Inflammatory Responses in Abdominal Aortic Aneurysm: Emerging Targets for Therapy?

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Disclosures

Christine Pham, MD has no relevant financial interests to disclose
AAA

• Common disease in individuals age 60 and over
• Among top 20 leading causes of death in the US
AAA is an inflammatory disease
Immune cells and inflammatory mediators in AAA

Immune Cells and Molecular Mediators in the Pathogenesis of the Abdominal Aortic Aneurysm. Rizas, Konstantinos; Ippagunta, Nikalesh; MD, MS; Tilson, Martin

DOI: 10.1097/CRD.0b013e3181b04698
Does anti-inflammatory intervention halt the progression of AAA?
Anti-inflammatory intervention in AAA

• A large body of preclinical evidence suggests that interference with the inflammatory process blocks or slows the progression of experimental AAA (reviewed in Dale et al. Arterioscler Thromb Vasc Biol 2015)

• Clinical trials, however, are far and few between and the results so far have been inconsistent (reviewed in Kokje et al. Eur J Vasc Endovasc Surg 2015)
Why the discordance?

• Mice (rats) are not human
  – preclinical data do not always translate to clinical successes
• The dosing/timing not optimal
  – Dosing/timing in preclinical studies is easily controlled; disease process in animals is uniform
  – Humans have different genetic makeup; they respond differently and progress at different rate
• It’s the wrong target(s)
  – C5aR vs TNF in RA
The search for inflammatory/immune targets continues…
Elastase-induced AAA

Thompson et al. Ann NY Acad Sci 2006
Cathepsin C (DPPI) deficiency protects against elastase-induced AAA

Pagano et al. PNAS 2007
DPPI promotes early PMN recruitment in AAA

Pagano et al. PNAS 2007
Reconstitution with WT PMN restores susceptibility to AAA in DPPI-deficient mice

Day0  Day1  Day2
Elastase  10^7 PMNs

Day14
Harvest

A

$P < 0.002$  $P < 0.001$

Increase in AD (mm)

Recipient:  DPPI/−  DPPI/−  WT  WT

Donor:  WT  DPPI/−  WT  DPPI/−

Pagano et al. PNAS 2007
Inflammatory responses in elastase-induced AAA

1. Injury (Elastase perfusion)
   - Fibrinogen
   - Lectin Pathway
     - MBL
     - IgG
   - Fibrin clot

2. Alternative Pathway Amplification Loop
   - C3, C5
   - C3a, C5a
   - C3b, Bb

3. Neutrophil
   - Endothelium
   - Inflammation → AAA (T cells, MΦ, others)

References:
- Pagano et al. PNAS 2007
- Zhou et al. PNAS 2012
- Zhou & Yan et al. PNAS 2013
- Zhou & Yan et al. J. Immunol 2013
Neutrophil extracellular traps (NETs)

• Innate immune response to bacterial infection (Brinkman et al. Science 2004)

• NETs have since been implicated in:
NETs are found in human AAA

- Unpublished data (Pham lab)
- Delbosc et al. Plos One 2011
NETs are formed in elastase-perfused aortas
DNase 1 dismantles NETs and protects against AAA
Neutrophil extracellular traps (NETs)
DNA-CRAMP complexes induce AAA

A

WT

DPPI

CRAMP DAPI

B

Increase in AD (%)

p < 0.0001

p < 0.0001

p < 0.001

p < 0.0001

Genotype: WT DPPI DPPI DPPI DPPI DPPI+DNA-sCRAMP

Treatment: - - DNA CRAMP DNA-CRAMP

C

WT

D2 Adventitia

Lumen

D3

Lumen

D14

Siglec-H

D

WT DPPI p < 0.01 p < 0.001

Siglec-H cells per cross section

E

p < 0.0001

DPPI DPPI + DNA-CRAMP

F

Siglec-H IFNα

Merge

DPPI

EF

Siglec-H IFNα

Merge

DPPI + DNA-CRAMP

EF
pDC depletion attenuates AAA, blocks T cell recruitment and suppresses MMP production

A

![Graph showing increase in AD (%)]

B

![Flow cytometry for WT, anti-PDCA1, and Ctrl IgG]

C

![Images of Ctrl IgG and anti-PDCA1 showing Lumen and CD3]

D

![Bar graph showing CD3+ cells per cross-section]

E

![Images of Lumen and Gelatinase activity]

F

![Bar graph showing Gelatinase activity]

Yan & Zhou et al. under submission
Type I IFN blockade attenuates AAA, T cell recruitment and MMP production

A

Increase in AD (%)

\[ \begin{array}{c|c|c}
   & WT & anti-IFN-AR-1 & Ctrl IgG \\
\hline
\text{ns} & \bullet & \bullet & \bullet \\
\text{p < 0.01} & \bullet & \Delta & \Delta \\
\text{p < 0.01} & \bullet & \Delta & \Delta \\
\end{array} \]

B

CD3+ cells per cross-section

\[ \begin{array}{c|c|c}
   & Ctrl IgG & anti-IFN-AR-1 \\
\hline
\text{p < 0.001} & \text{(images show staining for CD3, IFN-γ, and Merge)} \\
\end{array} \]

C

CD3, IFN-γ, Merge

D

IFN-γ (IntDen)

\[ \begin{array}{c|c|c}
   & Ctrl IgG & anti-IFN-AR-1 \\
\hline
\text{p < 0.001} & \text{(images show staining for CD3, IFN-γ, and Merge)} \\
\end{array} \]

E

Gelatinase activity

\[ \begin{array}{c|c|c}
   & Ctrl IgG & anti-IFN-AR-1 \\
\hline
\text{p < 0.002} & \text{(images show staining for CD3, IFN-γ, and Merge)} \\
\end{array} \]

Yan & Zhou et al. under submission
NET component LL-37 is abundantly expressed in human AAA tissues

Yan & Zhou et al. under submission
LL-37 co-localizes with pDCs in human AAA tissues
IFNα expression is elevated in AAA tissues and in the circulation

C

\[ p = 0.0479 \]

D

\[ p = 0.0122 \]

E

ns

F

\[ r = 0.0899 \]
Summary and remaining unanswered questions

- In the elastase-induced AAA model:
  - Neutrophils recruited to abdominal aortic wall elaborate NETs
  - NETs stimulate pDCs to release type I interferons
  - Type I interferons recruit and activate T cells (others) to perpetuate the chronic inflammatory responses

- Are NETs, pDCs, and type I interferons good therapeutic targets?

- What about other targets?

- Which targets do we pick and when is the best time for intervention?

- Should intervention be personalized given the wide range of manifestation/progression?
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