THE INVOLVEMENT OF CELL DEATH IN ABDOMINAL AORTIC ANEURYSM

Gillian W Cockerill
CELL DEATH

Nutrient Availability

Physiological remodelling oxidative damage

Infection

Autophagy
- Recycling of damaged organelles, pathogens
- Survival

Apoptosis
- Continued stress
- Death
- Physiological remodelling, oxidative damage
- Rapid phagocytosis

Necrosis
- Swelling organelle disruption, membrane rupture
- Inflammation
Apoptosis

- Membrane blebbing
- Nuclear condensation
- Shrinkage
Pathways of apoptosis and autophagy:

Ligand → Death receptor → Adapters → Active Caspase 8, 10 → Pro-caspase 8, 10 → tBID → Bcl 2 → BNIP3, Beclin 1 → Effector caspases → Apoptosis → mTOR → Autophagy

IGF I → IGF IR → PI3K → PIP3 → PDK → Akt → mTOR
Apoptosis in experimental aneurysm models:

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<tr>
<th>Tunel</th>
<th>FasL</th>
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Wistar

Brown Norway

Brown Norway/Kininogen deficient

Kaschina et al., Physiol Genomics 2004
AUTOPHAGY:

Clark et al., Heart 2007
Angiotensin II-induced ApoE deficient mouse model of AA:

Time (weeks) from pump implantation: 0, 1, 2, 4

A. B. C. B. [1,2] [3]

[4] Chemokine protein expression vs sham (day 3)

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<tr>
<th>Protein</th>
<th>Fold Increased</th>
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<tr>
<td>Rantes  (CCL5)</td>
<td>6.9</td>
</tr>
<tr>
<td>MIP-1  (CCL9)</td>
<td>3.4</td>
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<td>MCP-1  (CCL2)</td>
<td>1.70</td>
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[2] Saraff et al., ATVB.2003;23;1621-26
High-density lipoproteins - natures own nanoparticles:

- rHDLs
- CSL-111

- Pre-β: 5.58 nm
- α-4: 7.43 nm
- α-3: 8.05 nm
- α-2: 9.2 nm
- α-1: 11.0 nm
HDL inhibits AngII-induced caspase 3/7 activity in a site specific manner
HDL inhibits AngII-induced caspase 9 cleavage in a site specific manner.
HDL inhibits AngII-induced caspase 9 cleavage in a site specific manner

Torsney et al., ATVB 2012
Conversion of microtubule associated light chain (LC3) during autophagy:
HDL differentially regulates autophagy throughout the aortic tree

Torsney et al., ATVB 2012
CONCLUSIONS:

Apoptosis can be measured in aneurysms, and is modifiable in response to agents which inhibit aneurysm development.

Autophagy can be measured in aneurysms, and is modifiable in response to agents which inhibit aneurysm development.
• Cell death (apoptosis, autophagy, necrosis, anoikis etc.,) are part of the mechanism of the developing aneurysm.

• Cell death (apoptosis, autophagy, necrosis, anoikis etc.,) are part of the mechanism of vascular repair in aneurysm formation.

Understanding a little more about the relationship between cell death and AAA development will reveal new strategies/targets for treatment.
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