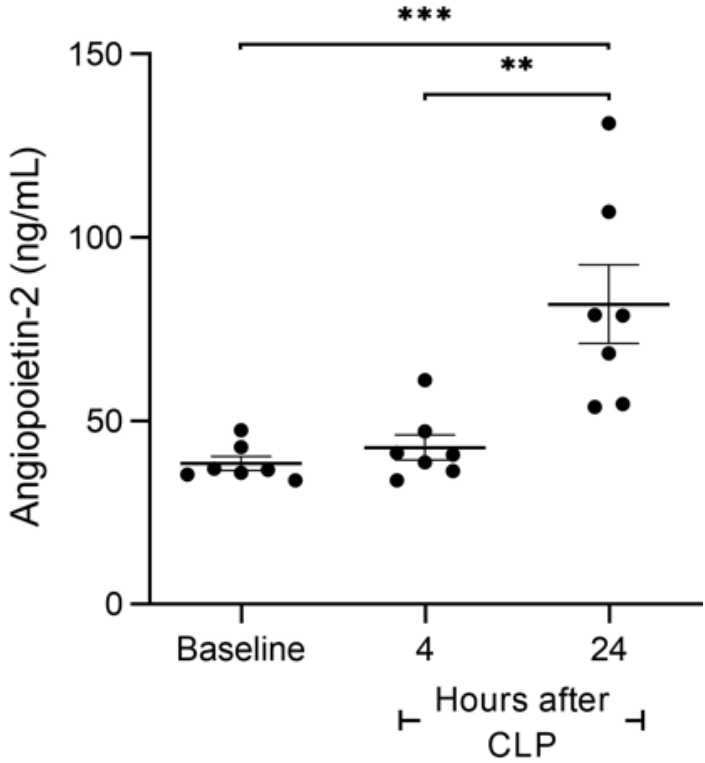
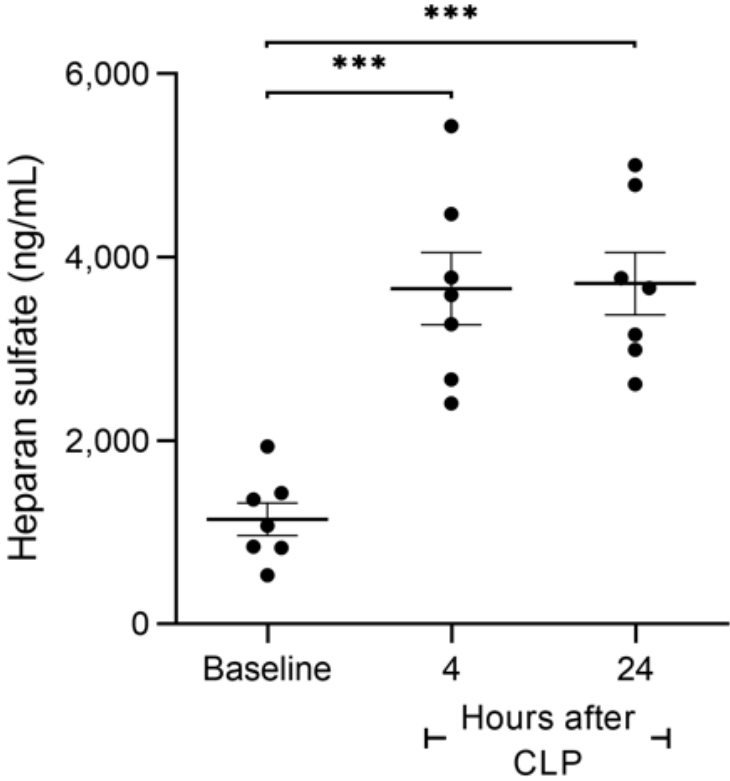
eGCX damage correlates with Angpt-2 release

Spearman's rank correlation between plasma levels of eGCX biomarkers and Angpt-2.

Study Population	eGCX Biomarker	rho	p-value	Ref.
Pediatric Trauma	Sdc-1	0.49	<0.001	Richter, <i>Shock</i> . 2019
Pediatric Sepsis	Hep Sulf	0.42	<0.001	Richter, <i>JCI Insight</i> . 2022
Adult Trauma (UAB)	Hep Sulf	0.28	0.02	Unpublished
Adult Trauma (PROPPR)	Sdc-1	0.39	<0.001	Unpublished



Heparan sulfate cleavage precedes Angpt-2 release:



Richter, RP et al. 2022. *JCI Insight*

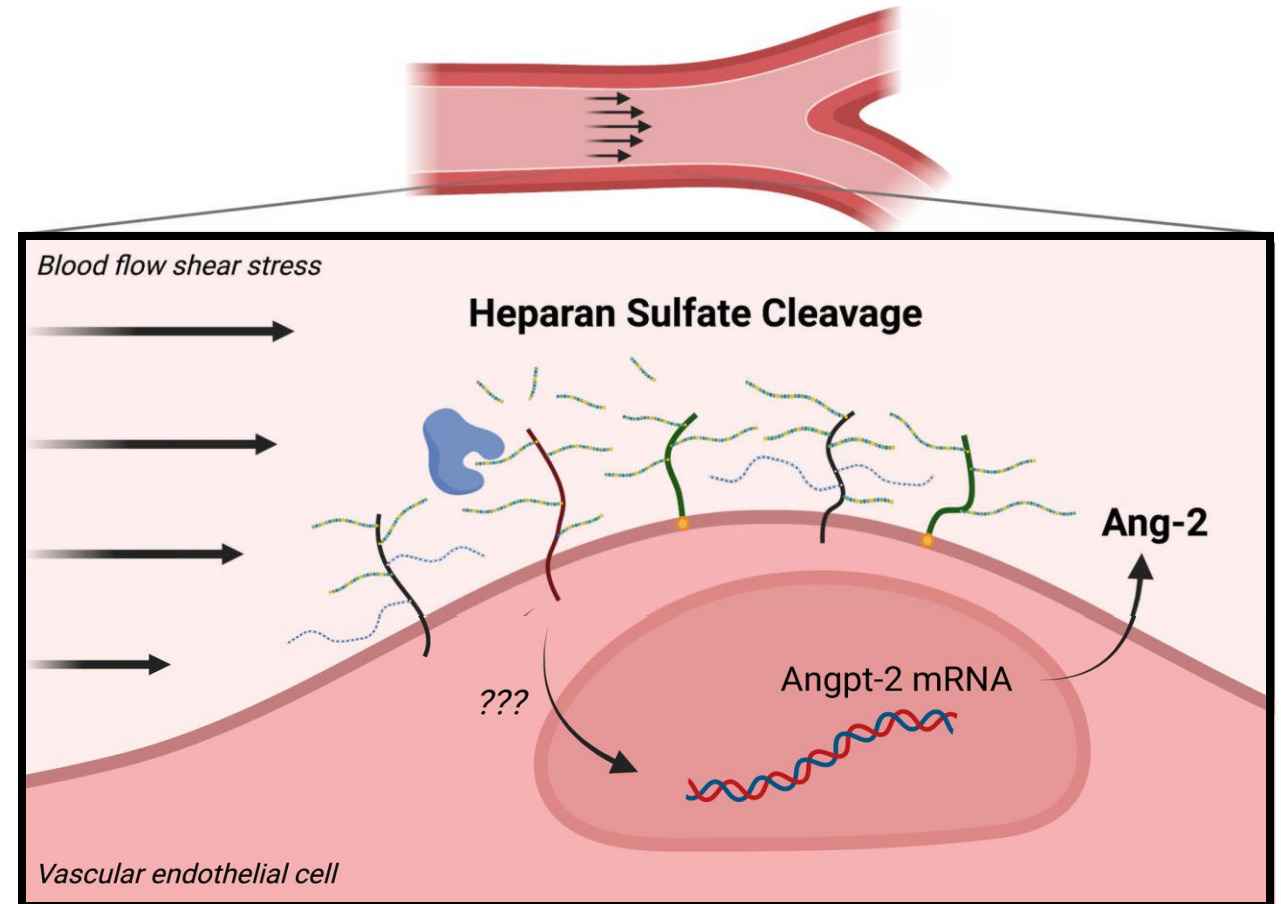


Hypothesis:
heparan sulfate cleavage
promotes endothelial cell
production of Angpt-2

