Commentary

Aortic aneurysm, CCN3 may solve the problem

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Aortic aneurysm was responsible for the death of over 150,000 people in the world in 2013, in increase by 50% since 1990 (1). They can form in any section of the aorta but are more commonly located in the abdominal aorta (AAA). It is characterized by an intense vascular inflammation and leukocyte infiltration which leads to a pathological remodeling and degradation of the aortic extracellular matrix (ECM) and alteration of smooth muscle function (2,3), which can lead to aortic rupture and life-threatening bleeding. No medical treatment is currently available to prevent rupture or to slowdown AAA progression. Surgery involving the placement of a stent graft or the replacement of the aneurysmal portion of the aorta with a graft is the only available option.

Extensive ongoing research is unraveling the modifications of ECM composition and their role in AAA (2,3). Increased collagenase, elastase, and MMP activity contribute to elastin fragmentation and types I and III fibrillar collagen loss (2). Such degradation of ECM may lead to aortic rupture. In a recent paper published in the *Journal of Clinical Investigation*, Zhang *et al.* reported the role of the ECM protein CCN3 in preventing abdominal aortic aneurysm in a murine model of the disease (4), paving the way for the development of non-surgical intervention to control aneurysm progression through therapeutic CCN3 upregulation.

Nephroblastoma overexpressed protein (NOV; CCN3) belongs to the CCN matricellular protein family. The other two founding members are cysteine-rich protein 61 (CYR61; CCN1) and connective tissue growth factor (CTGF; CCN2). They were initially identified as immediate-early genes whose secretion was induced by mitogenic factors. Wnt-induced signaling pathway proteins, referred as CCN4-6, complete the CCN family. All share a similar structure of four conserved domains homologous to insulin-like growth factor binding protein, von Willebrand factor type C, thrombospondin type I and a cysteine knot motif (5). CCN proteins bind cell surface integrins and receptors as well as growth factors (BMP, TGFβ) or ECM-associated proteins (laminin, fibrinogen, collagen), thus bridging spatially separated receptors and signaling molecules together. Such interactions promote ECM-intracellular signaling that regulate various cellular actions, including adhesion, migration, senescence and proliferation within several cell types, including epithelial, endothelial and smooth muscle cells (5-7). CCN1 is expressed by fibroblasts, endothelial cells and vascular smooth muscle cells and is clearly implicated in the development of the cardiovascular system, as CCN1-deficient animals suffer from embryonic death because of severe vascular integrity and placental defects (8). CCN2 is expressed by endothelial cells and vascular smooth muscle cells and pericytes. It is an important mediator of pericyte/endothelial cell interactions (9). CCN2-deficient mice suffer perinatal death due to respiratory failure (10). Although expressed by fibroblasts, endothelial cells and vascular smooth muscle cells, CCN3 appears to be different from CCN1 and CCN2, whose cell proliferative and inflammatory properties are well described (5,6,11,12). CCN3 negatively regulates endothelial inflammation via inhibition of NF-κB axis (13) and has anti-proliferative activity on cancer cells (14). CCN3 has the property to control neointimal hyperplasia in response to injury by limiting smooth muscle cell growth and migration (15).

In the context of AAA, Zhang *et al.* report a drastic downregulation of CCN3 expression in aorta tissues (4). They investigated the role CCN3 in two murine models of AAA (Ang II infusion in *ApoE*-deficient mice and elastase perfusion) and observed that AAA formation was

more aggressive in CCN3-deficient mice and associated with stronger inflammatory infiltrate (macrophages and T-cells), deterioration of ECM, smooth muscle cell loss, increased MMP activity and ROS production (4). Their most exciting result comes from the complete abrogation of AAA development in mice i.v. treated with a lentivirus-engineered to induce mild CCN3 overexpression. This latter result recalls the findings by Liu *et al*. who showed that CCN3 overexpression reduced atherosclerotic plaque area and inflammatory response in a murine model of atherosclerosis (16). In that context, CCN3 overexpression reduced disease progression but also reduced the levels of adhesion molecules (VCAM-1 and ICAM-1) and inflammatory mediators such as MMPs (16), as presently reported in the context of AAA (4).

Despite clear-cut differences between control animals and CCN3-deficient or CCN3 overexpressing mice, both studies exhibit similar weaknesses. At no point the mechanism of action of CCN3 was investigated. Consequently, the target cell(s) of CCN3 that mediate(s) the anti-inflammatory action of CCN3 is unknown. This raises the question of understanding whether CCN3 directly inhibits immune cell trafficking or whether CCN3 impacts the microenvironment of the vessels and subsequently the onset of inflammation. Another point concerns the receptor(s) of CCN3 as well as the signaling pathways triggered in the target cell. CCN3 is reported to bind integrin αVβ3 and α5β1 (17,18) but no experiments were undertaken in that direction and thus whether integrins are involved in the AAA events remains unknown. Strong interactions and overlapping or inhibiting properties take place between CCN proteins. For instance, CCN3 is upregulated in CCN2-deficient mice (19). A strong reduction of CCN1 and CCN2 expression is noted in response to CCN3 overexpression in atherosclerosis (16). Moreover, overexpression of the CCN3 gene or recombinant CCN3 protein administration markedly downregulates CCN2 activity in mesangial cells and kidney cortex, respectively (20,21). In regard of the inflammatory and chemotactic properties of CCN1 and CCN2 (5,6,11), analyzing the levels of CCN1 and CCN2 levels in AAA in Ccn3-deficient mice would be of interest to determine whether CCN3 may exert its anti-inflammatory effect through inhibition of CCN1 and/or CCN2, as supposed in atherosclerosis (16).

In conclusion, the results from Zhang *et al.* are clearly a breakthrough in the field of vascular physiopathology and raise several questions. Future research is required to decipher the mechanisms of action of CCN3 and its interactions with the other CCN proteins and to investigate whether local or systemic delivery of CCN3 may lessen inflammatory disease progression.

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Footnote

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