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Commentary

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TGF-β1-induced endothelial-mesenchymal transition: a potential contributor to fibrotic remodeling in atrial fibrillation?

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Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide, with an unmet therapeutic need. Fibrotic remodeling, in which collagen-producing atrial fibroblasts play a crucial role, substantially contributes to arrhythmia promotion and progression. In this issue of the JCI, Lai, Tsai, and co-authors reveal that TGF-β1 promoted endothelial-mesenchymal transition during AF and put forward the notion that, in the adult heart, atrial fibroblasts can originate from different cellular sources. These important findings extend our understanding of the origin, biology, and function of fibroblasts and offer possibilities for therapeutic targeting of fibrosis in AF.

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The precise role of de novo EndMT for fibroblast generation and fibrosis formation is poorly understood. While some studies support de novo synthesis in adult hearts, others consider EndMT a source of resident cardiac fibroblasts exclusively during embryogenesis (15, 16). This incon-
sistency could result from the markers used to trace EndMT. Lai, Tsai, and co-authors (13) used common markers of endothelial cells (CD31), fibroblasts, and myofibroblasts (vimentin and α-smooth muscle actin [α-SMA]), along with markers of EndMT (the transcription factors Twist, Snail, and Slug) to demonstrate EndMT. Despite their common use, these markers can non-specifically label several cell types. Transgenic mouse models are being developed for more accurate lineage tracing, and in vivo cellular tracing in humans using flurodeoxyglucose-PET (FDG-PET) and PET-MRI is emerging (17). Although further validation is needed, the work presented by Lai, Tsai, and colleagues (13) supports the notion that de novo EndMT may occur in the atria, particularly upon TGF-β1 stimulation. Nevertheless, it is unclear how EndMT-derived fibroblast-like cells contribute to fibrogenesis. Do they belong to the collagen-secreting myofibroblast population, or do they exert paracrine effects that independently activate resident fibroblasts? Since EndMT was not revealed in previous studies that focused on ventricular fibrosis (11, 15, 16), it is possible that de novo EndMT is an atrium-specific phenomenon. Overexpression of TGF-β1 in mice causes fibrosis in atria only and increases AF susceptibility (18). Atrial fibroblasts are more responsive to TGF-β1 and angiotensin II than are ventricular fibroblasts (19). Thus, atrial-ventricular differences offer a unique opportunity to develop atrium-selective antifibrotic targets.

Besides emerging evidence for a role of EMT and EndMT reactivation in profibrotic remodeling, activation of resident fibroblasts under disease conditions and during AF is a common finding. Given the paracrine or autocrine effects of profibrotic molecules, cardiac fibroblasts can proliferate and differentiate into collagen-secreting myofibroblasts (Figure 1). Pro-collagen is synthesized in myofibroblasts and secreted as soluble pro-collagens into the extracellular space, where it is processed, assembled into fibrils, and cross-linked (Figure 1). Several cross-linking enzymes including lysyl oxidases are upregulated in the atria of patients with AF (20). Cross-linking of elastin is irreversible, whereas cross-linking of collagen appears to be reversible, constituting a viable antifibrotic target.

Whether changes in collagen composition play a causal role in AF pathophysiology warrants direct inquiry. The heart contains mainly type I (approximately 85%) and type III (approximately 15%) collagen. Collagen type I forms thicker and stiffer fibers, while collagen type III forms finer reticular fibers that are more compliant, increasing tissue elasticity (21). Changes in the type I to type III collagen ratio have been found to occur with cardiac dysfunction in human and experimental studies (22), and upregulation of nonfibrillar collagen type VI was reported in patients with AF (23). Although nonfibrillar collagens are not organized in larger fibrillar bundles, they can still interact with type I and type III collagens. TGF-β1 and angiotensin II increase the synthesis and secretion of fibrillar and nonfibrillar collagens, and collagen type IV promotes the differentiation of fibroblasts into myofibroblasts (23). Thus, additional collagen types may exist in the heart and could contribute to fibroblast dysfunction. Future work should directly address this hypothesis.

Therapeutic considerations

Therapeutic targeting of cardiac fibrosis is challenging. Besides possible targeting of de novo fibroblast synthesis, as elegantly shown in the work by Lai, Tsai, and colleagues (13), the unique electrical properties of fibroblasts open up several therapeutic possibilities. Experimental data point toward a central role of Ca2+ entry through store-operated Ca2+ channels (SOCs) and transient receptor potential (TRP) channels in the activation and proliferation of fibroblasts and their differentiation into myofibroblasts (24) (Figure 1). Thus, targeting fibroblast Ca2+ handling might be another therapeutic option. There is evidence for a direct electrotonic coupling between myofibroblasts and cardiomyocytes that causes cardiomyocyte depolarization, potentially promoting triggered activity (10, 25). Finally, cardiac myofibroblasts are able to differentiate into matriffibrocytes, a phenotype recently defined in mouse and human scar tissue that is characterized by a loss of proliferation ability, a decrease in α-SMA expression, and a reduced capacity to secrete collagen (25). Hence, future work should assess whether matriffibrocytes exist in atrial tissue and whether and how they influence the susceptibility to fibrinous remodeling and AF.

Lai, Tsai, and co-authors (13) add important insights into the complex origin and function of cardiac fibroblasts and offer possibilities for therapeutic targeting of fibrosis in AF.

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