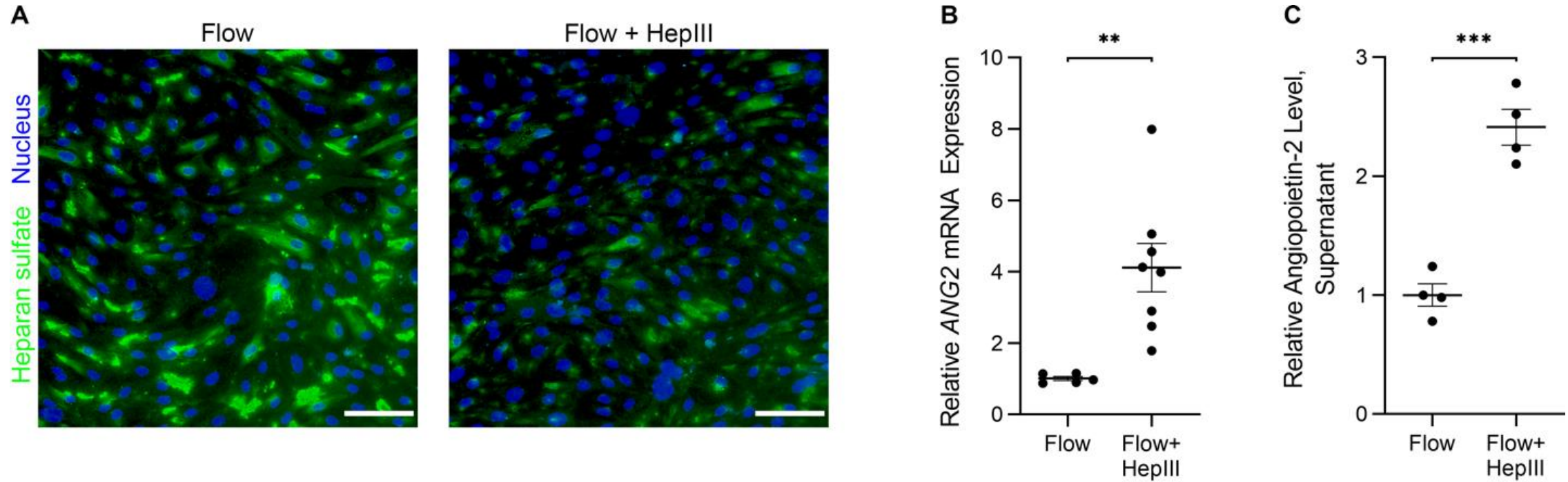


In Vitro Studies:

- ❖ Bioengineered flow model
 - laminar shear stress
- ❖ Primary human lung microvascular endothelial cells (HLMVEC)
 - passage 3-6
- ❖ Heparinase-III (200mU/mL)

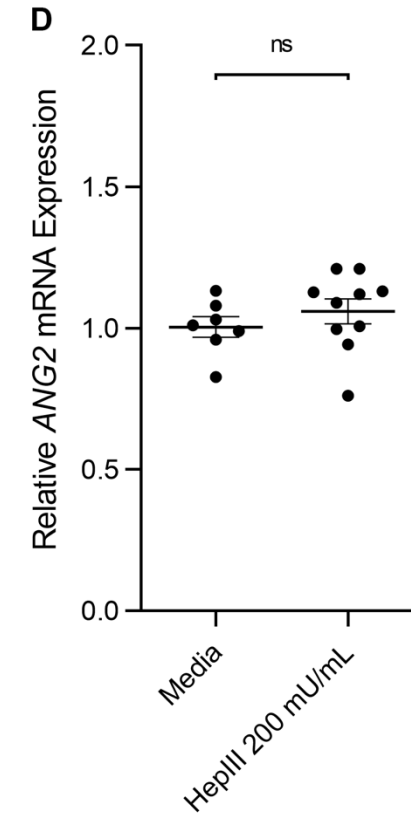
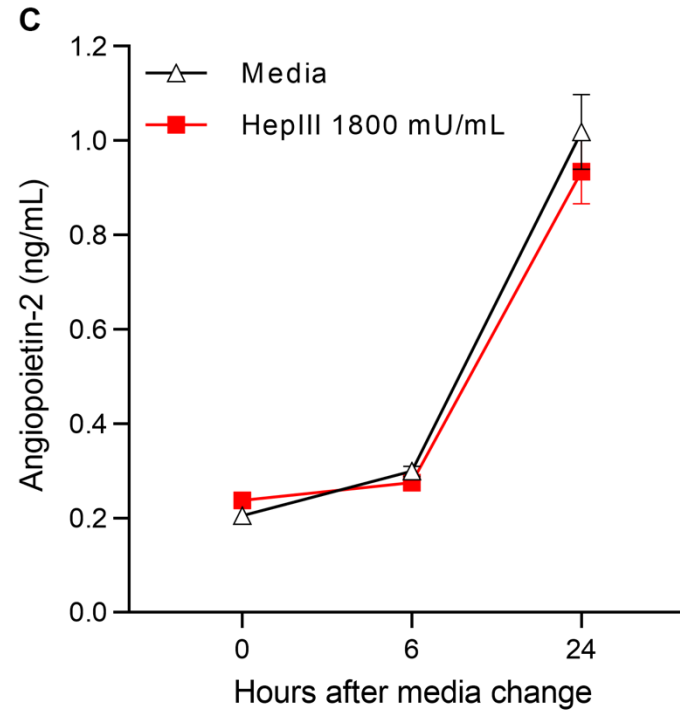
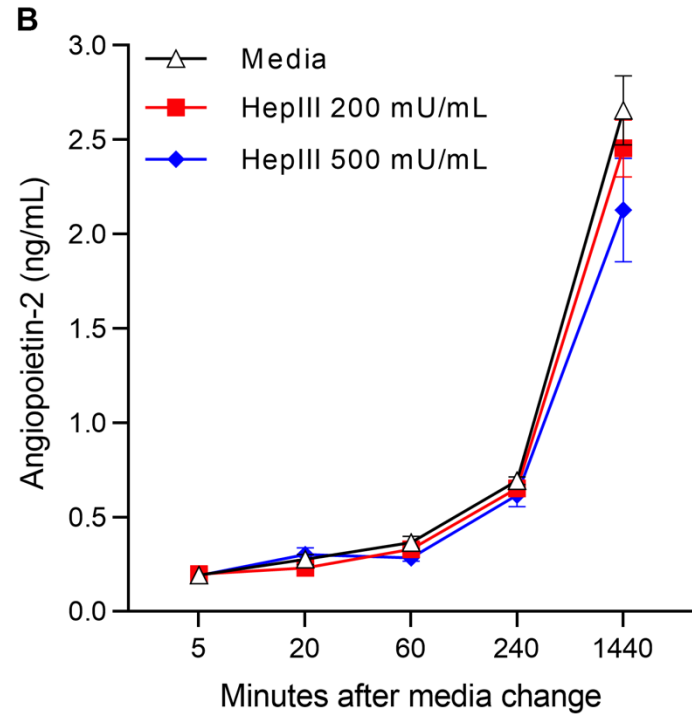


Heparan sulfate cleavage promotes Angpt-2 expression in flow conditioned HLMVEC:



