Traumatic Brain Injury-Associated Coagulopathy

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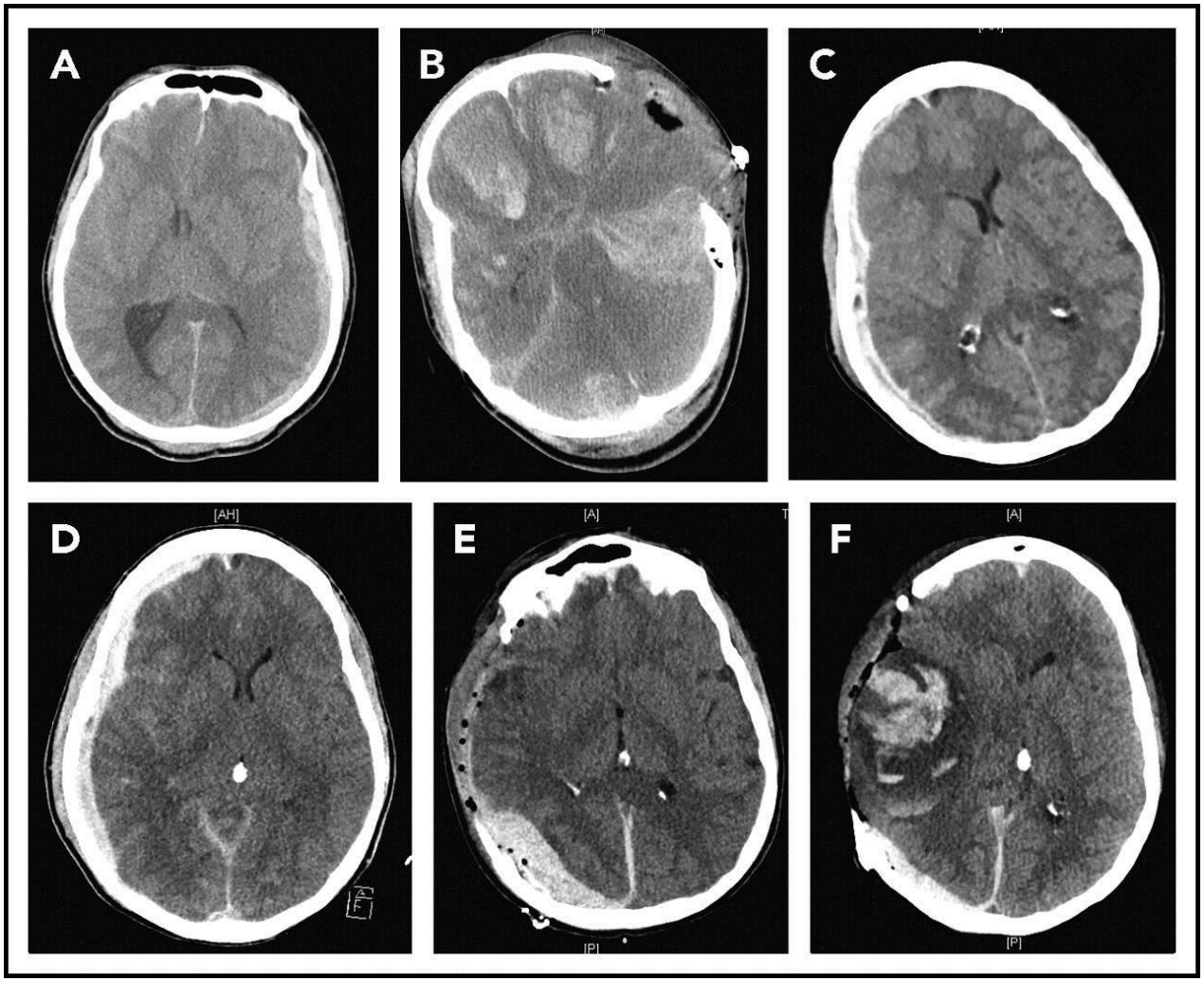
Case in Point



Jianning Zhang et al. Blood 2018;131:2001-2006

Trauma-induced Coagulopathy

Secondary bleeding after traumatic injury

closely associated with higher transfusion requirements, longer intensive care unit and hospital stays, and poor clinical outcomes.

Common causes are:

1. significant blood loss
2. hemodilution due to fluid resuscitation
3. hypothermia and metabolic acidosis
4. substantial damage to the endothelium
5. consumption

Cause of TBI-induced Coagulopathy

Extracranial trauma vs. TBI

1. Significant blood loss
2. Hemodilution due to fluid resuscitation
3. Hypothermia and metabolic acidosis
4. Substantial damage to the endothelium
5. Consumption

Cause of TBI-induced Coagulopathy

Extracranial trauma vs. TBI

1. ~~Significant blood loss~~
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Cause of TBI-induced Coagulopathy

Extracranial trauma vs. TBI

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Cause of TBI-induced Coagulopathy

Extracranial trauma vs. TBI

1. ~~Significant blood loss~~
2. ~~Hemodilution due to fluid resuscitation~~
3. ~~Hypothermia and metabolic acidosis~~
4. ~~Substantial damage to the endothelium~~
5. Consumption

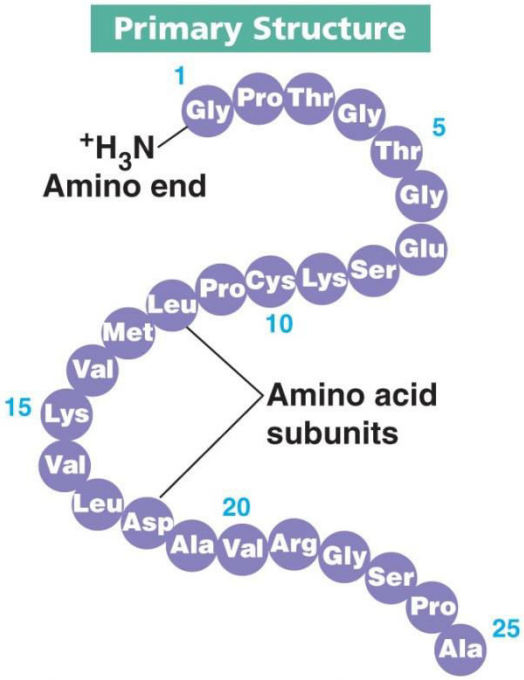
TBI-induced Coagulopathy

TBI-induced coagulopathy follows a unique course of laboratory changes: D-dimer/fibrinogen degradation products appear first, followed by fibrinogen depletion, and then prolonged pT/pTT.

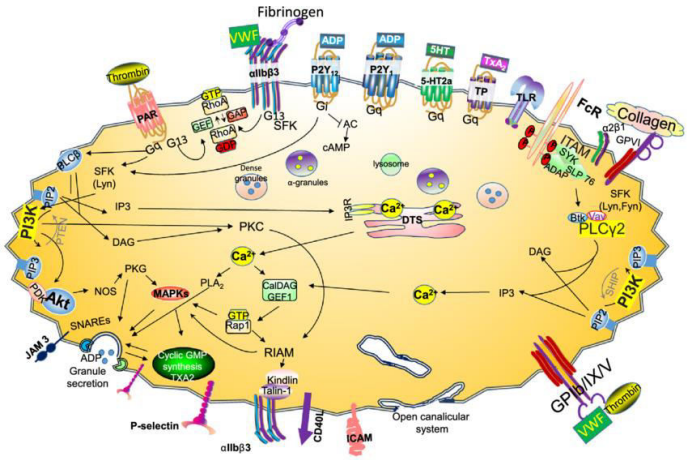
Our Hypothesis

Highly procoagulant brain-derived microvesicles (BDMVs) are produced from injured brain and released into circulation. These BDMVs induce a hyper-coagulable state that rapidly turns into consumptive coagulopathy.

