Abdominal Aortic Aneurysms

Subjects: Medicine, Research & Experimental

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This entry outlines recent preclinical and clinical advances in molecular imaging of abdominal aortic aneurysms (AAA) with a focus on molecular magnetic resonance imaging (MRI) of the extracellular matrix (ECM). In addition, developments in pharmacologic treatment of AAA targeting the ECM are reviewed and results from animal studies are contrasted with clinical trials. Abdominal aortic aneurysm (AAA) is an often fatal disease without non-invasive pharmacologic treatment options. The ECM, with collagen type I and elastin as major components, is the key structural component of the aortic wall and is recognized as a target tissue for both initiation and the progression of AAA. Molecular imaging allows in vivo measurement and characterization of biological processes at the cellular and molecular level and sets forth to visualize molecular abnormalities at an early stage of disease, facilitating novel diagnostic and therapeutic pathways. By providing surrogate criteria for the in vivo evaluation of the effects of pharmacological therapies, molecular imaging techniques targeting the ECM may facilitate the development of pharmacological drugs. In addition, molecular targets can also be used within theranostic approaches that have the potential for timely diagnosis and simultaneous medical therapy. Recent successes in preclinical studies suggest future opportunities for clinical translation. However, further clinical studies are needed to validate the most promising molecular targets for human application.

Keywords: abdominal aortic aneurysm ; extracellular matrix ; pharmacological treatment

1. Introduction

Abdominal aortic aneurysm (AAA) is a fatal, but often asymptomatic disease with controversial treatment and insufficient prediction of complications [1][2]. The extracellular matrix (ECM), with collagen type I and elastin as main components, is the key structural component of the aortic wall and is recognized as a target tissue for both the onset and the progression of AAA. While large and fast-growing AAAs are indicated for surgery/vascular repair, management of medium-sized AAAs remains challenging [3]. Currently, there is no effective treatment, which can slow down or prevent AAA growth.

In clinical routine, morphological criteria for the determination of the aortic diameter on ultrasound, computed tomography (CT) and MRI have been used in accordance with guidelines as evaluation criteria for therapeutic intervention or conservative therapy. By contrast, molecular imaging enables an in vivo measurement and characterization of biological processes at cellular and molecular level and sets forth to visualize molecular abnormalities at an early stage of disease, facilitating novel diagnostic and also therapeutic pathways [4]. MRI is a non-ionizing modality well suited for imaging and characterizing the relatively thin arterial vessel wall as it allows imaging with high spatial resolution and excellent soft tissue contrast [5]. By combining molecular imaging with MR target-specific probes, pathological processes can be detected and characterized in vivo [6]. This information can provide new insights into the pathogenesis of diseases in vivo and help to develop new diagnostic targets and monitor potential therapeutic success. By providing surrogate criteria for the in vivo evaluation of the effects of pharmacological therapies, molecular imaging techniques targeting the ECM may facilitate the development of pharmacological drugs. In addition, they can help to improve the clinical efficacy of medical therapies by guiding the intensity of treatment based on the properties of the molecular tissue. For example, molecular imaging of the ECM could on the one hand enable non-invasive assessment of aneurysmal tissue changes and rupture risk, and on the other hand allow to monitor the levels of key ECM proteins in response to therapeutic intervention, such as elastin and collagen [7].

2. The Role of the Extracellular Matrix in AAA

In each organ, the composition of the ECM has a different three-dimensional structure and a constant pattern of remodeling to regulate tissue homeostasis [8]. Within the vascular system, the ECM is essential to resist the range of blood pressures and shear forces acting on the vessel walls. Development of AAA involves localized inflammatory response with proinflammatory cells (e.g., macrophages) and degradation/remodeling of the ECM. Disturbances in the synthesis and proteolytic degradation of the aortic structural ECM proteins, particularly collagen and elastin, have been