Richter, RP et al. 2022. *JCI Insight*

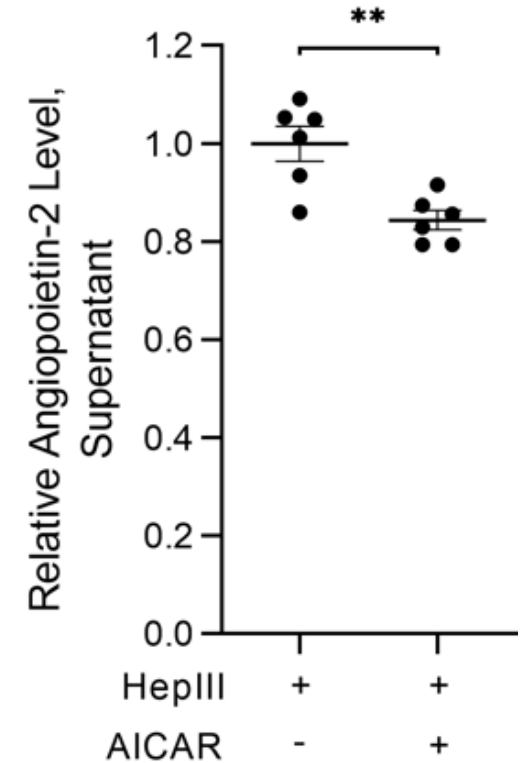
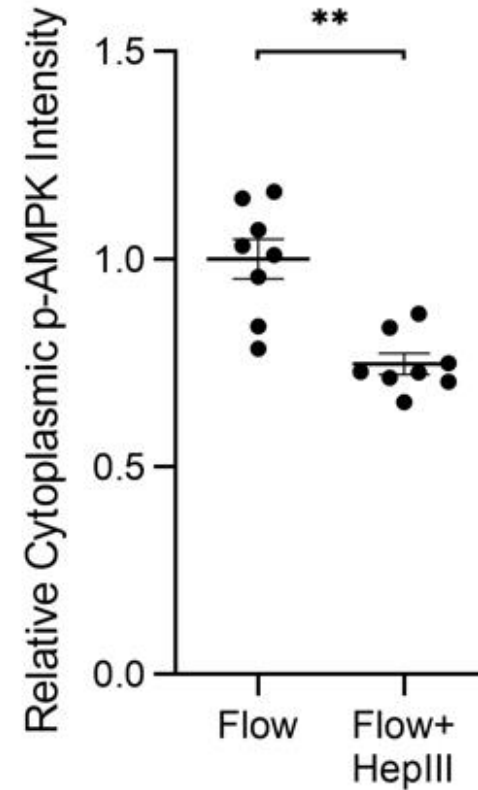
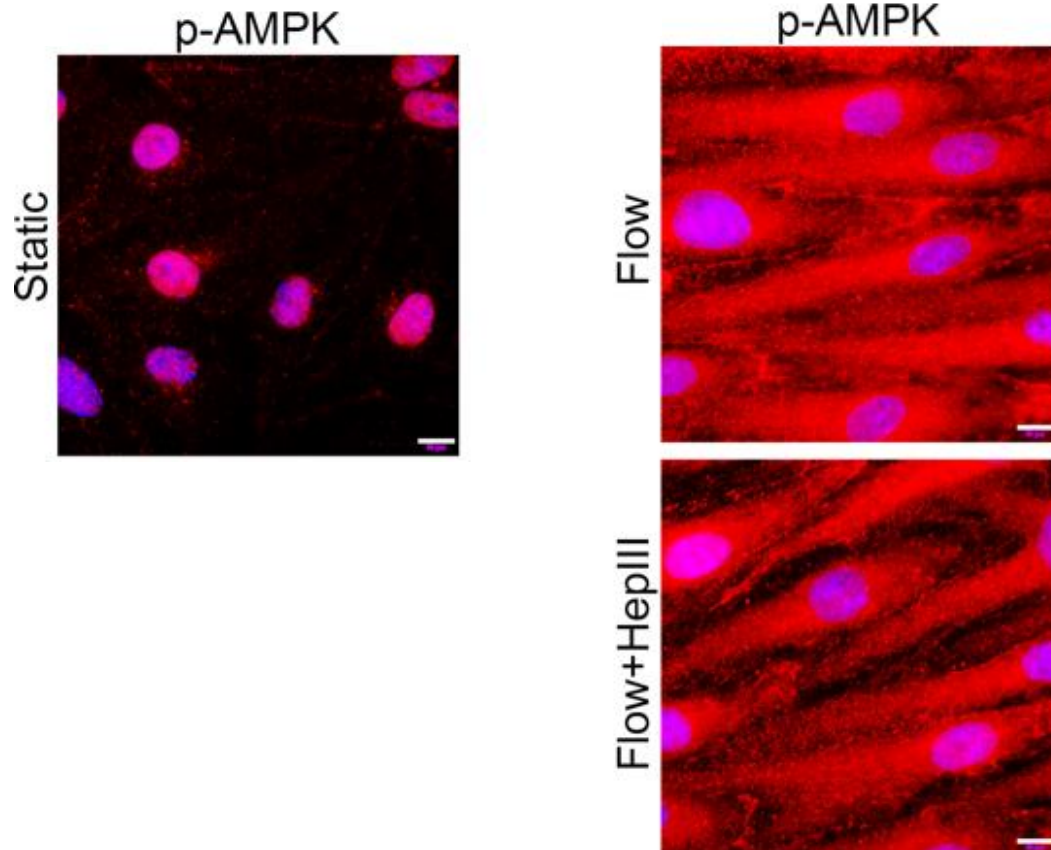
...but not in *statically* cultured HLMVEC



