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Editorial

ADAM8 in the cardiovascular system: An innocent bystander with clinical use?

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Several key players in inflammation as well as atherosclerosis development are regulated by proteolysis close to the cell surface in a process called regulated intramembrane proteolysis, leading to ectodomain shedding, mediated by proteases of the A disintegrin and metalloproteinases (ADAMs) family. To date, 12 proteolytically active ADAMs have been identified, one of which is ADAM8 that is characterized by its autocatalytic properties resulting in a soluble form of ADAM8 (sADAM8), in addition to the classical transmembrane bound form [1,2]. Several members of the ADAMs family, including ADAM9, 10, 15 and 17, have been shown to be expressed in atherosclerotic plaques in humans and their expression was increased upon lesion development or associated with plaque rupture [3–6]. Recently, Theodorou et al. also demonstrated expression of ADAM8 in human atherosclerotic lesions, which was associated with foam cells and further increased with plaque progression [7]. However, expression itself does not prove a protein's contribution to disease development or progression. ADAM10 and ADAM17 were already shown to play a causal role in murine atherosclerosis development. For ADAM17, it has been shown that there are clear and contrasting cell-type specific effects on atherosclerosis formation [8]. Myeloid ADAM17 deficient mice were shown to have increased atherosclerotic lesion development, while endothelial ADAM17 deficient mice demonstrated reduced plaque sizes compared to controls. For ADAM17, it, however, seems that the myeloid compartment plays a more dominant role, as ADAM17 hypomorphic mice which have low residual *Adam17* expression also showed enhanced lesion development mainly due to increased tumor necrosis factor receptor 2 (TNFR2) signalling [9]. For ADAM10, it was observed that myeloid ADAM10 plays a causal role in the development of atherosclerosis in mice, mainly by modulating plaque stability features by shifting the balance from inflammation toward fibrosis [10]. The role of vascular ADAM10 on atherogenesis still remains elusive, but it would be very interesting to investigate, as it has been shown previously that ADAM10 does influence endothelial cell function and thereby modulates angiogenesis [4]. In contrast to ADAM10 and ADAM17, the study by Theodorou et al. showed that neither haematopoietic nor whole body deficiency of ADAM8 in mice impacted on atherosclerotic lesion development [7], suggesting that ADAM8 is just an innocent bystander in this disease. Of note, mice do not show any signs of plaque rupture, which usually is the cause of clinical symptoms of cardiovascular disease in humans. Hence, one cannot rule out any role of ADAM8 in this detrimental process. Nevertheless, especially since it also exists in a soluble form, ADAM8 could still function as a diagnostic or even predictive biomarker for cardiovascular diseases.

Indeed, specific ADAM8 polymorphisms (rs2995300C and rs2275725A) and serum levels of sADAM8 were shown to be associated with lesion development and myocardial infarction in two independent human cohorts [11]. The study published by Schick et al. in this issue of *Atherosclerosis* [12], provides further evidence that ADAM8 expression is modulated by inflammatory conditions in both mice and men, thereby clearly associating with vascular diseases. Furthermore, the authors could show clear correlations between sADAM8 and disease severity and organ dysfunction, demonstrating a great potential for sADAM8 as biomarker.

In the study by Schick et al., it was demonstrated that vascular *Adam8* expression in regions that are prone to develop atherosclerosis is significantly upregulated in mice upon western type diet (WTD) feeding. Especially striking in light of the previously discussed upregulated expression and causal role for ADAM10 and ADAM17 in human atherosclerosis formation, the expression of *Adam10* and *Adam17* in the murine vasculature was not changed upon WTD feeding. In the current paper, this discrepancy is not further evaluated, leaving an interesting question open for further research. Besides the increased *Adam8* expression, the authors could also show that this expression is positively correlated to the expression of key inflammatory markers *Tnf* and *Vcam-1*. The increased vascular *Adam8* expression, which was shown to be present in both endothelial cells and leukocytes, also coincided with an increased serum soluble ADAM8 level, further supporting the notion that *Adam8* expression is elevated in WTD fed animals. Similar results were also obtained in another inflammatory mouse model, i.e. myocardial infarction, which is interesting towards translation of these re-

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sults as myocardial infarction is often the first clinical manifestation of atherosclerosis or coronary artery disease.

