

Atrial fibrosis and atrial fibrillation: The role of the TGF- β_1 signaling pathway

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Abstract

Background: Atrial fibrosis concurs with chronic atrial fibrillation (AF), a phenomenon that contributes to the resistance to restore and maintain sinus rhythm (SR). Fibrogenesis represents a complex process in which the transforming growth factor- β_1 (TGF- β_1) pathway may play a major role, e.g. in the setting of myocardial infarction. The present study addresses the potential contribution of the TGF- β_1 signaling pathway to atrial fibrosis in patients with AF.

Methods and results: Right atrial appendages of 163 patients were excised during heart surgery and grouped according to rhythm (SR vs. AF) and AF duration. Five groups were defined: SR, paroxysmal/chronic persistent AF (<6 months), chronic permanent AF (CAF) of 7–24 months, 25–60 months, and >60 months duration. Collagen content of atria, determined morphometrically, revealed a steady and significant increase in patients with SR ($14.6 \pm 8.9\%$) up to patients with CAF of >60 months ($28.1 \pm 7.1\%$). Likewise, expression of TGF- β_1 mRNA and protein, TGF- β -receptor-II protein, profibrotic phospho-Smad-2 and -4 proteins increased. However, the TGF- β_1 effect appeared to decline with increasing AF duration, characterized by a decrease in TGF- β -receptor-I protein, increases of TGF- β inhibiting Smad-7 protein and a reduction of phospho-Smad-2.

Conclusions: Human atrial fibrogenesis in patients with atrial fibrillation is accompanied by a biphasic response, an early increase and later loss of responsiveness to TGF- β_1 . It appears that fibrosis progresses despite compensatory changes in the TGF- β -signaling pathway. The sequential changes in the contribution of different profibrotic processes during the establishment of AF may offer the opportunity to selectively interfere with the atrial remodeling process at different stages.

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1. Introduction

Atrial fibrillation (AF) causes substantial morbidity and mortality. Its prevalence places it as the most common clinically significant arrhythmia and is expected to increase

even more in the coming years as the general population ages further. Its incidence doubles with each successive decade of life beyond 50 years [1]. AF is known to alter the structural and electrophysiological properties of the atrial tissue [2]. Among the electrophysiological changes sustaining AF are impaired atrial conduction and increased atrial anisotropy leading to chaotic rather than linear electrical propagation. Both of these factors favor atrial micro-reentry helping to sustain the arrhythmia [3,4]. Atrial fibrosis is thought to promote these changes. Previously, we found atrial fibrosis

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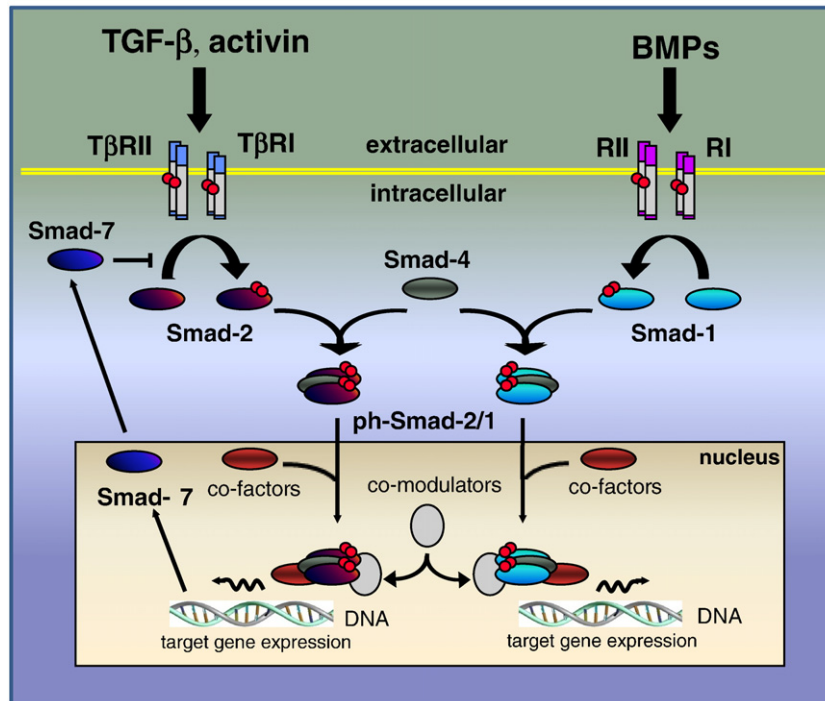


