CCN3: stopping that achy, breaky aorta

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Abstract Abdominal aortic aneurysm (AAA) affects between 2 and 8 % of males over the age of 65. Mortality if ruptured is 85 to 90 %, Recent data by Zhang and colleagues (J Clin Invest 126(4):1282–1299 2016) suggest that CCN3 might be used to treat AAA. This Bits and Bytes summarizes these findings.

Keywords CCN3 · Cardiovascular disease · Abdominal aortic aneurysm · CCN family · Matricellular proteins · Nov

Data published by the National Centre for Health Statistics revealed that aortic aneurysm accounts for 0.7 % of total deaths in is a leading causes of death for people aged 60–84 years in the USA (http://www.cdc.gov/nchs/data/dvs/LCWK1_2006.pdf). Abdominal aortic aneurysm (AAA) is characterized by progressive vessel dilation, apparently caused by chronic weakening of the arterial wall, resulting in an increased risk of fatal rupture which is thought to occur when the aortic wall is unable to oppose the luminal blood pressure (resulting in the wall tangential stress exceeding the tensile strength of the vessel (Schurink et al. 2000).

There are no established prognostic markers or drug treatments for AAA (Golledge and Norman 2009). Given that extracellular matrix (ECM) provides structure for the arterial wall, it is not suprising that alterations in ECM homeostasis are vascular pathologies such as AAA (Xu and Shi 2014).

However, the underlying mechanism of how the ECM is regulated the vascular wall in AAA is largely unknown.

Matricellular proteins are secreted non-structural ECM components. The CCN (*Cyr61*, *Ctgf*, *Nov*) family of matricellular proteins regulate a wide range of biologic functions and hence are considered to be valuable targets for drug intervention (Jun and Lau 2011).

CCN3 is expressed in smooth muscle cells and endothelial cells (Ellis et al. 2000; Lin et al. 2010), but its role in vascular function is largely unknown.

In a recent report published in JCI, Zhang and colleagues (2016) explore the role of CCN3 in AAA. They found that CCN3 expression was reduced in AAA smooth muscle cells in humans. They found that ablation of CCN3 exacerbated abdominal aortic dilation following elastase perfusion or angiotensin II administration. In the latter model, loss of CCN3 correlated with death due to aortic rupture. Moreover, CCN3-deficient mice developed more severe AAA and had more severe intramural hematoma formation and ECM breakdown. In both models, loss of CCN3 also resulted in increased inflammatory responses. Elevated MMP activity was observed in aortas of CCN3-deficient mice after Ang II infusion. Ang II infusion potently increased markers of superoxide generation; this effect was pronounced in the absence of CCN3. Also, apocynin, an antioxidant, ablated the in vivo effects of loss of CCN3, implicating reactive oxygen species in the AAA phenotype caused by CCN3 ablation. Adenoviral overexpression of CCN3 rescued the phenotype caused by loss of CCN3, directly implicating CCN3 in the development of AAA.

These results illustrate the importance of CCN3 in maintaining normal vascular health and suggest that increasing CCN3 levels therapeutically may be used to control aortic dilation and the development of aortic aneurysms.

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