shown to be critical to AAA pathogenesis [9]. Besides elastolysis and collagen lysis, which are reasonably well known, there is as yet little information on changes in other ECM proteins [10]. Prior proteomics analyses revealed thrombospondin 1 and 2, periostin, fibronectin und tenascin to be significantly altered proteins in the ECM of aneurysm tissue [10][11]. The protein thrombospondin 1 is a large glycosylated secretory protein with adhesive properties towards ECM components, including collagen, fibrinogen and fibronectin [11]. Periostin (fasciclin 1 family) is an ECM protein, which interacts with integrin molecules on cell surfaces, providing signals for tissue development and remodeling [12] and promoting the secretion of matrix metalloproteinases (MMPs) from cardiac cells [13]. In a mouse model of AAA, it was shown, that periostin was upregulated during the progression of AAA, particularly at times when active inflammation caused destruction of the ECM [14]. Periostin could thus function both in terms of a clinical biomarker of disease activity in AAA and in terms of a therapeutic target for patients with AAA. Fibronectin is another important glycoprotein of the aortic ECM and its expression has been reported to be increased in AAA of patients with tricuspid aortic valve stenosis or bicuspid aortic valve [15].

2.1. Molecular Magnetic Resonance Imaging for Identification of Potential Diagnostic Targets and Monitoring of Therapeutic Success

Molecular MRI includes both targeted probes with selective binding to molecular targets and probes that accumulate passively within cells (e.g., by phagocytosis) [16]. A major strategy of molecular MRI to achieve specificity for the target is the coupling of small molecules, peptides or antibodies with clinically approved MRI contrast agents such as gadopentetate (Gd-DTPA) or gadoteridol (Gd-HPDO3A) [17]. In addition, T2-weighted contrast agents such as iron oxide particles can be used to track or label cells.

In vivo imaging of AAA wall inflammation and ECM remodeling has previously been achieved using ultrasmall superparamagnetic particles of iron oxide (USPIOs), elastin-specific MRI contrast agents (Gd-ESMA) as well as collagen- and fibrin-binding probes [18][19][20][21][22]. One advantage of USPIOs is that the substance is clinically approved and can therefore already be used in human studies. The principle of USPIO MRI is that these particles are taken up by phagocytic cells, especially macrophages, and allow visualization and quantification of inflammatory processes in the aortic wall using T2/T2* sequences. In angiotensin-II (Ang-II) infused apolipoprotein E (ApoE) -/- mice, the combined use of USPIO and EP-3533, a collagen-specific gadolinium-bound probe, allowed evaluation of ECM remodeling, inflammatory activity, and prediction of rupture events (refer to Figure 1) [19].

