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Targeting Endoglin, an Auxiliary TGF-β Coreceptor, to Prevent Fibrosis and Heart Failure

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Over the past 25 years, cardiovascular medicine has witnessed substantial progress in our understanding of the molecular pathogenesis, genetic etiologies as well as in the design of more efficacious therapeutic interventions. These advances have resulted in the dramatic reduction in the mortality of heart disease, especially in industrialized societies. Notwithstanding, both the prevalence and incidence of heart failure remain staggeringly high, posing new challenges and opportunities for prevention, diagnosis and management. Defined as the inability of the heart, as a mechanical pump, to meet the peripheral metabolic demands, this syndrome has many complex pathophysiological interactions among systolic performance, ventricular relaxation, impairments of contractility, and diastolic dysfunction. Both acquired (i.e., acute myocardial infarction) and genetic factors (mutations in genes encoding structural proteins) contribute to this clinical pathology but the development of overt heart failure ominously increases morbidity and decreases life-span.

Among the remarkable successes of the late twentieth century has been the wide-spread practice and profound impact that β-adrenergic receptor (AR) antagonists have had on reducing the mortality and morbidity of heart failure[1]. As reviewed recently by Michael Bristow[1], sobering lessons of this foregoing quintessential example of translational science, were the emerging basic studies on adrenergic receptor pharmacobiology, the importance of adrenergic drive in heart failure pathogenesis, initial human studies on shifts from β_1- to β_2–AR subpopulations in the failing heart[2], and both observational and randomized clinical trials to guide evidence-based practice. While *aficionados* used to the hype of the scientific news cycle are not easily persuaded, the ubiquitous claims of novel molecular targets for heart failure have not matched the disappointing and failure-prone pipeline in bringing new therapies to market. Without minimizing these efficacious drugs, there remain substantial unmet needs and opportunities, through intensive investments in basic and translational sciences, to improve the `standard of care' for heart failure treatment.

The failing heart is characterized by cellular and structural remodeling including cardiomyocyte hypertrophy and fibrotic deposition, which promote alterations in cardiac

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stiffness and function. Preventing deleterious aspects of this remodeling process has considerable appeal particularly for therapeutic purposes. A well-recognized mediator of tissue healing and fibrosis, transforming growth factor β1 (TGFβ1) is locally generated in most cell types, and several studies have shown beneficial value against pathological development of fibrosis. However, initial studies using blocking antibodies to neutralize TGFβ1 in various pathological states have proven to be either negative or inconclusive. For example, neutralizing anti-TGF-beta antibodies were shown by Sharma and coworkers to decrease diabetic renal alterations of renal hypertrophy and increases of the extracellular matrix in mice[3]. Frantz and coworkers demonstrated that pretreatment with intraperitoneal injection of TGFβ1 before myocardial infarction increased the mortality and post-ischemic left ventricular dysfunction[4]. Indeed, anti-TGFβ1 treatment profoundly reduced collagen synthesis and increased matrix-metalloproteinase expression in mice[4], indicating the pleiotropic effects of TGFβ1 might confound interventional strategies for heart failure.

In the current issue of the *Journal*, Kapur and coworkers use data collected from human samples and mouse models to build the case of a different approach to limit the pathological fibrosis linked causally to the TGFβ1 signaling pathway[5]. Endoglin, the TGFβ1 (but also 3) coreceptor is their target. The rationale for these studies were the associations between levels of endoglin, which are significantly increased in individuals with severe LV failure before implantation of the left ventricular assist device (LVAD) but are dramatically reversed to control levels in separate cohort after LVAD placement. Using human samples, Kapur et al confirmed that a critical source for endoglin was not the cardiomyocytes but the cardiac fibroblasts[5]. Endoglin expression is elevated in human failing hearts as well as in heart failure induced by pressure overload in mice.

The promising findings of this report warrant further investigations into the mechanisms governing expression of endoglin in cardiomyopathic states. The transmembrane glycoprotein (CD105), endoglin comprises a larger extracellular (561 amino acids) and shorter cytosolic domains, respectively[6]. It forms a heteromeric complex with tight binding affinity with either TGFβ1 or TGFβ3. In this capacity, endoglin, which is highly expressed in the vascular endothelium, endoglin modulates the effects of the TGFβ superfamily of proteins in vascular homeostasis, angiogenesis, remodeling and pathology[7]. As an auxiliary receptor of TGFβ1, endoglin modifies the synthesis of Type 1 collagen through regulatory pathways involving the downstream targets of TGFβ1 including pSmad-2/3 and plasminogen activator inhibitor 1 (PAI-1). Endoglin has dual roles for the activation and suppression of Smad1 and Smad3 through the TGFβ1 Type 1 receptors, ALK1 and ALK5, in cardiac fibroblasts, respectively. Mutations in human endoglin on chromosome 9q34ter result in autosomal dominant form of hereditary hemorrhagic telangiectasia type 1 (THH1, OMIM: #187300), a rare condition characterized by epistaxis and vascular malformations[8, 9]. Endoglin homozygote mutant mice are embryonic lethal while the heterozyogtes recapitulate THH1–While the first data presented established a correlative association between heart failure and endoglin, Kapur et al. decided to use those Eng+/− animals to further demonstrate a causal link.[10, 1114]