The notion that mainly leukocytes and endothelial cells express *ADAM8* in an inflammatory setting was confirmed in both disease models and was further validated in human *in-vitro* cultures (using TNF stimulations). Similar to the results in the disease models, ADAM8 expression in human endothelial cells and peripheral blood mononuclear cells (PBMCs) also correlated with various inflammatory markers, like CCL2. However, an important aspect to keep in mind here is that the authors also showed that this enhanced *ADAM8* expression did not directly cause the upregulation of the vascular inflammation markers, clearly highlighting that although there is a strong correlation, these results do not imply a causal role for ADAM8 in inflammation and atherosclerosis development. Nevertheless, they could demonstrate that the release of soluble ADAM8 was also increased upon inflammation. Especially, in combination with the notion that coronary artery disease patients showed increased serum levels of soluble ADAM8 compared to healthy controls, this supports the concept that soluble ADAM8 might be a promising biomarker.

A major concern that arises regarding the use of ADAM8 as a diagnostic (or even predictive) marker is specificity. Besides cardiovascular disease, ADAM8 has also been shown to correlate with and regulate amongst others lung inflammation [13], asthma [14] and chronic obstructive pulmonary disease [15]. Moreover, ADAM8 has been implicated in various types of cancer, especially mediating metastasis [16]. For example, Schlomann et al. showed that high levels of ADAM8 correlate with poor clinical outcome for pancreatic cancer patients [17]. Therefore, it remains to be seen whether ADAM8 alone could be used as a diagnostic marker for cardiovascular diseases, or any disease. Most likely a broader panel of biomarkers is required to enhance the specificity for a certain disease, as has been shown already for the diagnosis of gastric cancers, where a panel of markers, including ADAM8 along with VEGF and pepsinogen, resulted in an acceptable degree of specificity [18]. Therefore, the identification of disease-specific substrates of ADAM8 may be necessary to further progress the development of ADAM8 as diagnostic marker. Additionally, specific ADAM8 inhibitors are currently in development for the treatment of cancer metastasis and inflammatory diseases [19,20]. Although murine models did not show any causal effect of ADAM8 in atherosclerosis development, it would be very interesting to see whether the use of these inhibitors in humans could also have an impact on cardiovascular events, which might still be possible as it remains challenging to fully translate the causality aspect from the murine to human setting.

Still, relatively little is known about the substrates and functions of ADAM8. ADAM8 polymorphisms have been shown to impact on sADAM8 levels [11], however, it is thus far unknown whether polymorphisms could also impact on ADAM8 functions and perhaps prove to be better predictors or more specific for cardiovascular risk than measuring mere levels of sADAM8. Moreover, ADAM8 not only functions via its proteolytic activities, but also via its disintegrin domain which binds to β1-integrins, regulating integrin signalling, focal adhesion formation and cell migration. Whether integrin binding is also contained for the soluble form of ADAM8, remains to be determined. If this is the case, measuring the membrane-bound form of ADAM8 might be more relevant for a specific disease than measuring soluble levels in the circulation.

In conclusion, atherosclerosis studies in mice so far suggest ADAM8 mainly to be an innocent bystander in cardiovascular diseases. Nevertheless, previous studies and especially the study by Schick et al. clearly demonstrate a correlation of ADAM8 with disease progression and cardiovascular events like myocardial infarction in humans, indicating that serum levels of soluble ADAM8 might have benefit for diagnostic or even predictive purposes. However, since it has also been associated and implicated in various other inflammatory or malignant diseases, its specificity as a single biomarker seems to be severely limited. More research into differences in ADAM8 polymorphisms, its proteolytic vs integrin-binding activity and the predictive power of broader, more disease-specific biomarker panels for disease risk-assessment are required.

Conflict of interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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