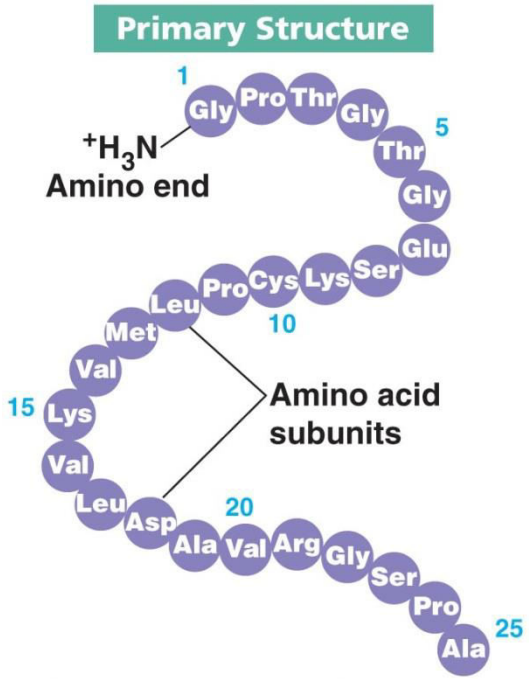
Cellular Microvesicles (MVs)



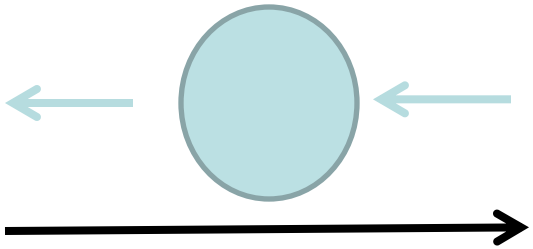
Platelet



Cellular Microvesicles (MVs)



Cellular debris microvesicles



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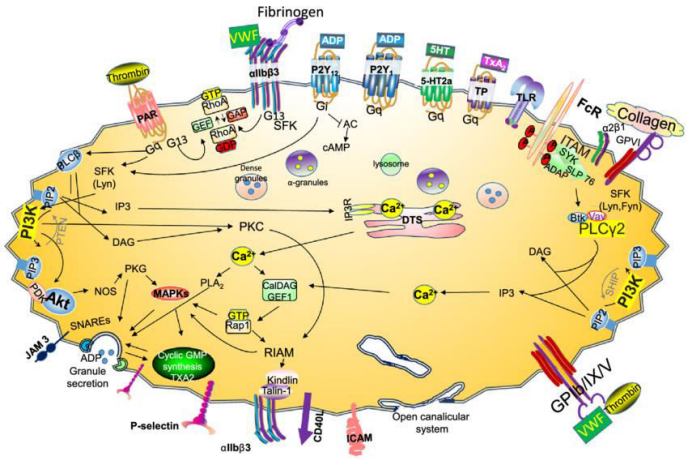


are diverse membrane and granule vesicles of 0.1-1 μM
come from ruptured apoptotic cells & active microvesiculation
carry membrane receptors and cargo molecules of parental cells

Topics

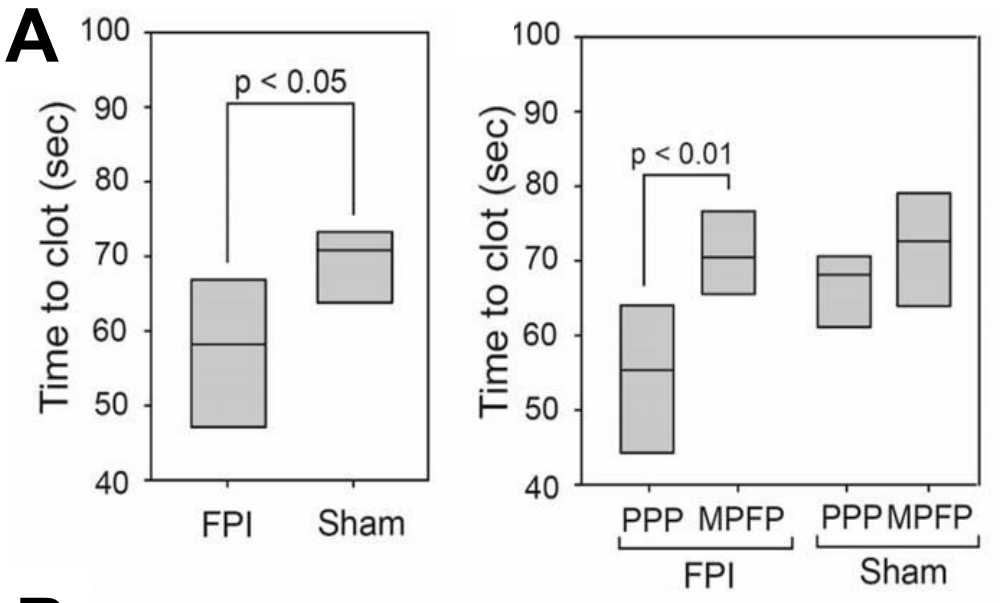
1. Brain-derived microvesicles induce consumptive coagulopathy.
2. Extracellular mitochondria promote coagulation and activate platelets.
3. Accelerating microvesicle clearance prevents TBI-induced coagulopathy and improves neurological functions.

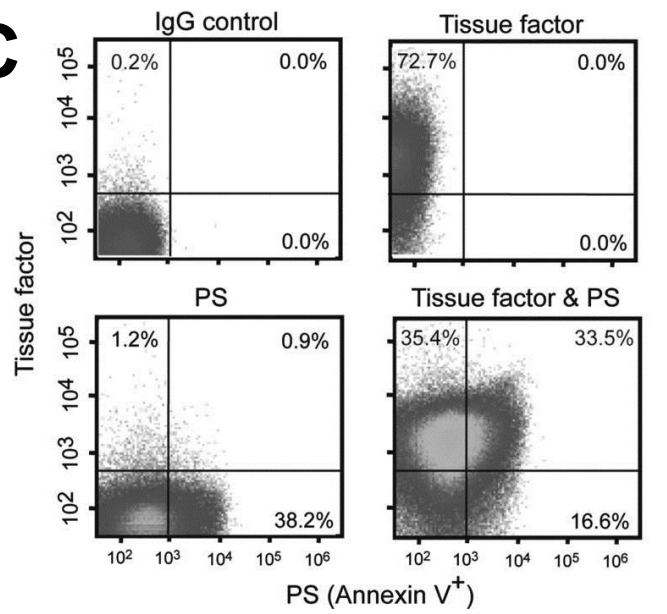
C57BL/6J mice subjected to fluid percussion injury (at 1.9 atm)