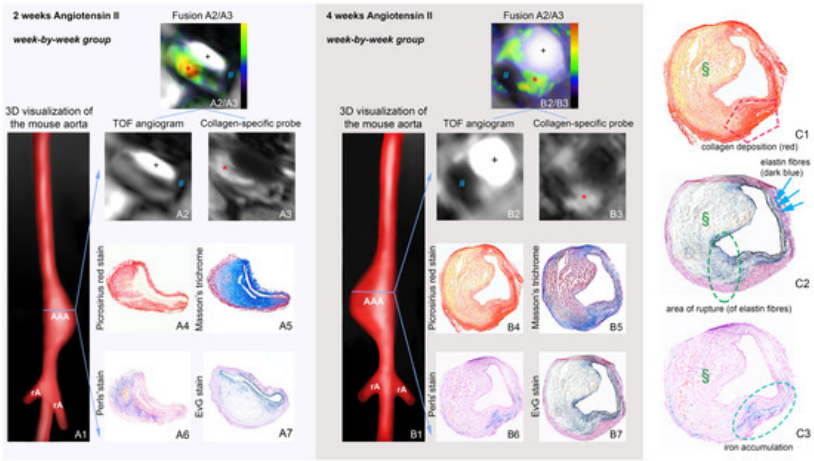

Figure 1. Molecular MRI (in vivo) using collagen- and inflammation-specific probes. (**A1**,**B1**) show 3D visualizations of 2- and 4-week-old AAAs. (**A2**,**B2**) show examples of oxide MRI with signal voids of different sizes for 2-week (**A2**) and 4-week (**B2**) AAAs. IR T1-weighted sequences show areas of intermediate signal enhancement of 2 weeks (**A3**) and four weeks (**B3**) AAA. (**A4**–**A7**) and (**B4**–**B7**) correspond to ex vivo histological measurements using Picrosirius red and Masson's trichrome for visualization of collagen fibers and Perls' staining for detection of inflammation-associated iron, confirming in vivo findings. (**C1**) illustrates compensatory collagen deposition in the aneurysmal wall after rupture. (**C2**) indicates the rupture site (green circle) with the ruptured elastin fibers and (**C3**) demonstrates iron accumulation at the rupture site. * Signal from the collagen-binding probe in the aneurysmal wall, # Signal void from the iron oxide particles, § Thrombus area. AAA suprarenal abdominal aortic aneurysm, rA renal artery, + Vascular lumen in arterial TOF. This figure was originally published in Adams et al., [19] (open access article, distributed under the terms of the Creative Commons Attribution License).

In a recently published prospective multicenter cohort study (MA3RS) including 342 patients with abdominal aortic aneurysms, USPIO enhancement was associated with higher risk of aortic rupture or repair, reduced event-free survival

from aneurysm rupture or repair, and aneurysm expansion, although it was not independent of clinical risk factors and thus had limited additional value beyond current clinical risk prediction [23]. In a sub-cohort of the MA^{3}RS study, USPIO enhancement showed no correlation with computed tomography angiogram (CTA) predictions of stress areas, so that localization of rupture-prone areas in the clinical setting has not yet been successful [24].

A further crucial process in AAA development, related in part to inflammation, is remodeling of the ECM. Dysfunctional ECM remodeling may reduce wall stability and promote AAA formation. Gd-ESMA is an elastin-specific MRI probe that showed high potential in quantitative imaging of vascular diseases [25]. By specific binding of elastin, molecular MRI allowed prediction of the site of rupture before aortic dilatation and visualization of inflammatory processes in the development of AAA in a mouse model [25][26].

Another protein that may be increased in AAA due to dysfunctional ECM remodeling is tropoelastin, a monomeric precursor of cross-linked elastin [27]. A recent study using quantitative molecular tropoelastin (Gd-TESMA)- enhanced MRI found that it could identify dysfunctional ECM remodeling by being specifically expressed in regions of AAA and correlating with AAA development and expansion (Figure 2) [27].

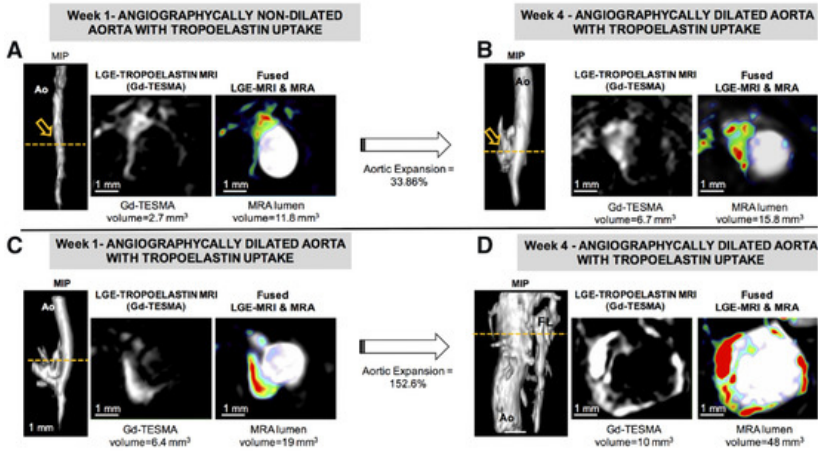

Figure 2. Gd-TESMA MRI shows increased tropoelastin expression in the dilated aortic segments (**C**,**D**). (**A**–**D**) MRA and late gadolinium enhancement (LGE)-MRI of a control (**A**,**B**) and an Ang II-infused ApoE-/- mouse with aortic dilatation (**C**,**D**) scanned with the tropoelastin contrast agent. Fusion of MRA and LGE-MRI images of an Ang II-infused ApoE-/- mouse after administration of Gd-TESMA show that the uptake of tropoelastin is restricted to the dilated aortic wall. Abbreviations: Ao, aorta; LRA: left renal artery; MIP, maximum intensity projection; RRA, right renal artery. Adapted from: Lavin et al., [27] (open access article, distributed under the terms of the Creative Commons Attribution License).

