Abdominal Aortic Aneurysm by Hyperhomocysteinemia - Role of Matrix Metalloproteinases

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INTRODUCTION

Abdominal Aortic Aneurysm (AAA) is a rather rare, but irreversible, dilatation of abdominal aortic tract, usually classified by their size in two types: small aneurysms (diameter less than 5.5 cm.) and large aneurysms (diameter greater than 5.5 cm.) [1]. Large aneurysm is much more likely to rupture than small. The 5-year survival rate is 48% in patients with small aneurysms, whereas it is only 6% in those with large aneurysms. The incidence of AAA ranges from 1.3% to 12.5% and clearly prevails in aged individuals and in male gender [2]. Its rupture is a dramatic event that may result in abdominal and/or back pain, low blood pressure, or low consciousness, and often in death. It is responsible of approximately 8000 annual deaths in the United Kingdom and up 15,000 in the United States. In Italy, the annual mortality is about 6000 cases [3,4]. Although several studies indicate that AAA incidence may be declining, AAA mortality has not declined globally [5].

The pathogenesis of AAA is multifactorial and includes advanced age, smoking, positive family history, atherosclerosis, systemic hypertension, diabetes, dyslipidemia, obesity and male sex [6]. But, several studies have demonstrated that Hyperhomocysteinemia (HHcy) is also associated with the formation, size, and expansion rate of AAA [7-10].

HOMOCYSTEINE

Homocysteine is an intermediate amino acid of methionine metabolism that can be further metabolized via two alternative pathways:

A) Homocysteine irreversibly degrades to cysteine, through the transsulfuration pathway.

B) Homocysteine can be remethylated to methionine. Defects in remethylation or in transsulfuration result in increased homocysteine plasma levels [11]. In the remethylation pathway, a methyl group (CH₃) can be transferred from methionine to some substrates (trans-methylation), such as DNA, neurotransmitters, different proteins, lipids and a variety of small molecules. Particularly, DNA methylation is a process by which a methyl group is added to DNA molecule at CpG (cytosine-phosphate-guanine) site. HHcy causes DNA-hypomethylation by DNA-Methyl Transferases (DNAMTs) inhibition, because the prevalence of S-Adenosyl-Homocysteine (SAH) on S-Adenosyl-Methionine (SAM). A reduced DNA methylation is responsible for some, common human diseases [12] and, among these, degradation of Extra Cellular Matrix (ECM).

It is known that HHcy has correlated with several vascular insults, such as Coronary Artery Disease (CAD), brain vessels disease (stroke) or peripheral diseases (arterial and/or venous thrombosis, and others [13]. But, HHcy may also associated with the formation, size, and expansion of AAA [14,15], particularly in older men [16]. Referring to AAA formation in hyperhomocysteinemic patients, Giusti et al. also reported an increase in total plasma homocysteine levels in patients with aortic dissection or AAA [17]. Too, a large meta-analysis recently performed by Cao and colleagues provided evidence that homocysteine was a predictor of increased risk of AAA [18]. Several experiences indicate that, the main cause of AAA formation induced by HHcy is DNA hypomethylation acting on ECM [19].

PATHOGENESIS OF AAA BY HHCY

Several mechanisms can be responsible for vascular dysfunction [20,21]. Referring to the patients with HHcy, it is known that the sulfur amino acid triggers the expression and release of pro-inflammatory cytokines able to induce chemokine-expression [22,23]. Concerning that, multiple evidences suggest an increase of pro-inflammatory cytokines, such as IL6, TNF-alfa, IL1-beta. IFN-gamma, IL17A in either plasma or tissue extract from AAA [24]. On the other hand in experimental models, Liu et al. demonstrated that HHcy can amplify Angiotensin II-induced adventitial inflammation. The event, started in the adventitial layer, subsequently progresses toward the intima. Concordantly, inflammatory cells (macrophages, T-lymphocytes, and B-lymphocytes) are before observed in the tunica adventitia of aneurysmal tissue and subsequently are found in the intima. The process happens via activation of the adventitial fibroblasts NADP oxidase. Specifically, angiotensin II-enhanced NADPH oxidase activity contributes to Adhesion Molecule (ICAM) expression, leukocyte infiltration, and vascular growth [25]. Increased homocysteine levels can also induce intracellular calcium mobilization, causing platelets’ activation. The consequent intraluminal thrombus formation has potential implications to aneurysm growth and rupture [26]. Other mechanisms coming in AAA formation are: altered lipid metabolism with enhancement of LDL oxidation and lipid peroxidation [27], and smooth muscle cells proliferation [28]. Impaired fibrinolysis by reduction of Tissue-Type Plasminogen Activator (t-PA) is another pathogenetic factor of vascular impairment [29-31] (Table 1).
EXTRACELLULAR MATRIX

But, the main factor deriving from HHcy is the activation and the degradation of ECM via epigenetic changes (DNA hypomethylation, histone modifications, etc.) [32,33]. ECM is a non-cellular network present within the connective cells composed by macromolecules and glycoproteins, that provide structural and biochemical support to the cells. Enzymes, such as Matrix Metalloproteinases (MMPs or matrixins) and their inhibitors (TIMPs), are also present in the ECM network. But, the basement of ECM is composed by fibrous proteins, such as collagen, laminin, fibronectin, and elastin. These have multiple functions, such as constituents of basal membranes, of cells' adhesion molecules, of structures to maintain tissue architecture or to impart elasticity to tissue.