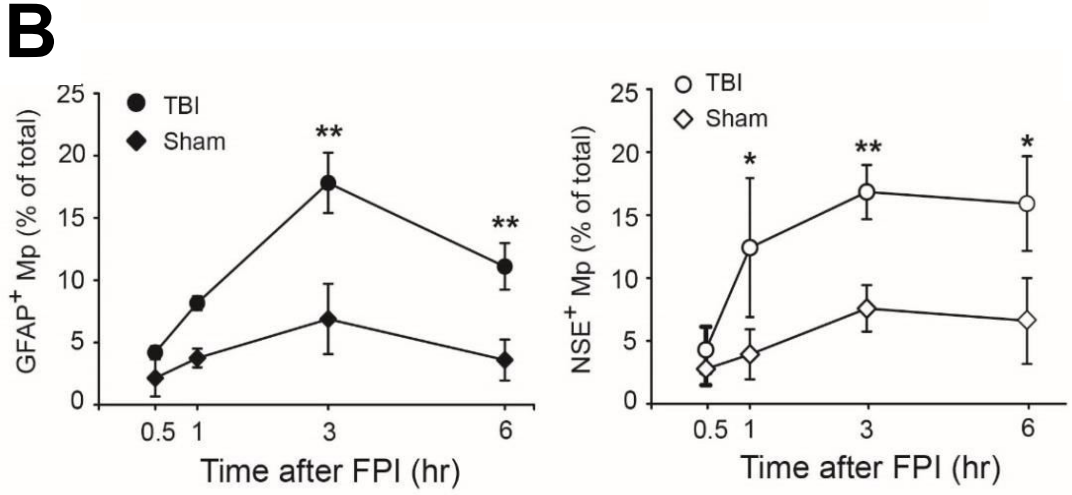
Topics

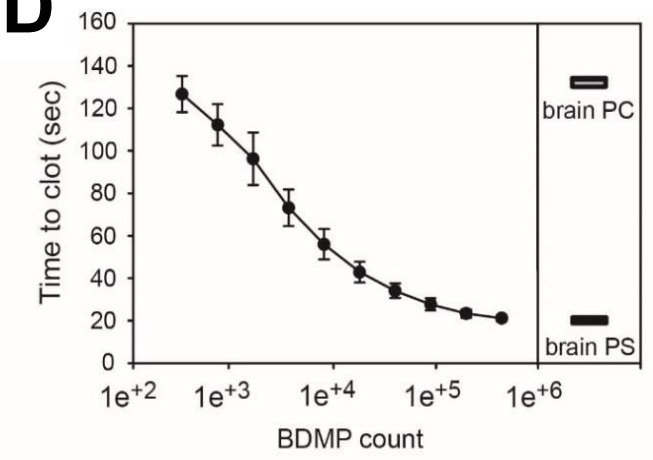
1. Brain-derived microvesicles induce consumptive coagulopathy.

Injured Brain Released Procoagulant BDMVs



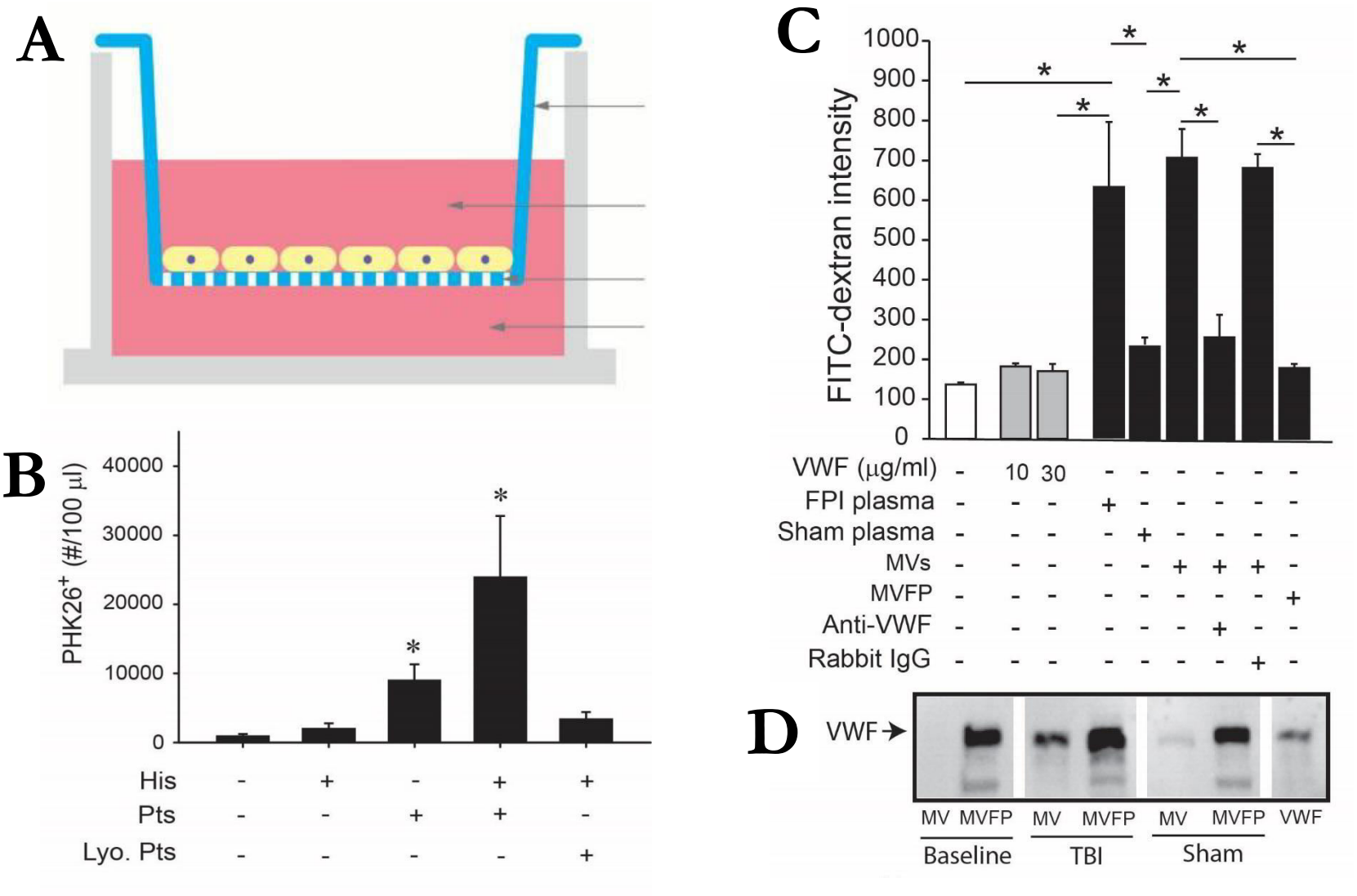






Ye Tian et al. Blood 2015;125:2151-2159

BDMVs Synergized with Platelets to Disrupt the Endothelial Barrier



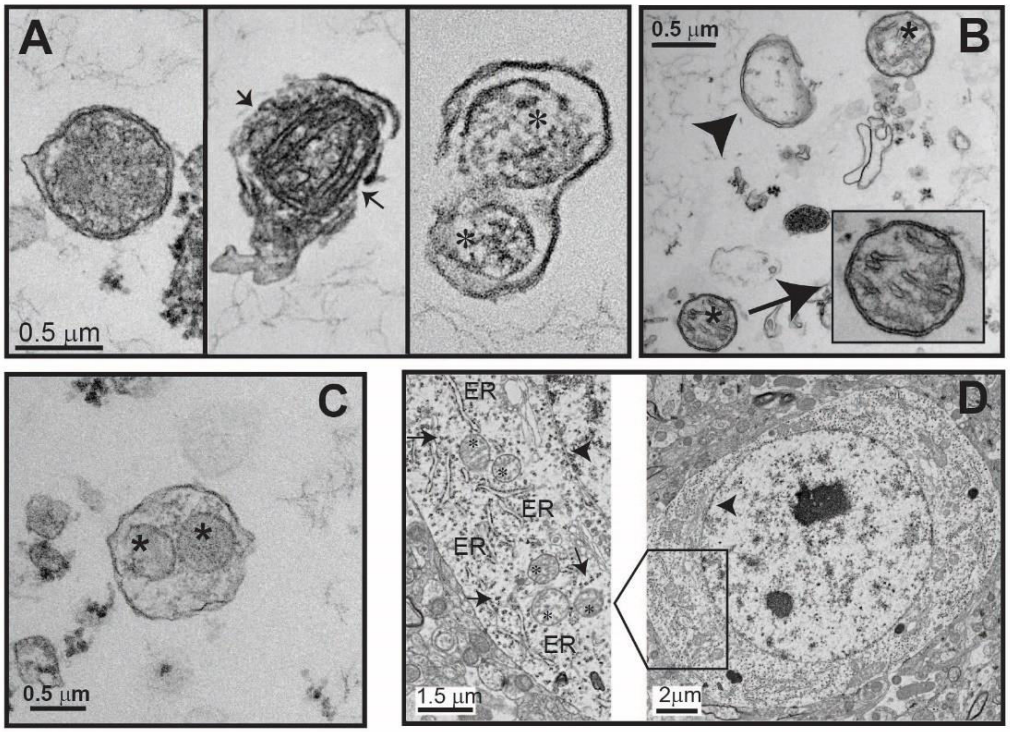
Ye Tian et al. Blood 2015;125:2151-2159 and Wu YG, et al Blood 2018 in press