MMPs are also associated with changes in the ECM and the development of AAA. P947 is a gadolinium (DOTA)-binding molecular probe that specifically binds to MMPs, particularly MMP-2 and MMP-9. In AAA-induced wistar rats, P947 MRI images showed good colocalization of the sample with MMPs in wall areas of inflammatory events [28].

MMP tracers have also been developed for nuclear imaging. The ^{99}mTc-labeled homolog, RP805 predicted vessel expansion and rupture probability in Ang-II-induced murine AAA [29]. Another study investigated the ^{99}mTc-labelled pan-MMP inhibitor RYM1 and demonstrated a higher uptake of the tracer in AAA compared to nondilated aorta [30]. In addition, RYM1 enabled detection of inflammation (correlation with CD68 expression) and ECM remodeling (correlation with MMP activity) (Figure 3) [30].

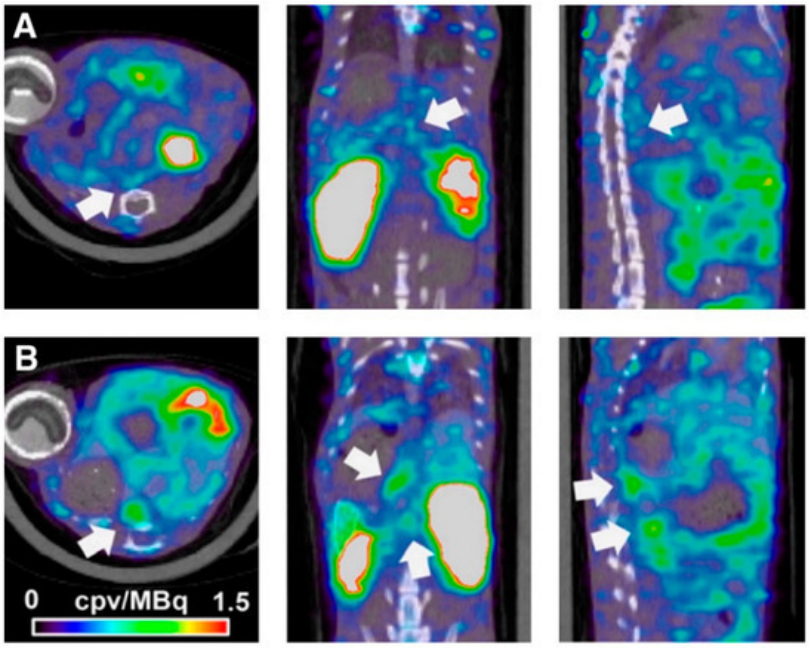

Figure 3. Example images for 99mTc-RYM1 imaging of AAA. A and B show examples of fused 99mTc-RYM1 SPECT/CT images from mice with little ECM remodeling (**A**) and aneurysm (**B**) groups, classified on the basis of visual in situ analysis of the abdominal aortae. Transversal (left), coronal (middle), and sagittal (right) views are provided. Arrows indicate the areas of maximal tracer uptake within the abdominal aortae. Adapted from Toczek et al. [30] © SNMMI.

A recent study by *Yao* et al. investigated a smart activatable MRI nanoprobe to target MMP in early-stage AAA in a mouse model and found that their probe allowed for the detection of MMP activity within the aneurysmal wall, thus representing a potential noninvasive method to predict the risk of rupture in AAA [31].