Before enshrining these encouraging data, several caveats pertaining to the genetic interactions underlying the co-expression of endoglin and TGFβ1 and disease pathogenesis should be addressed in future studies. The current paper shows that sEng modifies TGFβ1 signaling resulting in the suppression of Type 1 collagen synthesis in cultured fibroblasts and, correspondingly, in cardiac fibrosis induced after PO-induced systolic dysfunction in mice[5]. However, the authors do neither describe the status of the THH1 model nor consider the suspected impact of genetic modifiers that reduce the clinical manifestations in C57BL/6 mice compared with other strains[12]. Because variable onset and penetrance are likely under

similar genetic influences, levels of endoglin might have both diagnostic and therapeutic implications for personalized medicine.

The current work has translational importance and emerging clinical implications for the detection and management of heart disease. As previously reported, endoglin is an attractive biomarker of heart failure[13]. In a small cohort of 183 patients with acute myocardial infarction (AMI), lower levels of endoglin measured by ELISA in AMI correlated with increased mortality compared with controls. Cardiac fibrosis is most commonly encountered accompanying acute myocardial infarction in which reparative processes promote collagen deposition and extracellular matrix remodeling to limit pump failure and myocardial dysfunction. Given the compelling evidence that sEng expression mediates a negative feedback mechanism to attenuate fibrosis, it is conceivable that sEng administration to block post-MI fibrosis would be inappropriate owing to the delicate balance to achieve reparative fibrosis while avoiding post-infarction rupture, aneurysmal formation or both. Besides diabetics, the levels of endoglin expression have been studied in hypertensive populations as well[14]. The fortuitous effects of sEng to block cardiac fibrosis in pressure overload heart failure might suggest opportunities to modify adverse remodeling of hypertensive heart disease. Of interest, downregulation of Eng that mimics THH1 also causes pulmonary hypertension in genetically modified mice[11, 15], suggesting its therapeutic application would be limited to acute intervals.

It is tempting to speculate that the potential antifibrotic properties of endoglin might stimulate investigations in related fields associated with fibrosis-prone tissue beds, besides the left ventricle, such as the atria. Chronic atrial fibrillation triggers structural, ionic and electrical remodeling in which cardiac fibrosis predominates. High catecholamine states associated with chronic atrial fibrillation might trigger heart failure associated with significant morbidity and mortality. In symptomatic patients, attempts in selected patients to control symptoms with rhythm-control using anti-arrhythmic drugs are invariably futile warranting referral for radiofrequency (RF) ablation therapy. However, recent studies by Marrouche and coworkers have drawn attention to the inverse relationship between success rates of RF ablation therapy and the scar burden in the left atria and associated pulmonary veins, the substrate for AF[16]. It is conceivable that successful development of antifibrotic agents could be added to the armamentarium of therapeutic agents to reverse left atrial fibrosis remodeling.

When pump failure ensues in selected patients mechanical support with the aid of left ventricular assist disease (LVAD) is employed either as destination therapy or a bridge to transplantation. Higher levels of endoglin and TGFβ1 are reported in individuals who are candidates for cardiac transplantation with end-stage heart failure. The mechanisms by which mechanical support with LVAD for end-stage reverses endoglin to normal values remain poorly understood. Four-fold elevation of Eng expression reported by Kapur et al in the myocardium of pre-LVAD placement, which is entirely reversible post-LVAD, raises the intriguing possibility that impairment of endoglin processing and function accompanies the LV dysfunction. The present work builds on previous studies, which have shown endoglin regulates angiotensin-mediated fibrosis via the AT-1 receptor[17] as well as in noncardiac sites including the intestine[18].

To join the vaulted list of success stories, further preclinical studies of endoglin will be needed. Kapur and colleagues are to be commended for their use of complementary experiments in human and mouse tissues[5], which buttress their hope this work will translate beyond the `valley of death.' Clinical benefits of β-adrenergic receptor (AR) antagonists, angiotensin-converting enzyme or receptor blockers and, perhaps, aldosterone antagonists are widely believed to modify the profibrotic responses. Likewise, β-adrenergic antagonists

by mitigating excess catecholamines might decrease arrhythmogenesis caused by fibrosis during the development and progression of heart failure. Future studies will determine whether s-endoglin will improve outcomes compared with current regimens, an encouraging milestone that might predict higher success rates in phase III clinical trials.

In summary, both expression and signaling of endoglin, which involve complex interactions with the superfamily of TGFβ receptors, has undoubtedly been linked to profibrotic pathways during disease pathogenesis. The compelling findings of decreased cardiac fibrosis induced by the downregulation of endoglin opens the window to exploit therapeutic potential for heart failure and, perhaps, other fibrosis-prone clinical states In the regard, we should cautiously interpret the present data while increasing our focus to improve the sensitivity and specificity of our interventions in terms preclinical testing and selective targeting, in defined subpopulations, of individuals with heart and related vascular diseases.

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