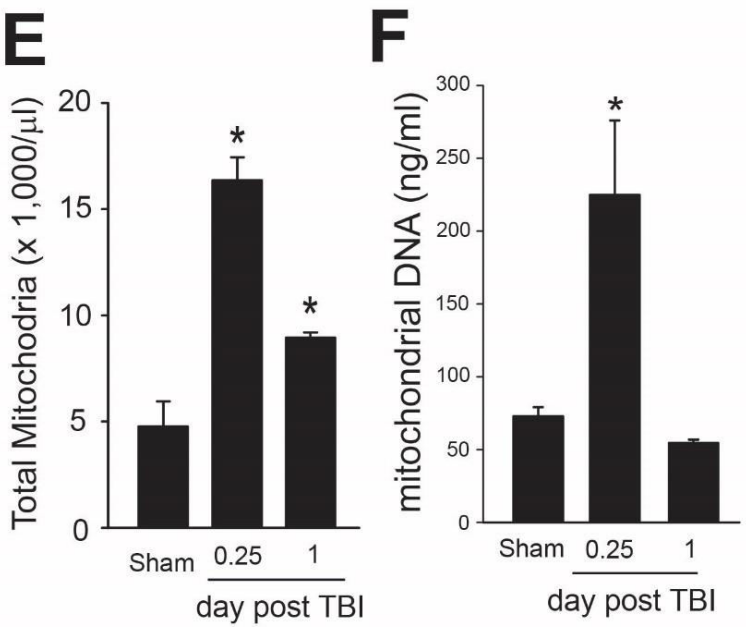
Topics

2. Extracellular mitochondria promote coagulation and activate platelets.

Extracellular Mitochondria (exMTs) Were a Major Type of Microvesicles

Anti-cardiolipin antibody had the highest titer (1:16,000) in plasma of acute TBI mice.

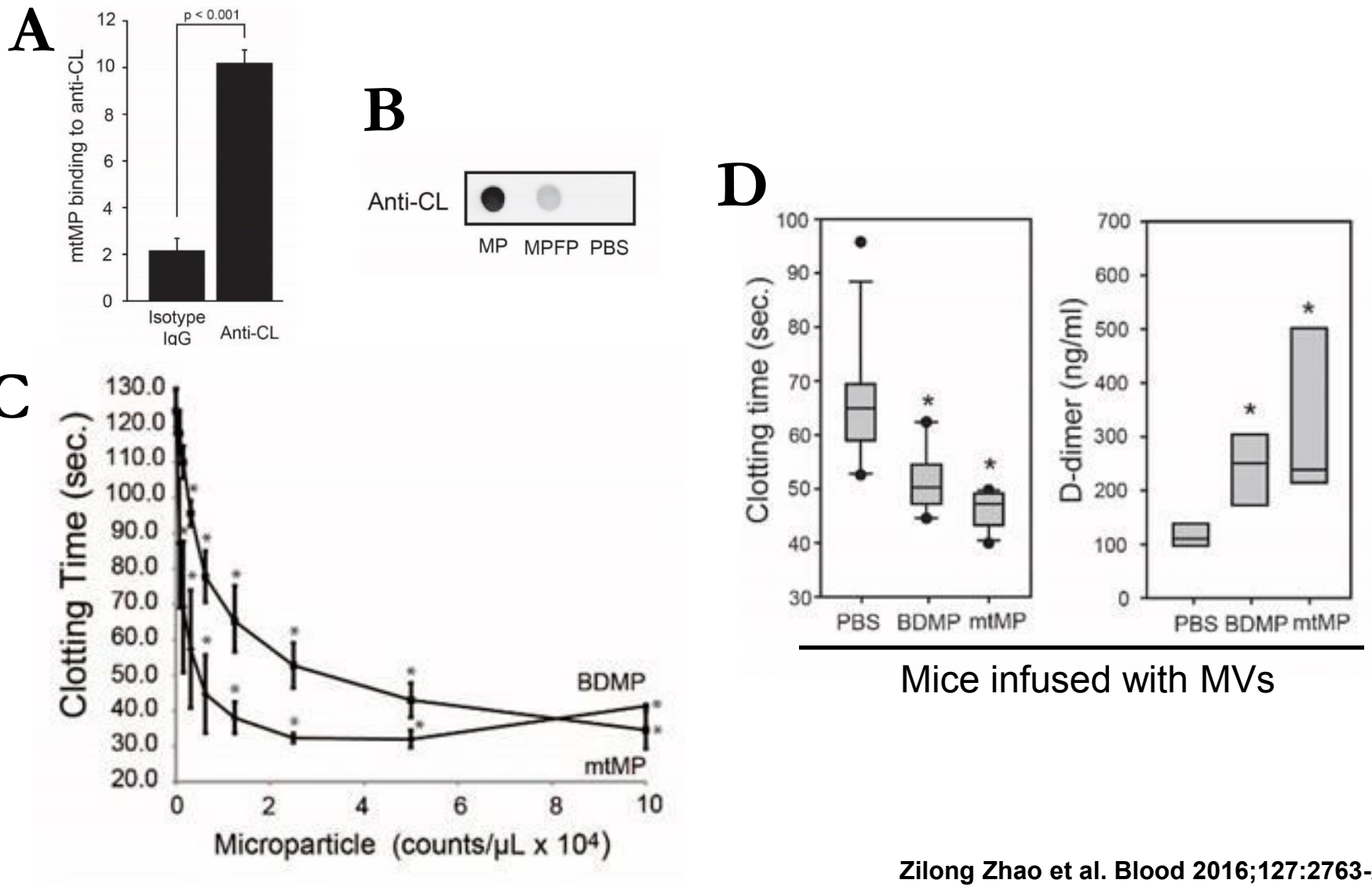




exMTs account for 55.2% of all annexin V^+ MPs in samples collected from mice 6 hrs post TBI

