Is Emilin-1 a molecular link contributing to the extension of thoracic aortic aneurysm dissection and increasing the magnitude of the associated hypertension

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Patients with acute aortic dissection, the dominant condition in acute aortic syndromes, have a high mortality [1]. Within types of thoracic aortic dissection, the more extensive the TAD the worse the prognosis [2]. Thus, factors influencing the extent of the TAD are important considerations. The initial presentation of acute aortic dissection is severe chest pain and hypertension. The presence of hypertension is a key element of thoracic aortic dissection (TAD) [3]. The hypertension in acute aortic syndromes is often severe and difficult to treat. From another perspective, a significant proportion of patients presenting to the emergency department with hypertensive crisis with severe blood pressure elevations have an aortic dissection [4].

Thus, refractory hypertension or high blood pressure which is difficult to control or treat, is a major component of acute aortic syndromes. Importantly hypertension is a significant independent predictor of in-hospital mortality in acute aortic syndromes after considering other factors in multivariate analysis [5]. The mechanism of the hypertension in this clinical setting has usually been attributed to severe chest pain and sympathetic activation. Recent data from proteomic analysis of thoracic aortic dissection suggests a new possible molecular mechanism that may lead to increases in both the extent of a TAD and the associated hypertension.

Proteomic analysis of aortic tissues from patients with aortic dissection and hypertension found that emilin-1 was down-regulated by approximately 2.3 fold compared to age and sex matched controls [6]. The data from protein screening was validated by Western blotting [6]. Degradation of proteins in the aortic wall would be anticipated from activation of enzymes such as matrix metalloproteases (MMP) in the aortic wall in aortic aneurysms leading to TAD [6-9]. Indeed, Emilin is a substrate for MMP as demonstrated by its release from human radial arteries incubated with different MMPs [10]. The degradation of Emilin-1 has potential implications as a factor altering the extent of the TAD and increasing the magnitude of the hypertension in acute aortic dissection.

Emilin (Elastin Microfibril Interface Located protein), first identified as a glycoprotein in the aorta of chick is associated with elastic fibers [11-12]. Human Emilin, or Emilin-1, consists of an N-terminal signal peptide, a cysteine-rich domain, a coiled-coil motif, a collagen-like domain, and a C1q-like motif [13]. Emilin-1 is distributed in tissues where elastic recoil is a component of tissue function such as in the aorta [13]. Emilin-1 is localized at the interface between elastin and microfibrils in the artery and undoubtedly operates to facilitate the function of elastin [13] which plays an important role in arterial structure and function [14].

While the precise factor(s) initiating TAD is still debated, mechanical or functional failure of the aortic elastin is considered to predisposes to TAD and further aneurysmal dilatation [15]. EMILIN-1-deficient aorta is associated with an increase in the space between the endothelial cell membrane and the internal elastic lamella as well as abnormal cell surface-elastic fiber connections for smooth muscle cells [16]. Degradation of Emilin-1 in the aorta in TAD limits the role of Emilin-1 to stabilize the molecular interactions between elastic fibers [16]. This would be anticipated to extend the dissection process and/or removes a constraint for aortic expansion.

Hypertension is not only a significant component of TAD [3] but is also an important predictor of TAD mortality [5]. Emilin-1 is a regulator of blood pressure as blood pressure is significantly increased in the absence of Emilin [17]. EMILIN-1 null mice have an increase in systolic blood pressure by 20 mmHg compared to wild type mice and systolic blood pressure is increased 10 mmHg in heterozygous animals [17]. Diastolic blood pressure is also elevated and the increase in blood pressure is attributable to an increase in vascular resistance [17]. This action of Emilin involves its ability to prevent pro Transforming Growth Factor – beta (TGF-β processing to TGF-β which occurs through proteolytic cleavage in the extracellular space [17]. Thus, a reduction of the ability of Emilin-1 to downregulate the production of TGF-β increases TGF-β and its effects on cell signalling in the vasculature. The role of TGF-β in hypertension is complex [18] and suggests that the blood pressure elevation secondary to reduced Emilin may not be entirely attributable to its role on TGF-β. More importantly is the question how much local aortic destruction of Emilin-1 can be translated into increases in blood pressure which to date has been considered to operative in small resistance vessels [17]. The aorta does influence blood pressure mainly systolic blood pressure and TGF-β can increase aortic stiffness [19] and to that extent can be a component of the hypertensive response to aortic dissection.

TGF-β is involved in the development of aortic aneurysms as genetic defects in TGF-β are associated with aortic aneurysms [20-21]. The precise role and molecular mechanisms underlying this relationship, however, has been characterized as elusive and controversial [22].

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Enhanced TGF-β signaling as well as TGF-β receptor mutations have been implicated in in aneurysm formation [22-25]. It has been proposed that different cell types within the aortic wall responds differently to TGF-β so that the balance of effects of TGF-β in conjunction with other factors, dictate the net effect [23]. TGF-β-induced smooth muscle cell apoptosis and stimulates the differentiation of fibroblasts into myofibroblasts which accelerates aneurysm formation [8]. Gene mutations in TGF-β can increase of TGF-β signalling, as manifested by increased TGF-β in the aorta and phosphorylation of targets such as SMAD2, ERK1/2, and Connective Tissue Growth Factor [20,21]. Overexpression of TGF-β in Marfan's syndrome impacts various components of the arterial wall including hyaluronic synthesis and apoptosis which limit tissue repair and likely contribute to aneurysm expansion [26]. Thus, reduction in Emilin-1, a negative regulator of TGF-β should lead to aortic expansion.

In summary, there is intriguing new data on a new molecular mechanism to account for an expansion of aortic dissection and the increase in blood pressure in aortic dissection. Direct testing of this linkage through acute administration of TBF-β inhibitors may lead to an improvement in clinical management of TAD.

Competing interests

There are no conflicts of interest or any relationship with industry and financial associations that might pose a conflict of interest.

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