Role of Platelet Inflammatory Axis in Cerebral Aneurysm Formation

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Introduction and Methods

- Biological mechanisms of why aneurysms continue to grow are not understood.
- It is known that a unique micro-environment develops within the aneurysm.
- Platelets have a versatile role in hemostasis, inflammation, chemotaxis, scaffold formation, and wound repair.
- We hypothesized that platelets play a crucial pro-inflammatory function in cerebral aneurysm formation and healing.
- We have identified a cytokine, CXCL7, and its respective receptors CXCR1 and CXCR2 as potential targets.
Methods

• cerebral aneurysm formation was induced in C57BL/6 mice by ligating the right renal artery, left common carotid artery, and an intracranial injection of 0.8% elastase in C57BL/6 mice. Angiotensin II (Ang II) releasing pump was implanted and a high salt diet (8% NaCl, 0.12% BAPN) was fed to induce hypertension

• CXCL1 antibody blockade was performed using 100 mg/mL anti-CXCL1 rat IgG injected retro-orbitally over a 2-week period, and aneurysm formation was quantified

• Clopidogrel was administered at 10 mg/kg, in normal saline, by oral lavage, daily

• Intracranial vessels were collected from mice 3-days, 1-week, or 2-weeks post surgery and used for analysis via immunohistochemistry for MECA-32, CXCL1, CXCL2, CXCL5-6, NIMP-R14, F4/80, and/or VCAM-1.

• platelet aggregates were visualized using CD31 staining

• electron microscopy images were done using SEM technique in University of Pittsburgh Core Lab
Previous Results

Nowicki et al. Hypertension, 2014
BAF 2012: North Shore University Hospital, Brain Aneurysm Center Chair of Research
Previous Results

Aneurysm Progression

1. High Shear Stress
2. COX-2
3. PGE2
4. NF-κβ
5. MMPs
6. VCAM-1
7. Neutrophils

MCP-1
CXCL1/IL-8

Low Shear Stress

Macrophages
Previous Results

Nowicki et al. JNIS, 2017
BAF 2013: Shirley Dudek Demmer Chair of Research
New Preliminary Results

[Image of micrographs and graph showing data on platelet within atheroma tissue]

- **Human**
- **Mouse**

- **Graph**
  - X-axis: Pro-inflammatory markers present
  - Y-axis: Platelet within atheroma tissue [% of stained samples]
  - Data points: COX-2 (n=6), CXCL1 (n=4), MCP-1 (n=14)
Remaining Work / Conclusions

Cytokine arrays
- 90+ cytokines to be evaluated

IHC
- CXCL1
- CXCL7
- CXCR1/2

H&E

Control
- Aneurysm surgery
- Aneurysm surgery + Tx

Clopidogrel
- aspirin
- anti-CXCR1/2

Stage I: 60 mice in experimental arms
Stage II: 40 additional mice in experimental arms

C57BL/6

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