Zilong Zhao et al. Blood 2016;127:2763-2772

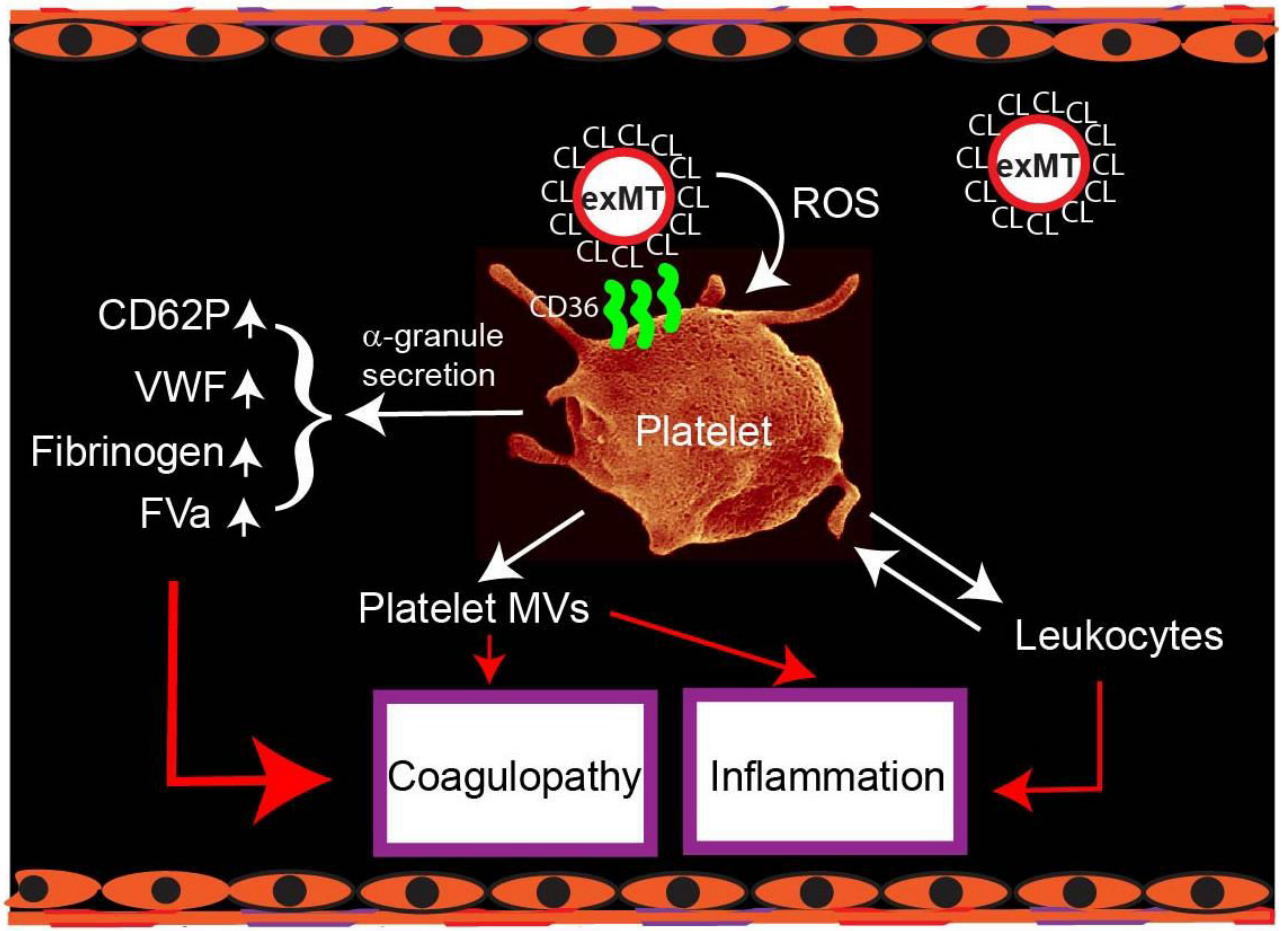
Cardiolipin (CL) Exposed on exMTs Promoted Coagulation



Zilong Zhao et al. Blood 2016;127:2763-2772

exMTs Activated Platelets through Oxidative Stress

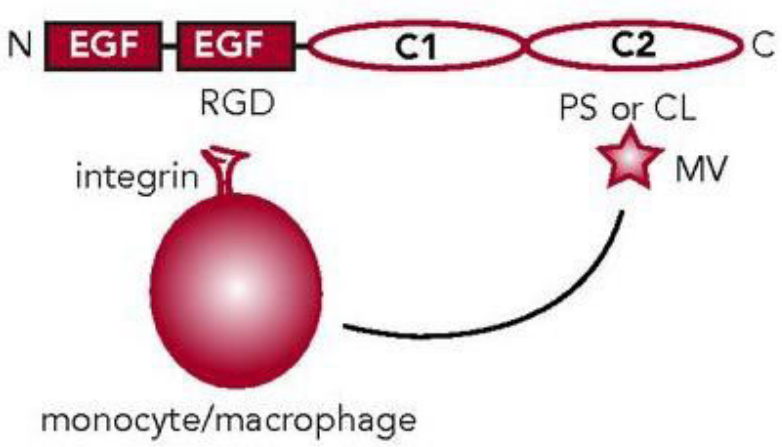
exMTs 1) were metabolically active, 2) bound platelets through CL-CD36 interaction, and 3) induced granule secretion by ROS, but not aggregation.