Summarizing, the essential functions of ECM includes [34]:

A) Formation of an essential support structure for the cells;
B) Control of communications among the cells;
C) Regulation of cells' processes (growth, migration, differentiation, etc.)

MATRIX METALLOPROTEINASES

As previously affirmed, some enzymatic compounds, called Matrix Metalloproteinases (MMPs), are present in ECM. These are a group of proteases that play an important role in the protein synthetic-lytic equilibrium of connective tissue.

MMPs are secreted in the latent form (pro-MMPs), requiring activation for their proteolytic activity. These enzymes contain a zinc ion and are inhibited by TIMPs. MMPs are divided into subclasses based upon substrate specificity, such as gelatinases, elastases, and collagenases [35]. Specifically, members of the gelatinase subclass, such as MMP2 and MMP9, have demonstrated an ability to degrade denatured fibrillar collagen (gelatin), elastin and types IV, V, and VII collagen. Referring to AAA formation, some evidences have recognized that elastin degradation contributes to their pathogenesis [36].

Under inflammatory conditions caused by HHcy, infiltrating macrophages, vascular smooth muscle cells, endothelial cells and adventitial fibroblasts of ECM secrete pro-MMPs that activate MMPs [37]. This condition induces a prevalence of MMPs on TIMPs, responsible for abdominal aortic dilation. In fact, contrarily to MMPs, TIMPs prevalence reduces the destruction abdominal aortic wall and, therefore, set oneself against AAA formation [38].

The ECM stimulation (induced by DNA hypomethylation) causes an imbalance of the TIMPs/MMPs ratio, with the prevalence of MMPs, acting such as an independent risk factor for AAA [25]. In fact, this imbalance enhances the proteolytic activity of MMPs on the aortic wall, favoring abdominal aortic dilatation. Referring this, in an in vitro study, Siennika et al. observed that MMP2, may favor the AAA formation by its proteolytic activity [39]. In addition, some previously published meta-analyses have confirmed that HHcy is a risk factor of AAA [40]. The proteolytic activity of MMPs is due to the synthesis of serine elastase that, acting on arterial smooth muscle cells, causes elastolysis by degradation of ECM located in the lamina media of abdominal aorta. The release of Reactive Oxygen Species (ROS), is implicated in AAA pathogenesis too [41,42]. However, whether homocysteine plays a direct causal role in the AAA pathogenesis or is merely an innocent bystander remains elusive too. In a Chinese Han population, Liu et al. report HHcy such as an independent risk factor for AAA [10]. In accordance, Brunelli et al. showed that risk increased AAA by up to six times in presence of HHcy, and this association was further observed in a subgroup without evidence of atherosclerosis [9]. In contrast, Naydeck et al. did not find any association between Hcy serum levels and AAA. Perhaps, this discrepancy may stem from the confounding effect of age, other conditions and/or diseases [43]. The succession of events induced by HHcy in the formation AAA are reported in Table II.

INTRALUMINAL THROMBUS

Some studies suggest that HHcy leads an alteration in coagulation and fibrinolysis. Specifically, it has been reported that homocysteine exhibits antifibrinolytic properties, by the reduction of tissue-type Plasminogen Activator (PA-1) gene expression. These observations indicate that HHcy modifies endothelial function in a pro-thrombotic manner and favors thrombogenesis. Intraluminal thrombus can either be eccentrically located or occupying the entire internal wall of the AAA (figure 1). It must be added that thrombus also works as a site of protease release and is correlated to the further dilation of AAA [44,45]. But, its role in the aneurysmatic rupture appears controversial. In fact, some authors supposed that thrombus accelerates AAA rupture [46], others suggest that intraluminal thrombus in AAA provides biomechanical advantage by decreasing...
wall stress [47]. We can reasonably conclude that a thrombus in AAA is associated with a higher AAA growth rate, but also a lower wall stress, with reduced probability of rupture [47].

CONCLUSIVE REMARKS

AAA consists in an abnormal dilatation of abdominal aorta, often associated with intraluminal thrombus, aortic wall rupture and elevated mortality. Its pathogenesis is multifactorial, but HHcy seems to be an independent risk factor for AAA formation. Enhancement of proteolytic effects induced by protease’s release, consequent to the activity of MMPs in ECM are the main mechanisms carried out by HHcy in the pathogenesis of AAA.

Intraluminal thrombus frequently complicates AAA HHcy acts by Tissue Factor (TF) and Plasminogen Activator Inhibitor-1 (PAI-1), that favor thrombogenesis and modifies endothelial function in a pro-thrombotic manner. But at present, whether intraluminal thrombus accelerates the AAA rupture or reduces the probability of that is debated. Concordantly, whether homocysteine levels play a role or is simply a marker in the AAA pathogenesis remains elusive. Finally, in consideration of the reduced expansion of AAA induced by TIMP’s nanoparticles, treatment with these could represent an option for preventing a further expansion of small AAA [48]. Therefore, a wide range investigations are requested to clarify these dilemmas.

REFERENCES