Richter, RP et al. 2022. *JCI Insight*

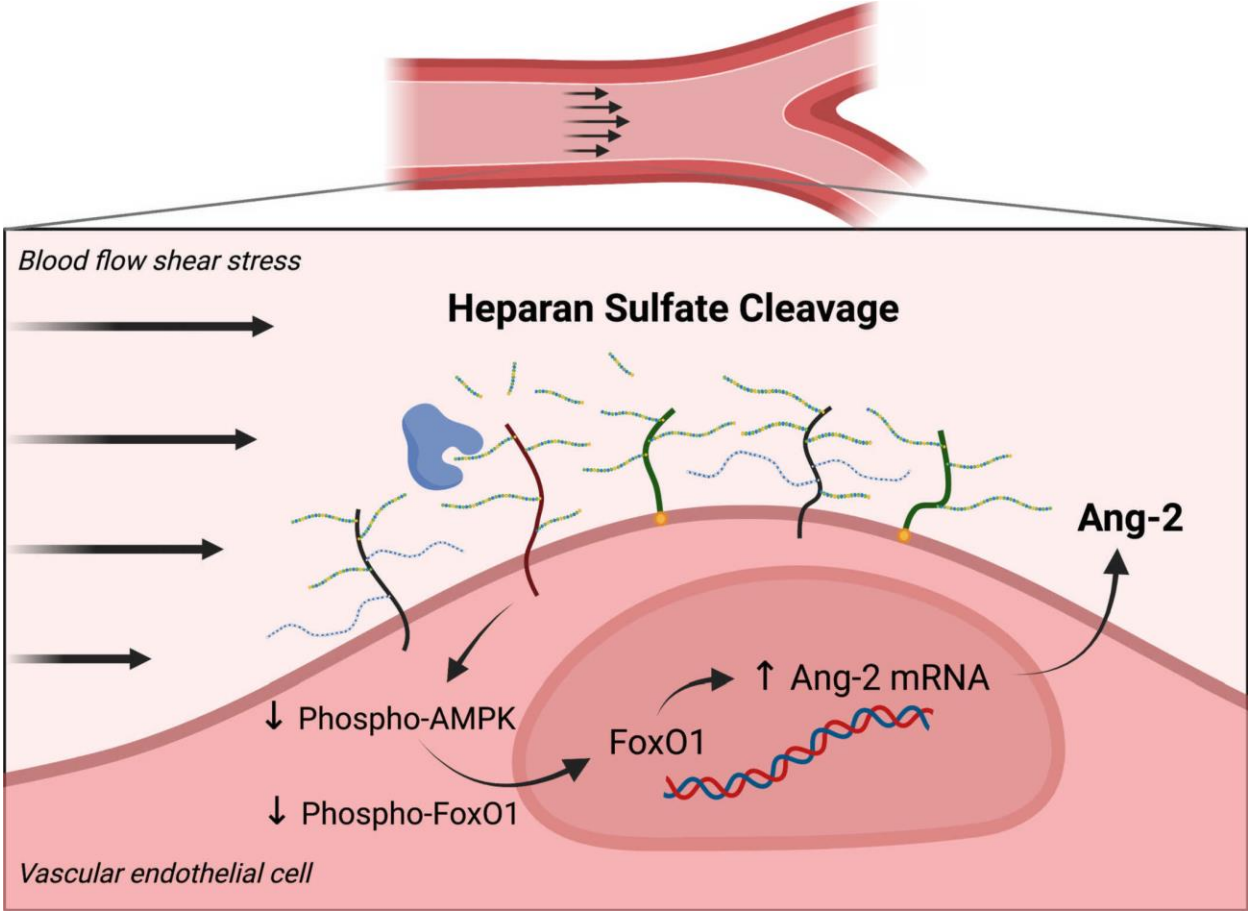


Heparan sulfate cleavage promotes Angpt-2 expression via deactivation of AMPK signaling



Richter, RP et al. 2022. *JCI Insight*

Heparan sulfate cleavage promotes Angpt-2 production



Richter, RP et al. 2022. *JCI Insight*

Trauma/Shock



- 1. Cleavage
- 2. Sulfation
- 3. Synthesis



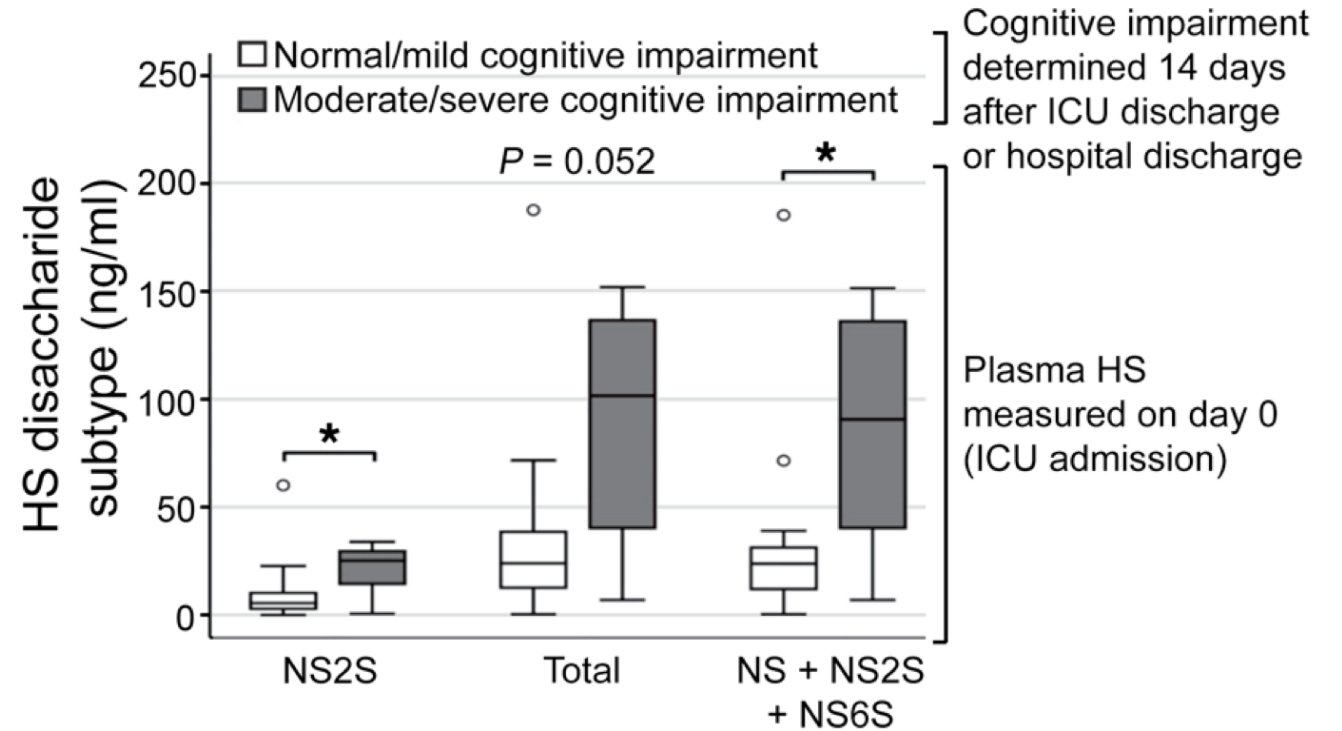
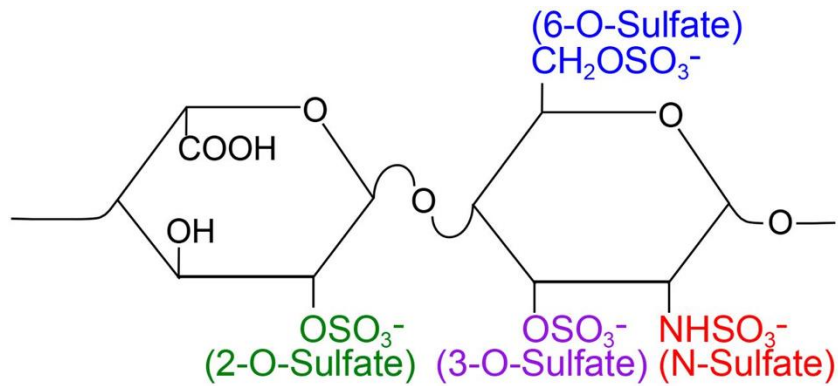
Endotheliopathy

Soluble heparan sulfate fragments are bioactive

- ❖ TLR4 activation → Cytokine production
- ❖ Growth factor signaling:
 - HS/FGF2/FGFR → cell proliferation, migration, angiogenesis, etc
 - HS interferes BDNF/TrkB → neurocognitive impairments