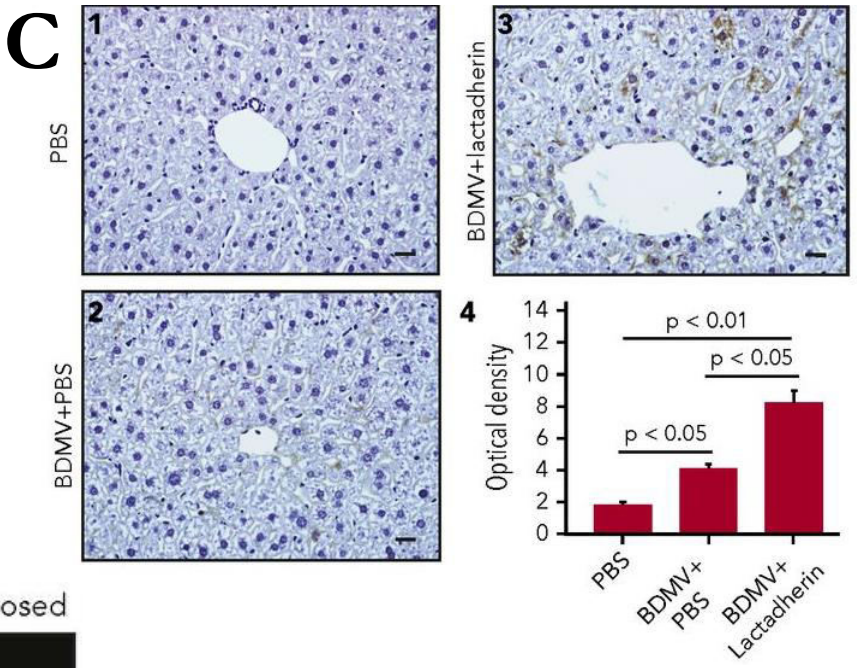


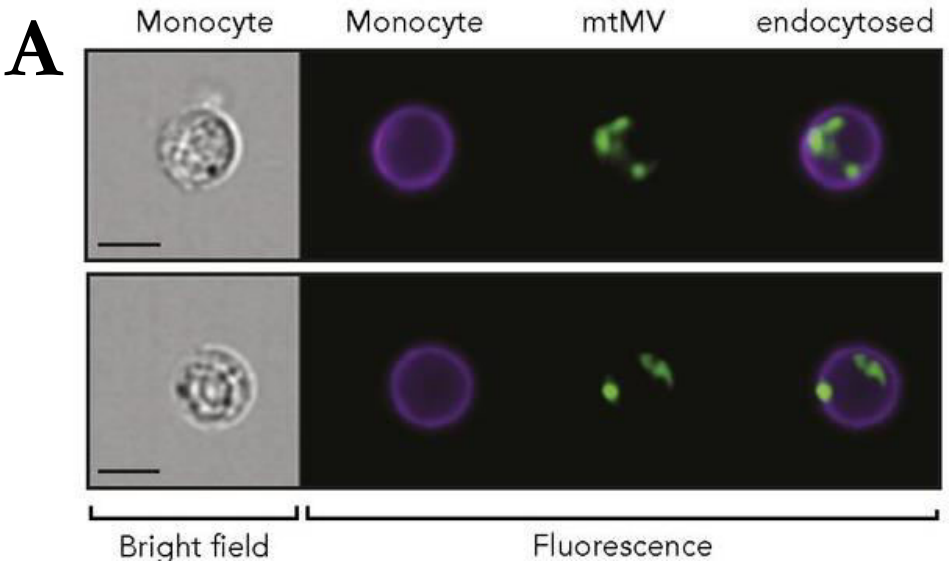
Topics

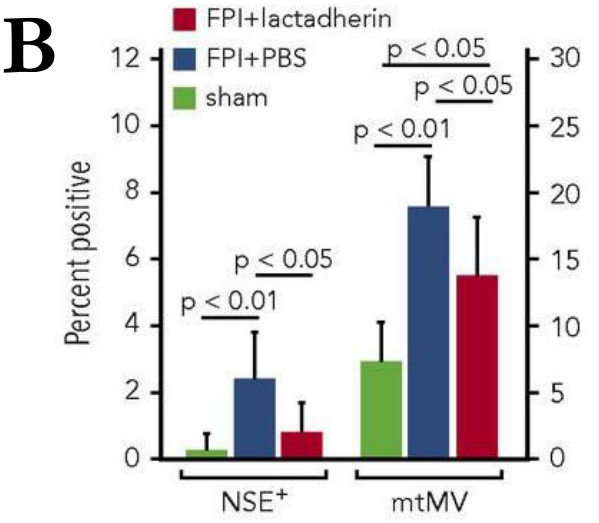
3. Accelerating microvesicle clearance prevents TBI-induced coagulopathy and improves neurological functions and survival.

Lactadherin Promoted Microvesicle Clearance



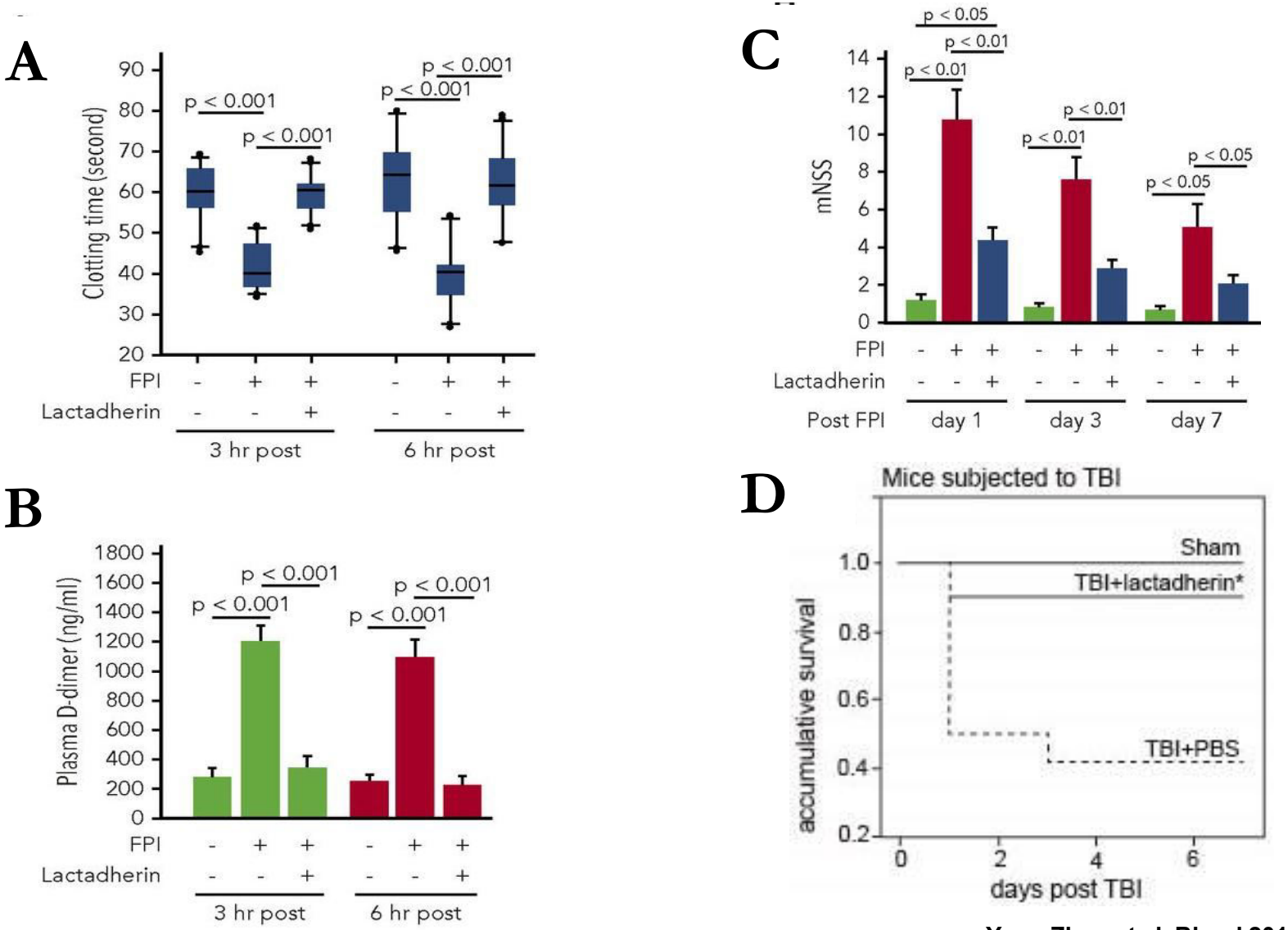






Yuan Zhou et al. Blood 2018;131:563-572

Lactadherin Improves Coagulopathy, Neurological Function, and Survival of TBI Mice



Yuan Zhou et al. Blood 2018;131:563-572

Summary

1. Traumatically injured brain release microvesicles that synergized with platelets to disrupt the blood-brain barrier.
2. Extracellular mitochondria account for > 50% annexin V^+ circulating MVs during acute traumatic brain injury.
3. The BDMVs and exMTs are procoagulant through PS and CL, respectively.
4. exMT-derived oxidative stress activates platelets to express procoagulant activity.
5. Enhancing MV clearance can prevent TBI-associated coagulopathy (and a long list of MV-associated pathologies).

Perspectives

1. **Clinical**
   - ❖ laboratory vs. clinical coagulopathy
   - ❖ transfusion medicine; body trauma vs. TBI
   - ❖ intermediate and long-term impact of laboratory coagulopathy, and preventive measures

2. **Research:**
   - ❖ a localized injury induces systemic changes
   - ❖ roles of different type of MVs in TBI and associated coagulopathy

Acknowledgement

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2. University of Washington
3. University of Texas Houston Health Science Center
4. Baylor College of Medicine
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6. Tianjin Medical University General Hospital
7. Institute of Pathology, Lanzhou University, School of Medicine
8. US Army Institute of Surgical Research

