Cardiovascular Research (2013) **99**, 592–594
doi:10.1093/cvr/cvt188

EDITORIAL

Selective atrial profibrotic signalling in mice and man

Larissa Fabritz[1,2]* and Paulus Kirchhof[1,2]*

[1]Centre of Cardiovascular Sciences, University of Birmingham and SWBH NHS Trust, Birmingham, UK; and [2]Department of Cardiology and Angiology, Hospital of the University of Münster, Münster, Germany

This editorial refers to 'Molecular basis of selective atrial fibrosis due to overexpression of transforming growth factor-β1' by D. Rahmutula *et al.*, pp. 769–779, this issue.

Although oral anticoagulation can prevent the majority of strokes in patients with atrial fibrillation (AF) if used as recommended in treatment guidelines,[1] patients with AF receiving optimal therapy still die prematurely, and are frequently hospitalized.[2] Hence, we need a deeper understanding of the mechanisms behind AF in patients to develop better treatment. Most of the currently used treatments for AF were initially developed to treat ventricular heart disease, e.g. angiotensin-converting enzyme inhibitors, digitalis, beta-adrenoceptor blockers, spironolactone, and most antiarrhythmic drugs. Understanding electrophysiological differences between the atria and ventricles have allowed the recent development of atrial antiarrhythmic drugs (dronedarone, vernakalant), with others undergoing clinical development. Catheter ablation of AF also illustrates how the understanding of an atrial arrhythmia mechanism, i.e. focal firing in and around the pulmonary veins, helped develop a specific AF treatment.

In this issue of *Cardiovascular Research*, Rahmutula *et al.*[3] characterize a molecular pathway leading to selective atrial fibrosis. By analysing human atrial and ventricular tissues, they identified an atrial preponderance of transforming growth factor-β (TGF-β) expression, and higher atrial TGF-β levels in patients who developed post-operative AF. They further studied the effects of increased TGF-β expression using a murine model of enhanced TGF- β expression under the control of the α-MHC promoter that is prone to inducible AF.[4,5] In this model, TGF-β expression is increased to a similar level in both ventricular and atrial cardiomyocytes as measured in young adults, but only the atria respond to this TGF-β expression by increased interstitial fibrosis.

Why does the same level of TGF-β overexpression cause fibrosis in the atria, but not in the ventricles? Published experiments provide ample room for speculation: TGF-β is an important activator of chemokines and attracts monocytes into the heart.[6] Micro-RNAs,[7] plasminogen activator-inhibitor 1,[8] or non-canonical, SMAD-independent activation of junction kinase can alter the response of cardiac and vascular tissue to TGF-β.[3,9] Of note, TGF-β also alters left-right differentiation of embryonal mesoderm.[10] Rahmutula *et al.* provide insights from gene array and gene expression analyses and protein chemistry in atrial and ventricular tissue in TGF-β transgenic and wild-type mice suggesting enhanced receptor binding, enhanced phosphorylation of receptor regulated (R-)SMAD2/3, reduced expression of the inhibitory SMAD7 in atria vs. ventricles. Hence, it appears that 'canonical' TGF-β signalling is the most likely mediator of selective atrial fibrosis in response to TGF-β (*Figure 1*). A similar signalling pattern has been described in patients with aortic aneurysm and mutations in the TGF-β receptor.[11]

The study has limitations: the number of human atrial samples acquired during open heart surgery was limited ($n = 17$), and even fewer patients had AF, only $n = 2$ spontaneous AF and $n = 4$ post-operative AF. Concerning the overexpression model, it may be relevant to consider that the α-MHC promoter is activated earlier in the atria than in the ventricles, possibly increasing atrial vulnerability.[5] Non-canonical TGF-β signalling cannot be fully excluded.[9] Bone morphogenic protein-10 (BMP-10), the 'right atrial mirror marker' of the left atrial gene *Pitx2*[12] is a target of TGF-β signalling and seems reduced in the gene array presented by Ramuhtula *et al.* We will need to carefully differentiate left and right atrial changes in future studies to better understand selective signalling pathways.

While these limitations call for replication of the findings in other models and cohorts, their hypothesis is supported by the translational approach 'from mice to men', by demonstration of enhanced TGF-β expression and activity in human atrial compared with the ventricular myocardium, and by attenuation of the fibrotic response to TGF-β by inhibiting the TGF-β receptor kinase support. Also, in a coincident clinical study, increased expression of connective tissue growth factor and TGF-β in patients with chronic AF ($n = 28$) is seen compared with others in sinus rhythm ($n = 12$).[13] Furthermore, dogs treated with the TGF-β inhibitor tranilast develop less AF in response to rapid pacing.[14] The study reported here may provide a molecular explanation for these findings.