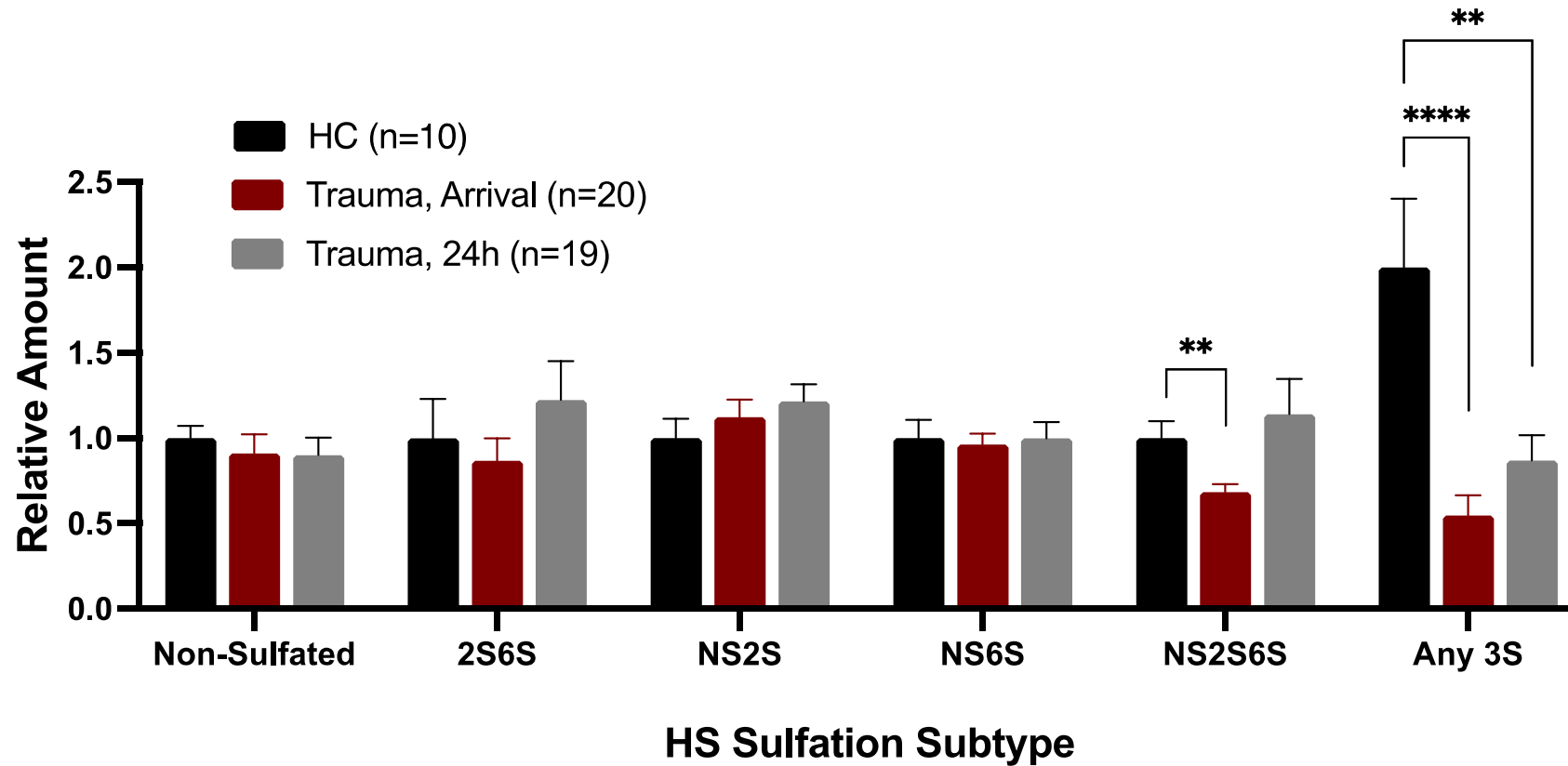
Sulfation patterning dictates HS bioactivity:



Hippensteel, J. 2019



Changes in sulfation pattern of soluble HS after trauma:



Unpublished data



Check for updates

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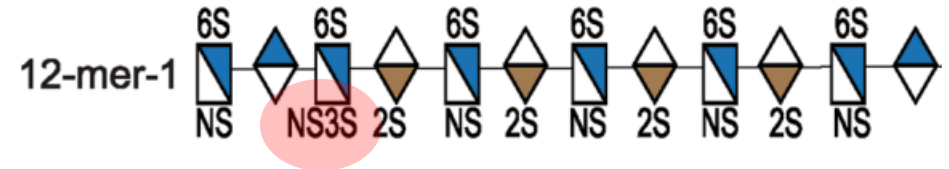
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A 3-O-sulfated heparan sulfate dodecasaccharide (12-mer) suppresses thromboinflammation and attenuates early organ injury following trauma and hemorrhagic shock

Maria del Pilar Huby Vidaurre¹, Baron K. Osborn¹, Kaylie D. Lowak¹, Michelle M. McDonald², Yao-Wei W. Wang¹, Veda Pa¹, Jillian R. Richter³, Yongmei Xu⁴, Katelyn Arnold⁴, Jian Liu⁴ and Jessica C. Cardenas^{1*}



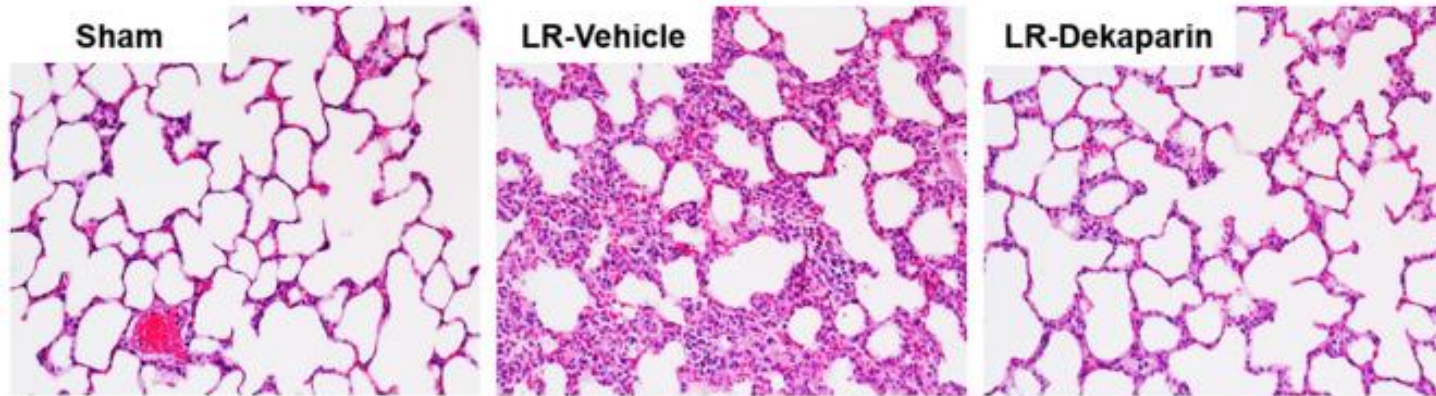
- ❖ Anti-coagulant:
 - Diminishes Factor Xa activity
- ❖ Anti-inflammatory:
 - Sequesters HMGB1

Arnold, K. 2020. Sci Rep

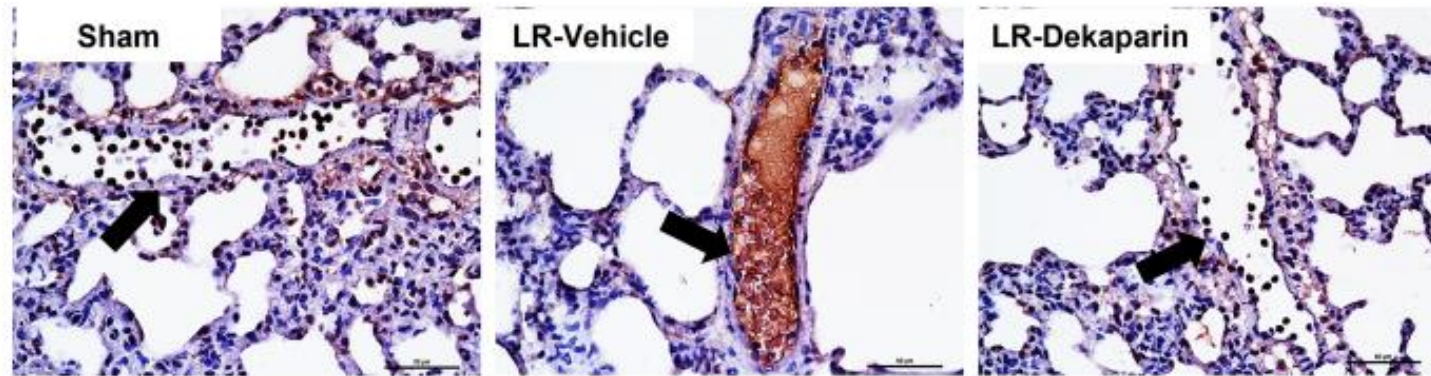


3-O-sulfated HS mimetic is protective against T/HS-induced organ injury:

Inflammation (H&E)



Fibrin Deposition



Vidaurre, M. 2023. *Front Immunol*



Trauma/Shock



- 1. Cleavage
- 2. Sulfation:
↓ 3-O-sulfated HS → thromboinflammation
- 3. Synthesis