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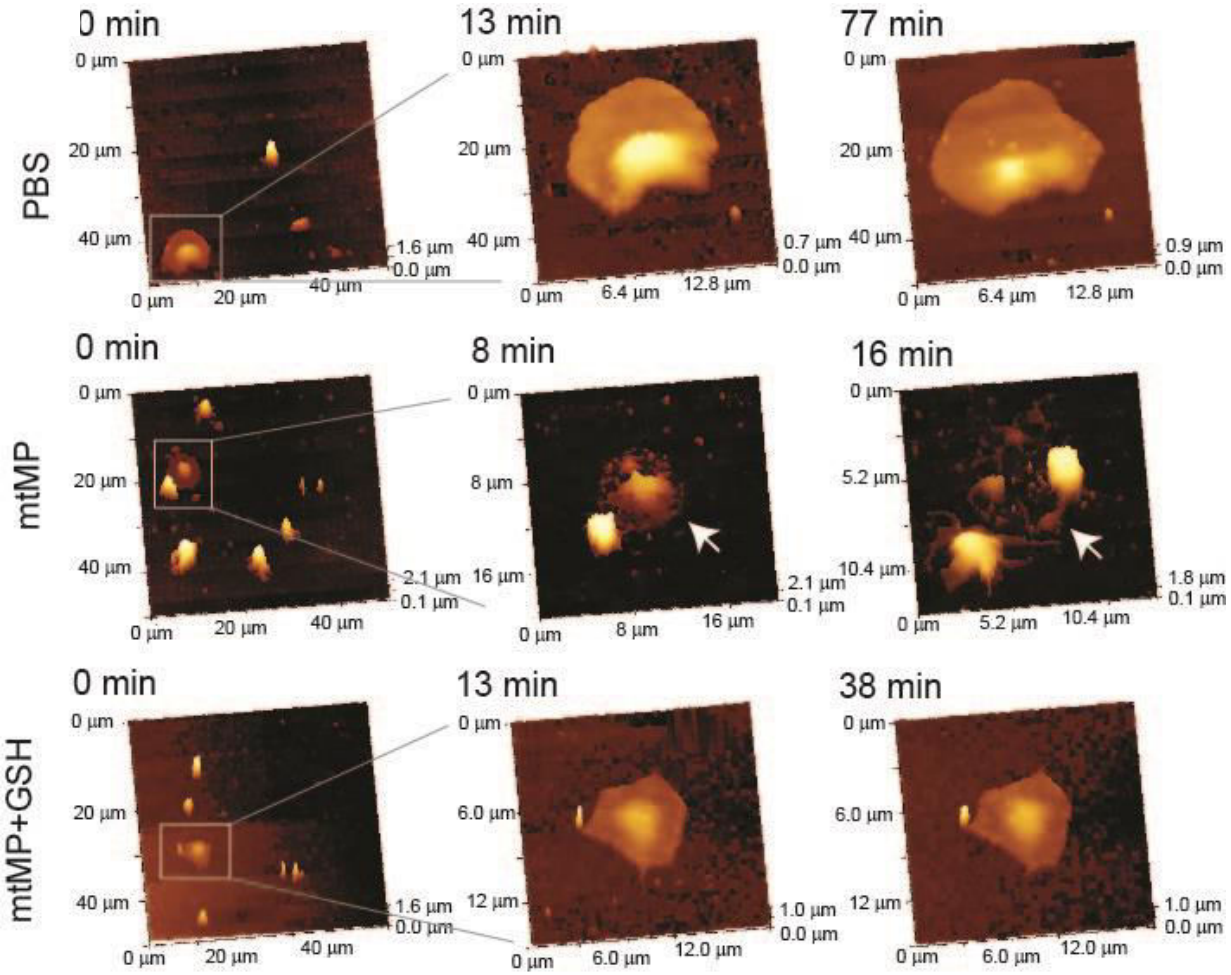
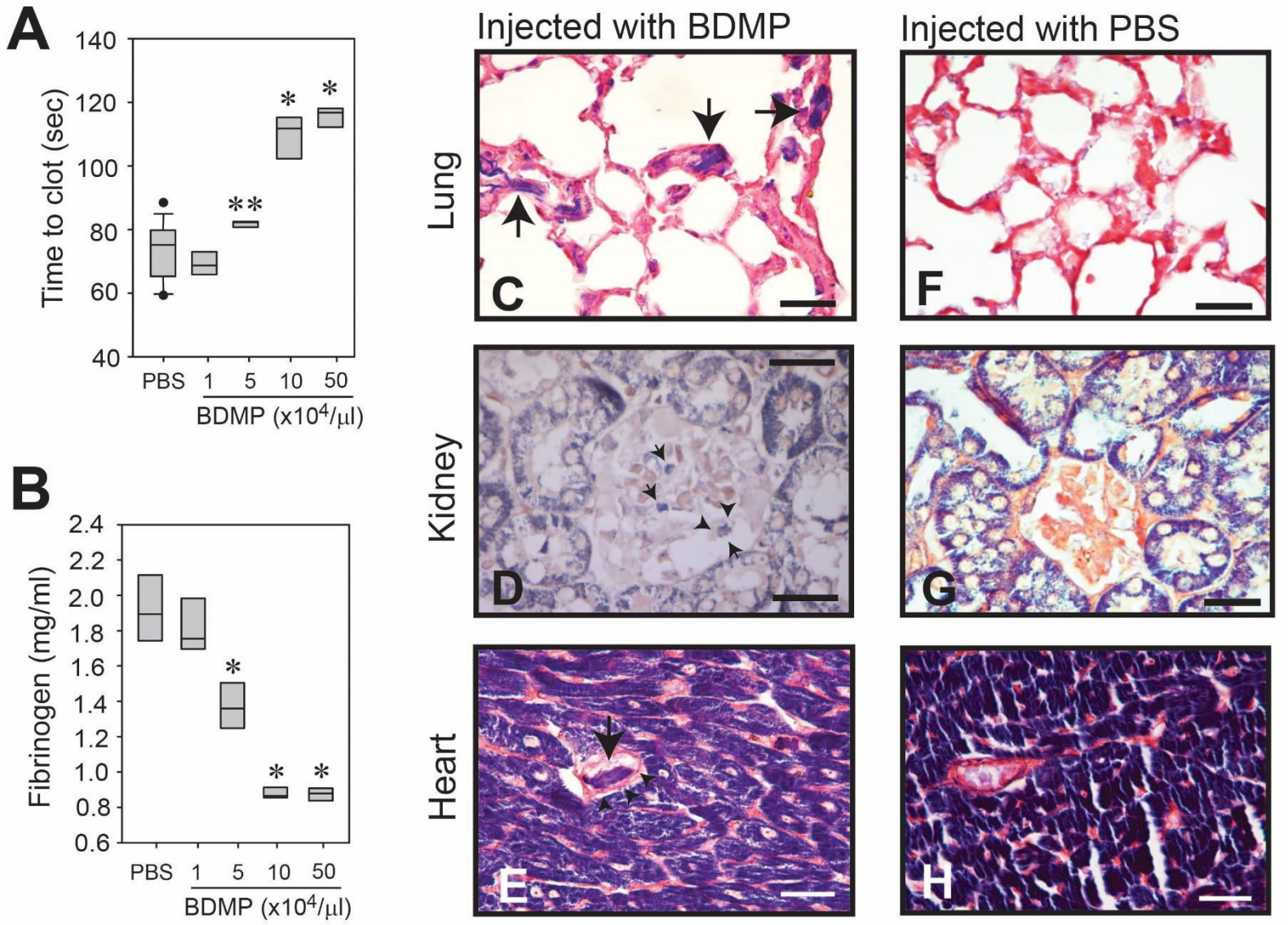
exMTs induces platelet microvesiculation through oxidative stress



BDMVs induced consumptive coagulopathy

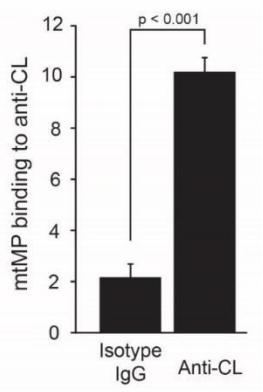


Cardiolipin (CL) exposed on exMTs promoted coagulation

Lipid mass spectrometry

	PC (%)	PE (%)	PS (%)	CL (%)
BDMV	40.9	29.4	15.3	0.3
exMV	36.1	33.8	0.7	18.1

A



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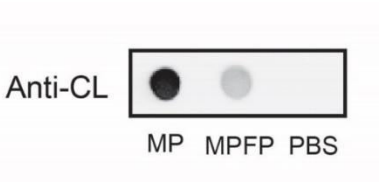