More consistent results were achieved in preclinical studies on integrin-targeted tracers. Integrin $\alpha_v\beta_3$ is upregulated in proliferating endothelial cells, VSMC and macrophages [32][33]. NC100692, a ^{99}mTc-cyclic RGD tracer for microSPECT-CT displayed increased uptake in murine carotid aneurysms and a correlation with inflammatory activity [34]. English et al. recently developed a specific agent of chemokine receptor type 2 (CCR2) with the PET tracer ^{64}Cu-DOTA-ECL1i [35]. CCR2 is expressed in macrophages/monocytes and mediates the migration of leukocytes to the inflammatory event in the vessel wall after injury. In induced AAA in Sprague-Dawley rats, ^{64}Cu-DOTA-ECL1i showed significantly increased uptake compared with sham controls and compared with aneurysms that did not rupture during progression [35].

2.2. Pharmacologic Treatment Strategies Targeted to the ECM

Experimental targets for pharmaceutical AAA stabilization, that target the ECM, are thrombospondin inhibitors [36], cysteine protease inhibitors [37], serine protease inhibitors [38], protease inhibitors such as MMP inhibitors [39], and interleukins [40]. Other potential targets include inhibition of c-Jun N-terminal kinase as well as miR-29b (microRNA), both of which demonstrated a reduction of AAA via modulation of the ECM metabolism [41][42].

In humans, elevated thrombospondin-1 (TSP-1) was associated with MMP activitaion, ECM degradation as well as tissue infiltration [43]. Cysteine cathepsins (Cat) are a diverse group of proteases that are abundant in VSMCs, macrophages and endothelial cells of atherosclerotic plaques and aneurysmal lesions. Among the cysteine cathepsins, Cat S directly modulates inflammatory and immune responses and apoptosis of VSMCs, whereby elevated expression levels in the vessel wall and plasma of human AAA were recently confirmed [44]. In AAA, blockade of Cat S induced ECM degradation is still in the preclinical phase [45][46]. Recent preliminary preclinical studies in murine models showed promising results for two serine protease inhibitors, serpina3n (SA3N)—a potent inhibitor of granzyme B [38] and ulinastatin [47].

3. Discussion and Outlook

Over the past 30 years, a variety of promising gadolinium-based molecular tracers have been developed and their utility confirmed in proof-of-concept animal studies. Nevertheless, only non-targeted contrast agents have made it to clinical approval for use in humans. A challenge in clinical translation is that toxicological testing is time-consuming and costly, requiring substantial financial resources. This contradicts the expected revenues, which are lower for molecular tracers than for clinically proven nonspecific contrast agents due to their limited application in specific settings. Nonetheless, these markers play a prominent role especially in preclinical research and, if validated, can non-invasively image new

therapeutic approaches, for example targeting ECM remodeling. In this context, the elastin-specific MRI probe Gd-ESMA and tropoelastin-specific MRI probe Gd-TESMA appear promising, as they can specifically detect the effect of therapeutic strategies affecting the elastin content in the aortic wall via their different pathways. Another novel approach are multitarget probes, which could allow for concurrent imaging of different pathophysiological processes at the molecular level. Molecular agents may also be used within theranostic approaches with the potential for timely diagnosis and concurrent medical therapy. Here, the use of miRNA-based targets is a novel and promising method.

Currently, there is no established pharmacologic therapy for the treatment of AAA. The apparent discordance between successes in preclinical studies and partly disappoint results in clinical trials suggests an incomplete understanding of the various pathological processes involved in the development of AAAs and points to possible inadequacies in animal models of the disease. To increase future therapeutic strategies, molecular imaging markers that can specifically visualize and quantify targets of pharmacological agents in ECM in a non-invasive manner hold promise for a better reflection of the pathophysiological processes behind the disease and during therapy. In addition, recent preclinical approaches in large animal models represent a promising option for evaluating therapeutic strategies and create better options for multiparametric functional imaging, which seems to be limited in parts by the low volume in small animal models. With the increasing availability of image-based molecular biomarkers and promising pharmacotherapies, as well as their evaluation in large animal models of AAA and initial human clinical trials, there is reason to hope that molecular therapeutic approaches targeting ECM will enter clinical research in the coming years.

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