Endotheliopathy



Trauma/Shock



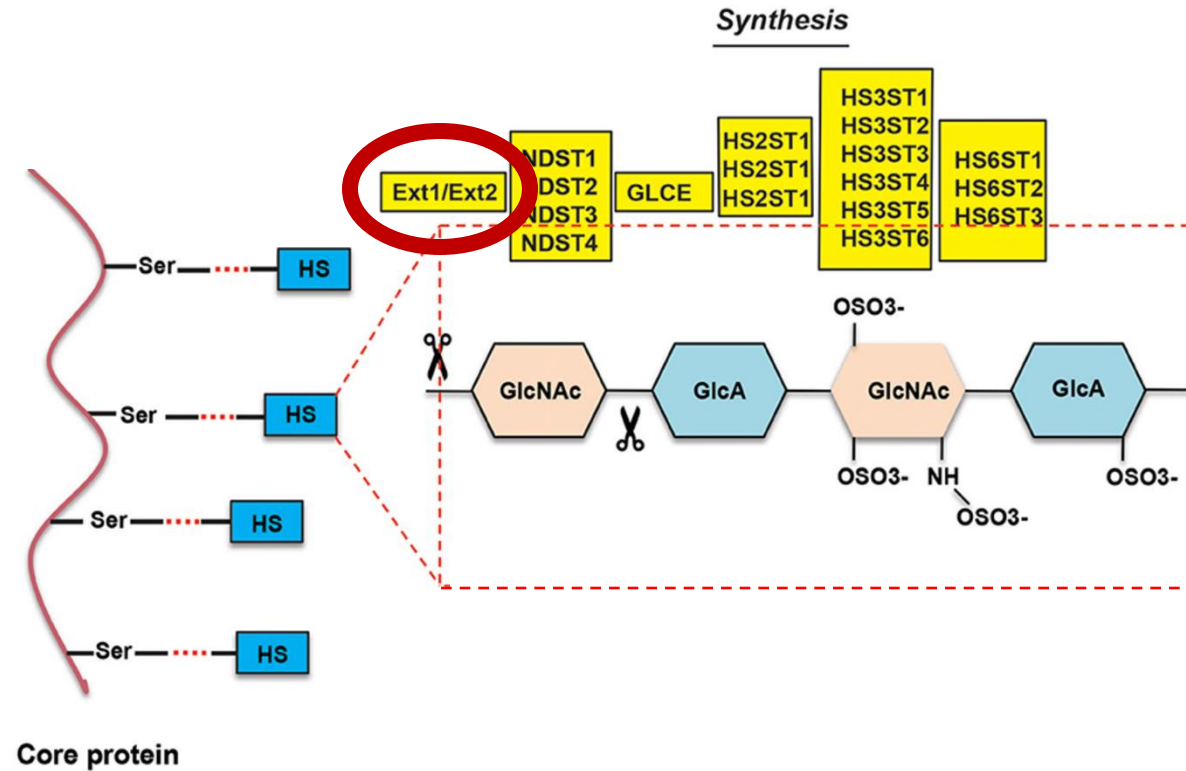
- 1. Cleavage
- 2. Sulfation
- 3. Synthesis



Endotheliopathy



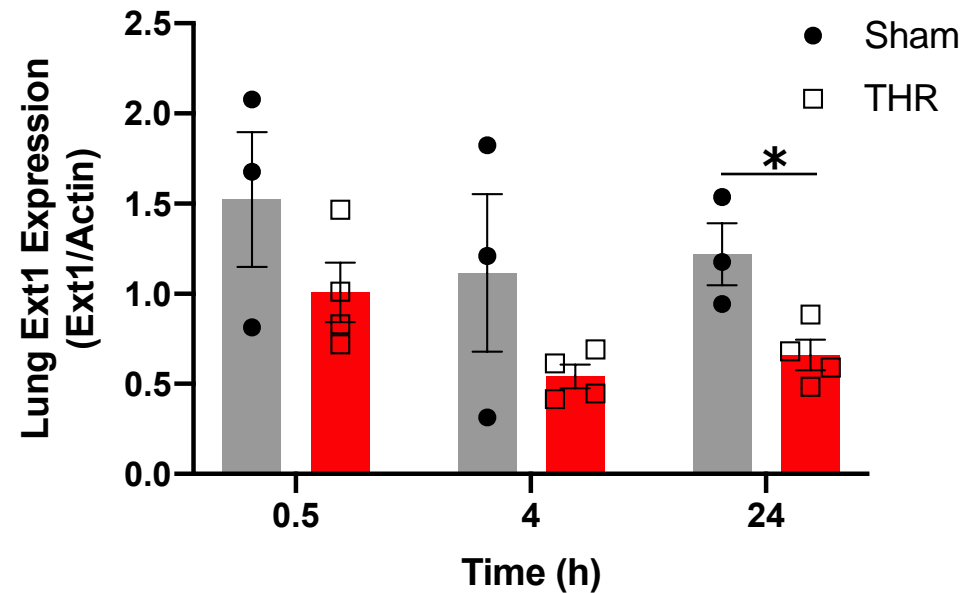
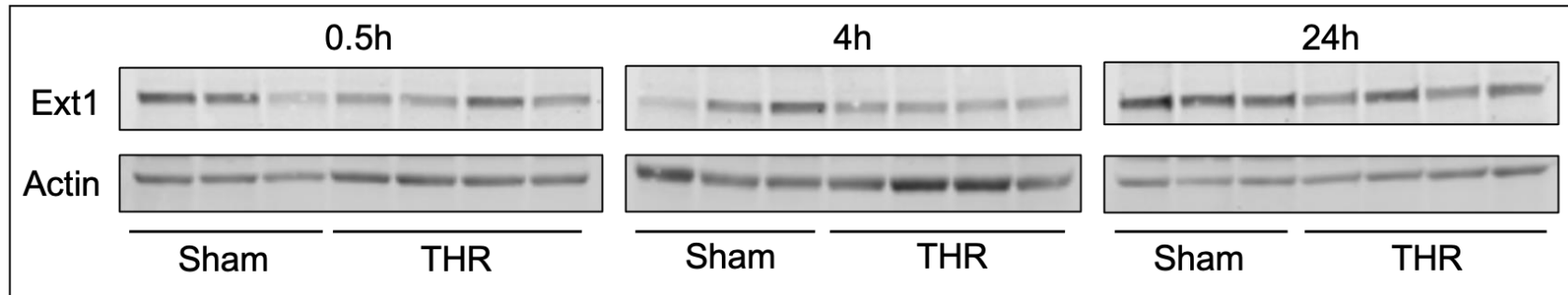
Exostosin-1 (Ext1) is required for HS synthesis