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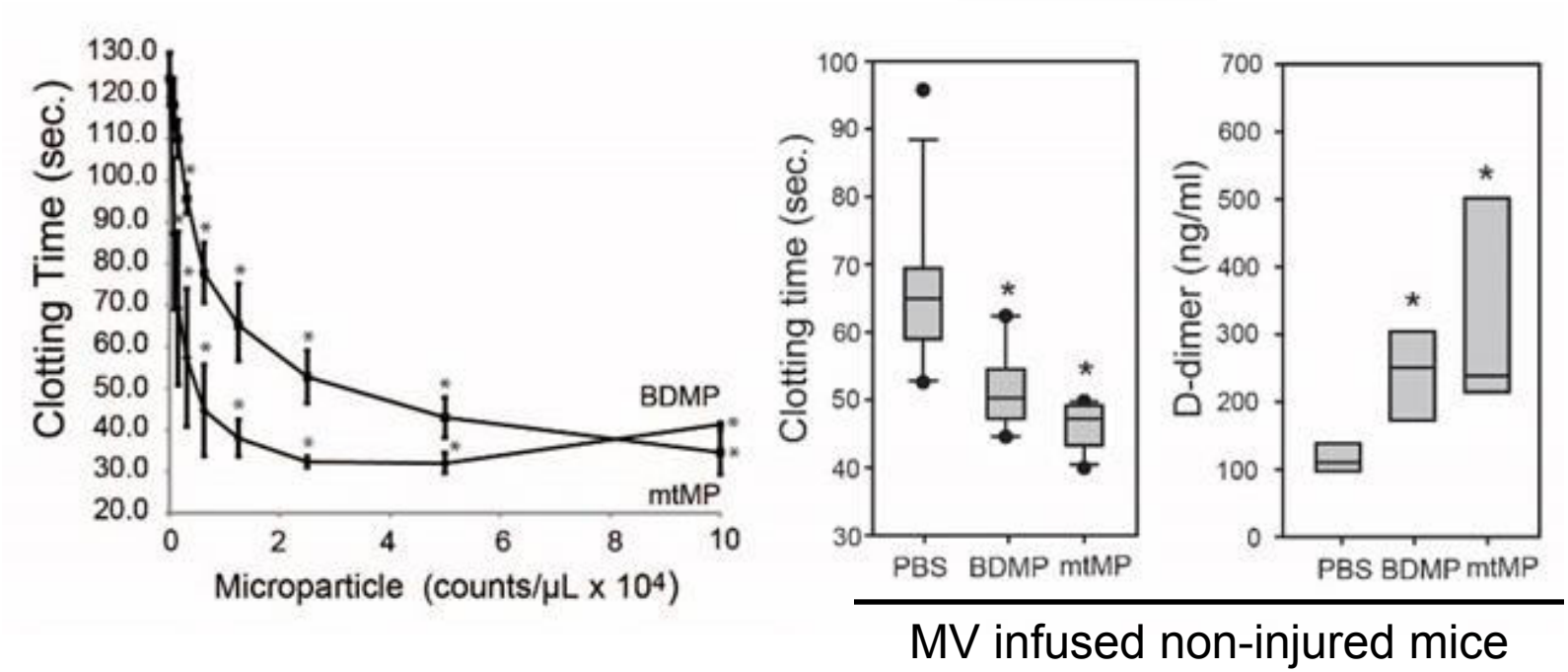
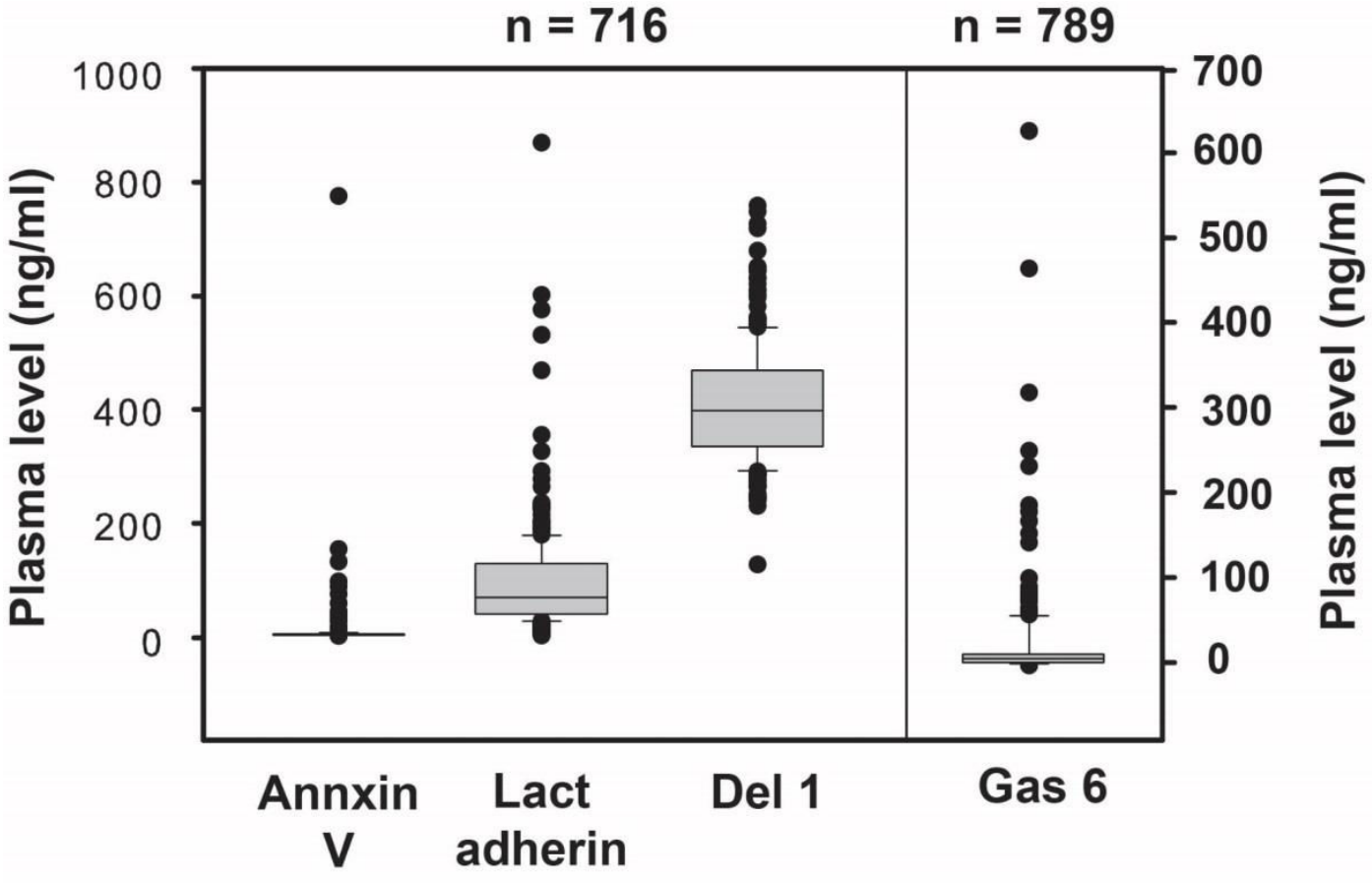


MV infused non-injured mice

Zilong Zhao et al. Blood 2016;127:2763-2772

Intrinsic MV clearance activity in humans



The question

What causes this consumptive coagulopathy?

Our Hypothesis

Highly procoagulant brain-derived microvesicles (BDMVs) are produced from injured brain and released into circulation. These BDMVs induce a hyper-coagulable state that rapidly turns into consumptive coagulopathy.