Fig. 1. Simplified scheme of the transforming growth factor- β (TGF- β) superfamily/Smad pathway. Following cytokine, e.g. TGF- β or BMP (bone morphogenetic protein), binding to the type II receptor (T β RII; RII), receptor kinases phosphorylate cytoplasmic domains and activate the type I receptor (T β RI; RI). The Smads then act as T β RI/RI activated signaling effectors, which, following receptor induced phosphorylation and interaction with co-Smad-4, translocate into the nucleus and activate transcription of selected target genes. Specific mechanisms at nearly all levels have been identified that activate or repress TGF- β signaling, among others inhibitory Smad-7.

to increase with the duration of AF [5] and to be associated with increasing age [6]. Once atrial fibrosis is established, it is only partly reversible and therefore contributes to sustain AF [7]. Thus, to develop safe and more effective treatments of AF a better understanding of the pathophysiological mechanisms underlying atrial fibrosis are urgently needed [2].

Many factors are known to influence cardiac fibrogenesis. Among those are congestive heart failure, valvular defects, and hypertensive cardiovascular disease [1]. Although atrial fibrosis is not the only risk factor for the development of AF, most risk factors for AF are simultaneously risk factors for cardiac fibrosis. Until recently, mostly ventricular fibrosis and remodeling has been studied. Importantly, experimental data have shown, that these findings cannot simply be transferred to the atrial level [8–10].

The TGF- β signaling pathway constitutes one of the central regulating systems in cardiac fibrogenesis [11,12]. The TGF- β superfamily includes more than 30 members including TGF- β types 1–3 and bone morphogenetic proteins (BMPs). This family of cytokines participates in development, differentiation, tissue repair, and tumorigenesis, but also modulates immune and endocrine functions. After ligand binding, intracellular signals are transmitted by 2 transmembrane serine/threonine kinase receptors, T β RI and II [13]. T β RI phosphorylates receptor-associated r-Smads (e.g. Smad-2), which in turn form heterodimers with co-

Smad-4. Subsequently, these complexes enter the nucleus to regulate transcription through transcriptional co-factors and co-modulators [14]. The resulting signal may be blocked by inhibitory i-Smads-7 [15] (Fig. 1).

Thus, the present study aims to quantify the degree of human atrial fibrosis associated with AF and to characterize fundamental changes in the TGF- β -system during different stages of AF-development.

2. Methods

2.1. Patients

Between June 2003 and March 2005 all patients scheduled for routine open heart surgery (OHS) at our medical center were screened for participation in this study. Of those screened, patients with relevant comorbidities such as malignancies, chronic inflammatory diseases, or acute infections were excluded. Informed consent in accordance with the local ethics committee (reference number EK2044) and the Declaration of Helsinki was obtained from $n=163$ patients. All patients were classified according to heart rhythm and duration of AF. 102 patients were in SR without history of AF (group 1). 17 patients had paroxysmal or chronic persistent AF (CPAF) for less than 6 months (group 2); 13 chronic permanent AF (CAF) for 7–24 months (group 3); 12 CAF for 25–60 months (group 4); and 19 CAF for >60 months (group 5). Please refer to Table 1 for detailed patient characteristics.

Patients' histories and previous electrocardiograms were used to establish type and duration of AF. Where in doubt family physicians were contacted for additional information. Paroxysmal (self-terminating but potentially recurrent) and chronic persistent (not spontaneously self-

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