Nagarjan, A. 2018. *Front. Endocrinol.*

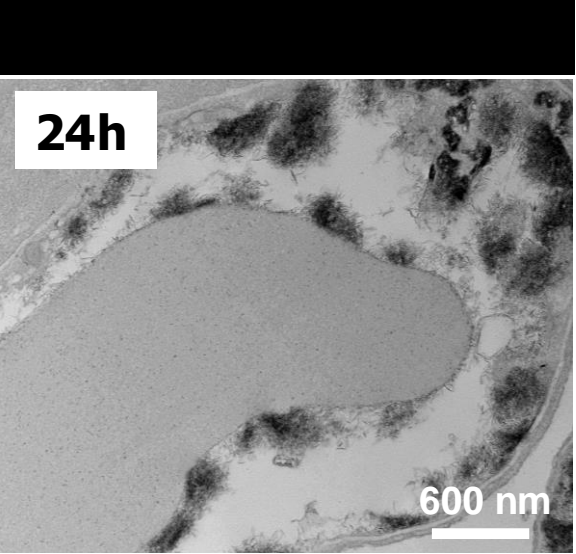
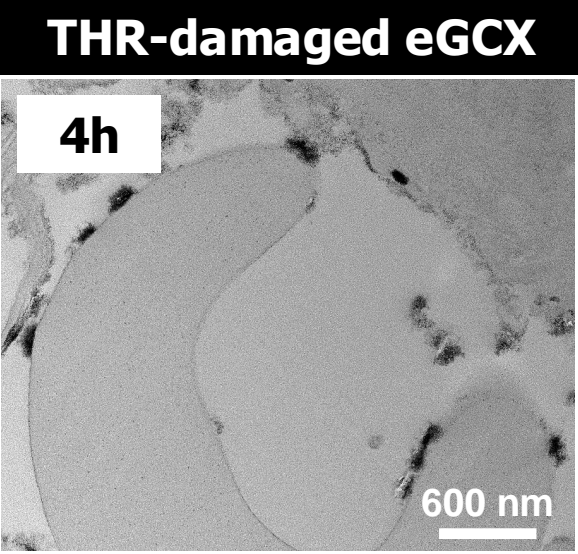
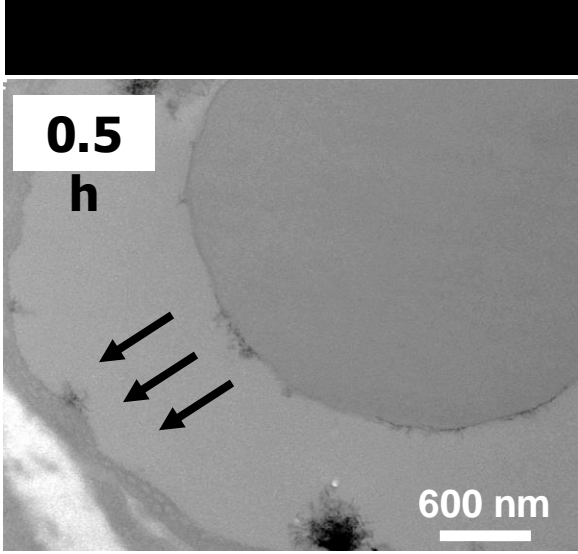
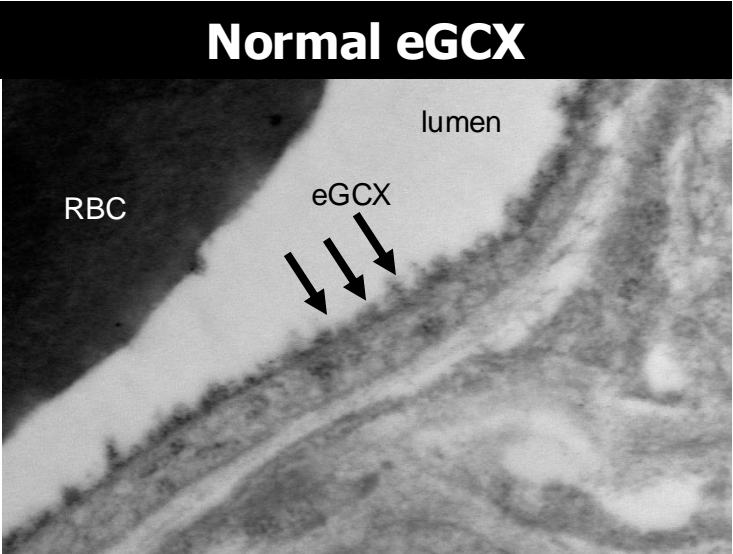


eGCX damage corresponds with decreased pulmonary Ext1 expression:



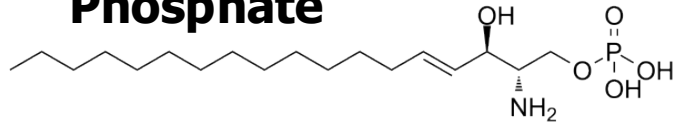
Unpublished data.

Pulmonary eGCX damage after THR:

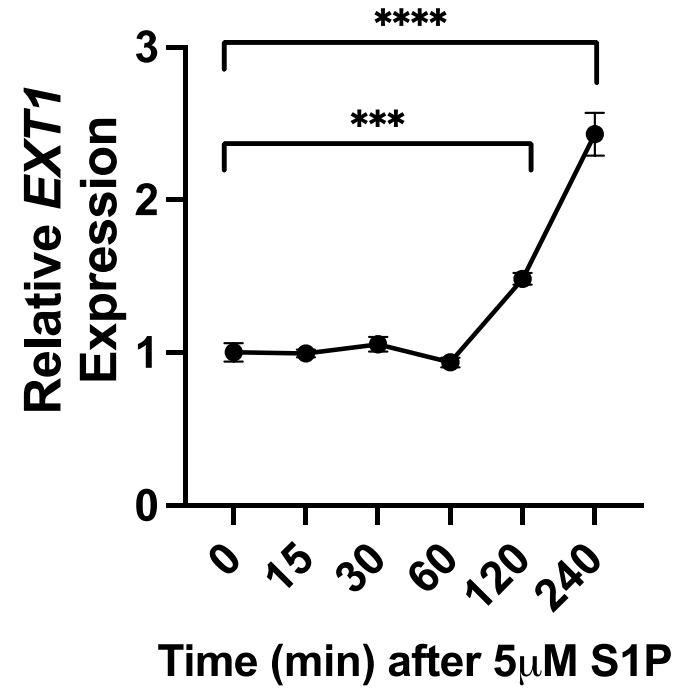
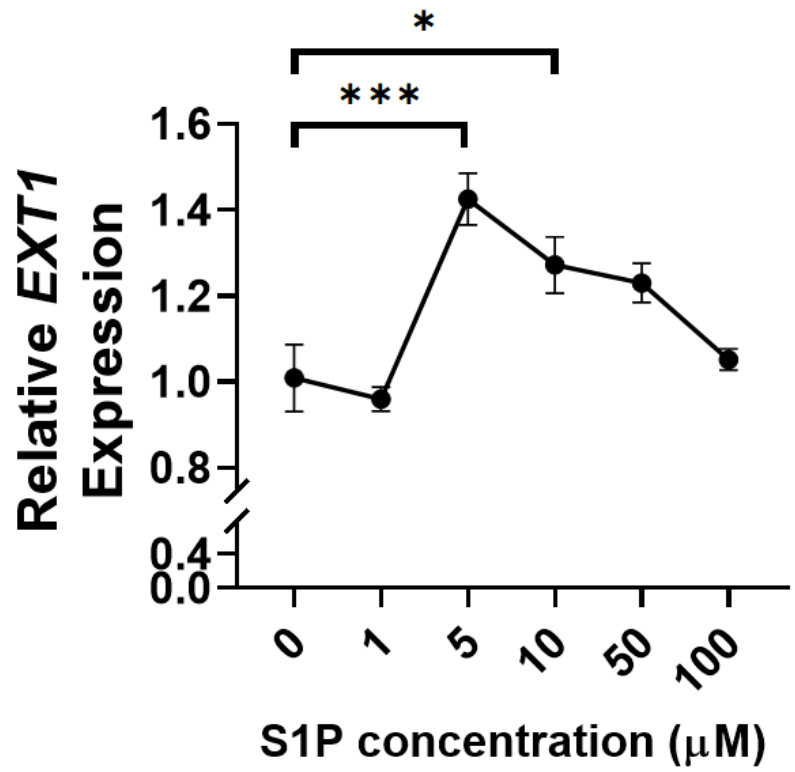


Targeting Ext1 expression with sphingosine-1-phosphate (S1P)