In summary, the results of this translational study suggest that inhibiting TGF-β signalling may help prevent atrial fibrosis more effectively than inhibiting the renin–angiotensin system.[15,16] Further studies are needed to identify the best therapeutic target and to understand the relevance of fibrosis and fibroblast activation for AF,[17,18] but the data suggest that the development of atrial-specific antifibrotic therapy is feasible.

Acknowledgements

We would like to thank Lucia Kirchhof for help with artwork and Genna Riley for comments.

Conflict of interest: See list of financial disclosures of PK on www.escardio.org.

* Corresponding author. Tel: +44 1214147042; fax: +44 1214158817, Email: p.kirchhof@bham.ac.uk (P.K.)/l.fabritz@bham.ac.uk (L.F.)

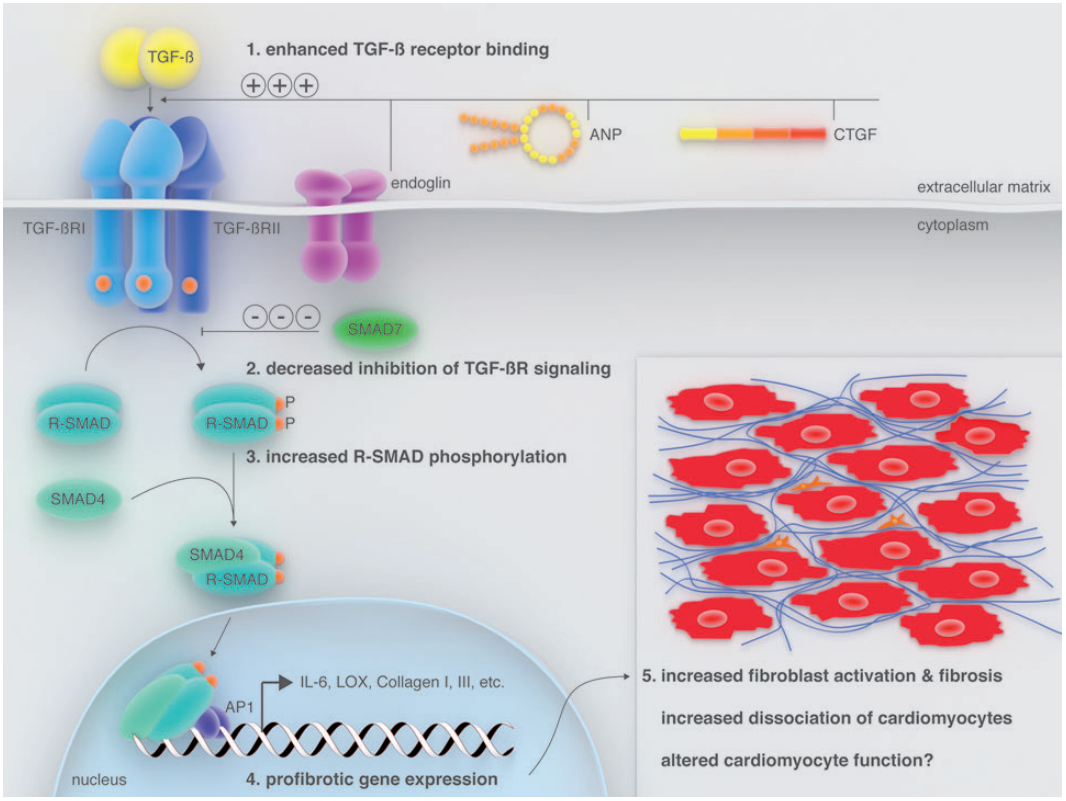

Figure 1 Scheme illustrating potential key steps in mechanism of selective atrial fibrosis in response to increased transforming growth factor beta (TGF-β) signalling: (1) enhanced binding of TGF-β to its receptor TGF-βR is favoured by increased expression of connective tissue growth factor (CTGF), increased endoglin expression and higher levels of atrial natriuretic peptides (ANP). (2) In addition, expression of the inhibitory SMAD7 (Sma and Mad Related Family) is lower in atria compared to ventricles, which in turn decreases inhibition of TGF-βR signalling in the atria. (3) The enhanced activation of TGF-βR in combination with decreased SMAD7 expression increases receptor regulated (R-)SMAD (here SMAD2 and (3) phosphorylation. (4) Phosphorylated R-SMAD forms a protein complex with SMAD4, moves into the cell nucleus and binds to DNA controlling target gene activity, leading to increased expression of activator protein 1 (AP1) regulated proteins. (5) The increased expression of profibrotic genes leads to fibroblast activation and fibrosis. Selective atrial interstitial fibrosis may translate into increased electrical dissociation of atrial myocardium and altered cardiomyocyte function 16, a potential substrate for atrial fibrillation (AF).

Funding

This work was supported by DFG FA413-3/1, SFB656MoBilA8, Kompetenznetz Vorhofflimmern Atrial Fibrillation competence NETwork (AFNET) Germany, Fondation Leducq (ENAFRA), and European Union (FP7, EUTRAF).

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