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Inadequate Reinforcement of Transmural Disruptions at Branch Points Subtends Aortic Aneurysm Formation in Apolipoprotein-E-Deficient Mice

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Background:

Infusion of angiotensin-II (Ang-II) in the apolipoprotein-e-deficient mouse (Apo-$E^{-/-}$) results in suprarenal abdominal aortic aneurysm (AAA) in 30-85% of cases. This study identifies the apparent mechanism that explains why some animals do, and others do not, develop AAA in this model.

Methods:

Male Apo-$E^{-/-}$ mice (age 12-13wks, n=27) were infused with Ang-II via subcutaneous minipumps (1000ng/kg/min n=21) or saline (n=6) and sacrificed at 4wks. After perfusion fixation, the aortas were excised, embedded in paraffin, sectioned (5µ thick, 250µ intervals), and stained for histomorphometry and immunohistochemistry. Aortas were considered aneurysmatic if they exceeded 50% dilatation over the saline infused group. Sites of transmural disruption of the media (TDM) were identified, characterized, and their relationship to the 4 major aortic side branches (celiac, superior mesenteric, and left and right renal arteries) determined.

Results:

The frequency of TDMs (from a few to >1000µm length) in the ang-II-infused mice that developed AAA (n=9) was similar those that did not develop AAA (n=12) (AAA-vs-no-AAA: 25(69%) of 36 vs 28(58%) of 48 branches, p=0.3 by Chi-square [-vs-Saline: 4(17%) of 23, p<0.001]). However, in the animals with AAA (compared to those without AAA), the mean maximum length of the TDMs was significantly larger (1.94±1.6 –vs- 0.65±0.5mm, p=0.007 by MW-U-test), the #mac-2^{+} macrophages per $0.01mm^2$ of defect area was significantly greater (32±10 –vs- 19±11, p<0.02 by Kruskal-Wallis with Conover-Inman post-hoc), the % of the area of attempted repair occupied by collagen was significantly less (17±13%-vs-44±15%, p=0.0009 by MW-U-test), and the density of collagen per unit length of media missing was also significantly less (0.13±0.2–vs-1.14±1.0, P=0.0001 by MW-U-test).

Conclusion:

Transmural defects and inflammatory cell infiltration at branch orifices subtend aneurysm formation in the Ang-II-infused, Apo$E^{-/-}$ mouse. Reinforcement of these defects by wall matrix appears to be a key intrinsic player in limiting AAA formation. Further studies are warranted to determine the precise role of hemodynamic forces in this model.