Sphingosine-1-Phosphate

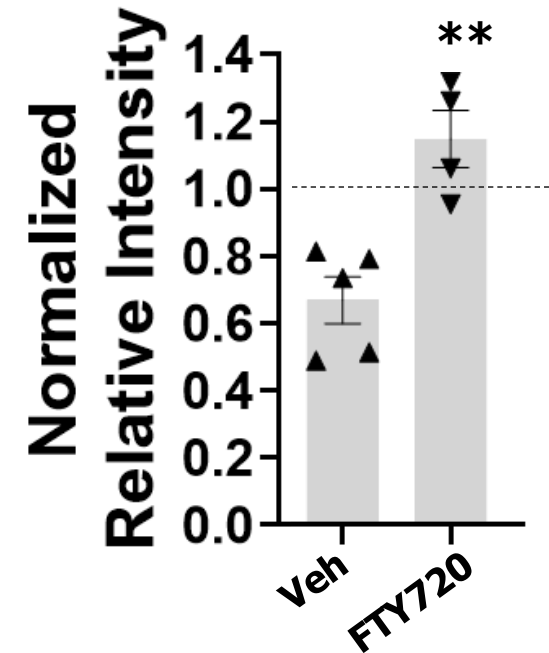
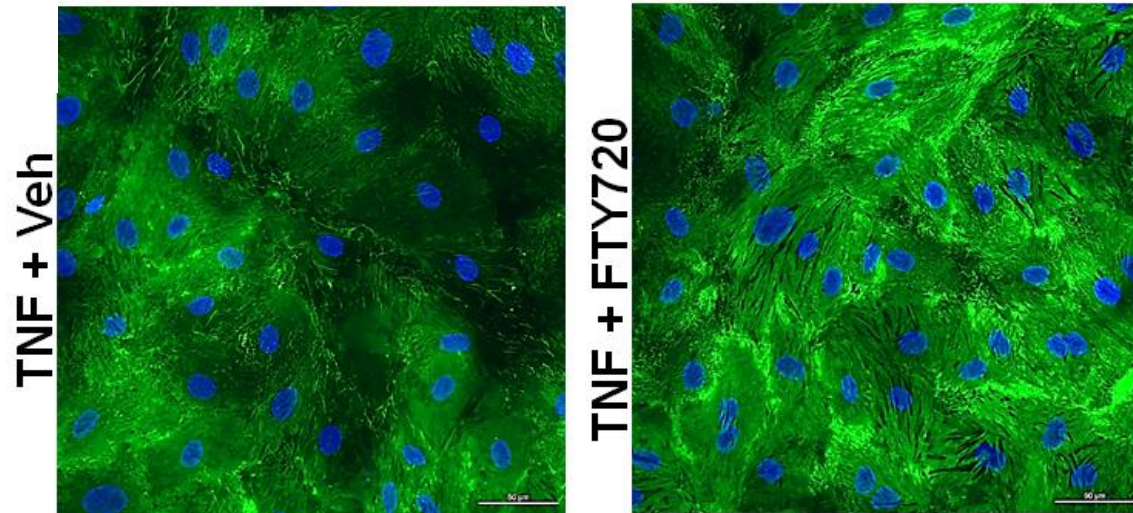


S1P increases *Ext1* expression



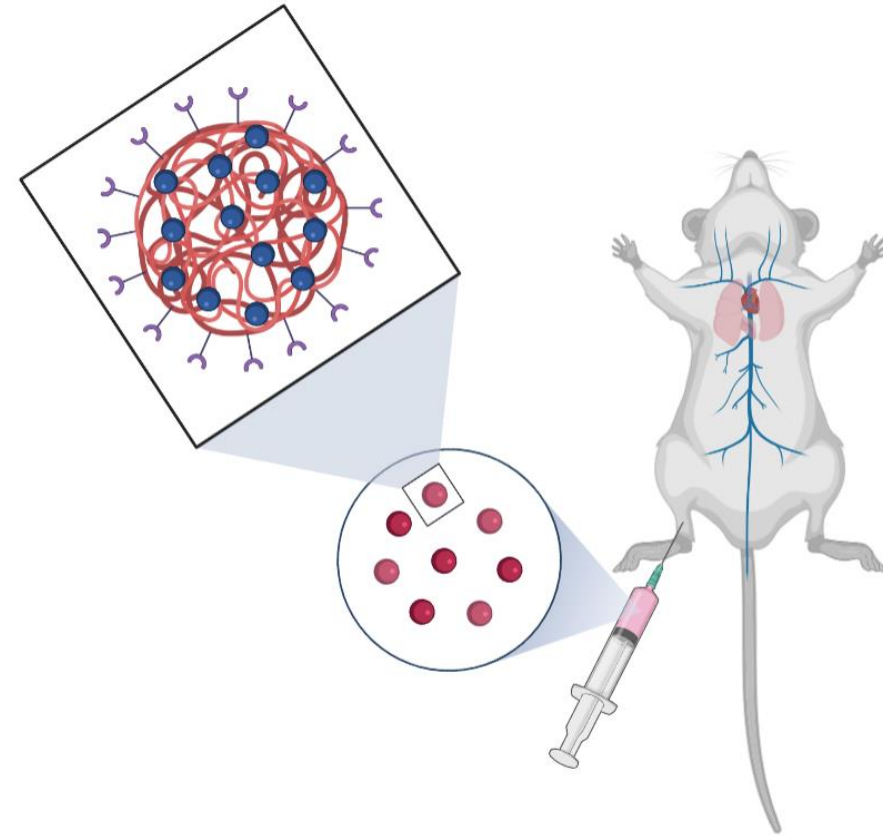
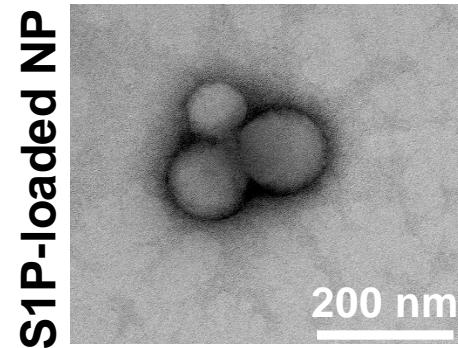
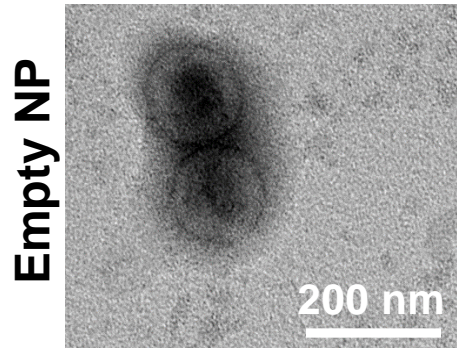
Unpublished data.

S1P treatment increases HS synthesis in damaged HLMVECs

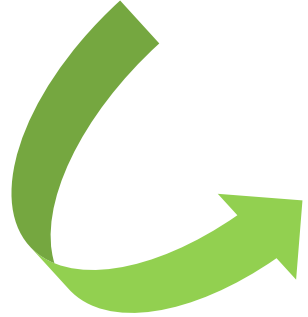


Unpublished data.

In vivo approach: S1P-loaded nanoparticles



Trauma/Shock



Executive Summary

1. ↓ HS Expression → ↑ Angpt-2
2. ↓ 3-O-sulfated HS → coagulation/inflammation
3. ↓ Ext1 → ↓ HS Synthesis



Endotheliopathy

Trauma/Shock

Resuscitation Strategies?



Executive Summary

1. ↓ HS Expression → ↑ Angpt-2
2. ↓ 3-O-sulfated HS → coagulation/inflammation
3. ↓ Ext1 → ↓ HS Synthesis



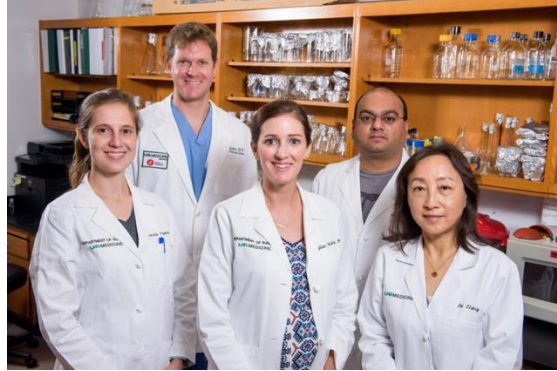
Targeted Therapies



Endotheliopathy

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- Dr. Jeff Kerby, MD PhD (*Trauma Surgery*)
- Dr. Ralph Sanderson, PhD (*HSPG Biology*)



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Thank you!



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