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Rac1 and Connective Tissue Growth Factor: The Missing Link Between Atrial Remodeling and the Pathogenesis of Atrial Fibrillation?

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Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, and a major cause of morbidity and mortality (1). AF typically occurs following cardiac surgery or in patients with hypertension, ischemic, valvular, structural, or metabolic heart disease (2). In some cases, AF has no clear etiology, often refers to as lone or idiopathic AF. Nevertheless, most patients with AF have increased left atrial size (3) and AF patients with left atrial enlargement have poorer cardiovascular prognosis compared to those with normal left atrial dimensions (4). However, left atrium enlargement could also be a consequence of AF (5). Histological biopsy studies in patients with lone AF revealed increased atrial inflammation and fibrosis (6). Indeed, fibrosis and extracellular matrix remodeling are important components of left atrial enlargement (7, 8), and increased left atrial volume is a strong predictor of postoperative AF (9). These findings suggest that left atrial fibrosis could contribute to the pathogenesis of AF. However, the precise signaling pathways that mediate these changes in the left atrium are not known.

To obtain greater insights into the pathophysiological mechanism of AF, Adam *et al.*, performed transcriptional profiling analysis on tissues from the left atrial appendage of patients in sinus rhythm (SR) or chronic AF undergoing mitral valve surgery (REF). Despite similar left atrial dimensions, patients with AF were found to have increased expression of genes that are involved in interstitial fibrosis such as collagen and connective tissue growth factor (CTGF). This was associated with increased expression of adheren junction protein, N-cadherin, and gap junction protein, connexin 43, which are important mediators of electrophysiological properties of the left atrium. The expression of connexin 40, however, was unchanged, which is in contrast to other clinical studies showing that AF is associated with somatic mutation or increased expression of connexin 40 (10,11).

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Previous studies have shown that angiotensin II activates Rac1, leading to collagen synthesis, fibrosis, and atrial remodeling (12). Interestingly, angiogensin receptor blockers have been shown to prevent new-onset and recurrent AF (13,14). The small GTP-binding protein, Rac1, is a member of the Rho GTPase superfamily of intracellular signal transducers, which is involved in the regulation of NADPH-dependent oxidative stress (15). The activity of Rac1 and Rac1-mediated NADPH-derived superoxide anion production are increased in the atria of patients and animals with AF (16,17). Furthermore, Rac1 mediates the downstream localization of connexin 43 by N-cadherin (18). Thus, it is likely that the upregulation of Rac1 contributes to the pathogenesis of AF. To determine whether Rac1 mediates atrial remodeling through increased expression of CTGF, N-cadherin, and connexin 43, the authors generated transgenic mice with cardiac-specific overexpression of a constitutive active Rac1 mutant, i.e., RacET mice. They found that RacET mice exhibited increased expression of CTGF, N-adherin, connexin 43, and interstitial fibrosis whether or not the mice were in SR or AF, suggesting that increased Rac1 activity and not AF precedes atrial remodeling.

Because Rac1 requires post-translational modification by isoprenylation for proper intracellular trafficking and function, Rac1 could potentially be inhibited by HMG-CoA reductase inhibitors or statins, which block isoprenoid synthesis (19). Indeed, statins inhibit angiotensin II-induced increased myocardial oxidative stress and cardiac remodeling by inhibiting Rac1-mediated NADPH oxidase activity (20,21). Furthermore, statin therapy is associated with reduced incidence of AF in postoperative patients (22). Consistent with these findings, the authors found that treatment of RacET mice with rosuvastatin decreased the expression of CTGF, N-cadherin, and connexin 43, and reduced the incidence of AF. Thus, these results suggest that inhibition of angiotensin II-induced Rac1 activity with angiotensin receptor blockers, Rac1 inhibitors, or statins may have therapeutic benefits in the prevention of atrial remodeling and the subsequent development of AF.

Although the results of this study support the conclusion that Rac1 and CTGF are involved in the pathogenesis of AF, the causality between Rac1, CTGF, and AF in humans remains unclear. For example, animals treated with angiotensin II exhibit increased myocardial Rac1 activity and develop cardiac fibrosis but not AF (21). Also, most of the RacET mice do not develop AF, despite comparable increases in the expression of CTGF, N-cadherin, and connexin 43, and interstitial fibrosis as that of RacET mice that do develop AF. Furthermore, it is unlikely that there are any pathological conditions in humans where AF is associated with a 30-fold increase in Rac1 expression similar to what was observed in the RacET mice used in this study. Finally, thus far, genetic mapping studies of patients who are more or less susceptible to or at risk for AF have not localized any mutations to the *Rac1* locus, which is located on chromosome 7p22 (23,24). Thus, the general applicability of these findings to patients with AF of various etiologies is uncertain.

The beneficial effects of statins on atrial remodeling and AF are suggestive of Rac1, but because statins could also inhibit other isoprenoid-dependent pathways, such as the Ras and Rho/Rho kinase (ROCK) pathways, their inhibitory effects on atrial fibrosis and AF may not be due entirely to Rac1 inhibition. Indeed, deletion or inhibition of ROCK1 also leads to decreased angiotensin II-induced CTGF expression and cardiac fibrosis (25,26). Thus, the potential benefits of statin therapy in AF may extend beyond their inhibitory effects on Rac1. For these reasons, it would probably have been more definitive to use a genetic *loss-of-function* rather than a *gain-of-function* model of Rac1 in order to demonstrate that Rac1 is obligatory for the development of AF. Thus, further studies are required to determine whether increased Rac1 activity and CTGF expression are necessary and/or sufficient to produce AF under various pathological conditions that are associated with AF in humans. Nevertheless, these findings do provide some of the mechanistic basis for the clinical benefits of angiotensin receptor

blockers or statins in patients with AF. Whether or not specific Rac1 inhibitors will have similar therapeutic benefits in patients with AF remains to be determined.

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