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EDITORIAL COMMENT

It's a SMAD, SMAD World

Cell Type–Specific SMAD Signaling in the Heart*

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In the report by Umbarkar et al. (1) in this issue of *JACC: Basic to Translational Science,* the outcome of targeted reductions in SMAD4, a downstream mediator in the transforming growth factor (TGF)-β signaling pathway, in cardiac myocytes is evaluated. As SMAD4 global deletion results in embryonic lethality (2), the authors set out to address the functional significance of SMAD4 expression in myocytes in the adult heart using an inducible transgenic approach. The resulting cardiac phenotype is characterized by significant differences in cardiac contractile function as measured both in individual cells and in whole hearts. Deletion of SMAD4 in cardiac myocytes leads to alterations in expression of cardiac myosin binding protein-C and in mRNA encoding a number of ion channels. Changes in protein expression are reflected in a slower heart beat in SMAD4 mutant mice versus wild-type counterparts. The authors conclude that SMAD4 functions in adult cardiac myocytes to maintain homeostatic activity and myocyte viability and performance.

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As Umbarkar et al. (1) point out, TGF-β is a well-characterized mediator of fibrotic collagen deposition in the heart. For example, inhibition of TGF-β signaling through administration of an anti-TGF-β antibody following induction of pressure overload, a murine model of cardiac fibrosis, is shown to reduce myocardial collagen content (3). Recently, targeted disruption of SMAD3, another downstream factor in the TGF-β signaling pathway, in activated fibroblasts is shown to reduce fibrotic deposition of collagen in response to pressure overload (4). In addition, signaling via TGF-β receptor II is demonstrated to be central to collagen accumulation resulting from cardiac myosin binding protein-C-induced cardiomyopathy, another model of cardiac fibrosis (5). Accordingly, TGF-β is an attractive target for therapies to treat fibrosis and has merited well-deserved attention in this regard. However, the pluripotent nature of TGF-β signaling, which is highly cell-type dependent, has led many to caution against global inhibition of TGF-β as a viable path to treat fibrosis. Umbarkar et al. (1) offer their recent findings as further proof that nontargeted inhibition of TGF-β activity is predicted to have adverse effects on other cell types in the heart, including cardiac myocytes.

Interestingly, in contrast to SMAD4, targeted deletion of SMAD3 in cardiac myocytes does not result in phenotypic alterations in cardiac function in the homeostatic adult heart (6). Whereas SMAD3 is implicated in the canonical TGF-β signaling pathway, SMAD4 is also known to act in bone morphogenic protein (BMP) signaling. TGF-β is member of the BMP super family, which contains at least 20 different members. Accordingly, BMP signaling in myocytes is predicted to also be influenced by diminished SMAD4 activity. Whereas relatively less is known concerning the role(s) of BMP signaling in the healthy adult heart, this area merits further investigation. The significant difference in cardiac myocyte physiology brought about by cell-specific SMAD4 deletion, not seen in the SMAD3-deleted myocyte-specific mice, suggests that signaling pathways associated with other BMP family members, in addition to TGF-β, might be significant

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for maintaining healthy cardiac myocyte activity in adult heart.

Two genetic pathologies associated with mutations in SMAD4 protein are Myhre's syndrome and juvenile polyposis—hereditary hemorrhagic telangiectasia (JP-HHT). Gain of function in SMAD4 gives rise to Myhre's syndrome characterized by short stature, dysmorphic facial features, and hearing loss among other pathologies (7). Recently, cardiovascular disruptions including pericardial disease and restrictive cardiomyopathy have been described in patients with Myhre's syndrome. To date, specific differences in myocyte function have not been reported in this syndrome; however, given the results presented by Umbarkar et al. (1), one might predict SMAD4-dependent phenotypic abnormalities in this cell type as well. Global loss of function of SMAD4 in people results in JP-HHT, characterized by arteriovenous malformations and early-onset colorectal cancer (8). Whether cardiac myocytes are affected in people with JP-HHT also remains to be determined, but might also provide interesting insight into the role of SMAD4 in cardiac myocytes.

TGF-β signaling is well accepted as a central determinant of cardiac fibroblast activity, particularly in regard to fibroblast activation and extracellular matrix (ECM) deposition and accumulation in fibrosis. However, receptors for TGF-β are expressed in multiple cell types in the heart, including smooth muscle cells, myocytes, endothelial cells, and inflammatory cells. As each cell type activates a distinct functional outcome in response to TGF-β stimulation, global inhibition of TGF-β is predicted to have consequences beyond fibroblast activation and ECM accumulation, as Umbarkar et al. (1) point out. In the heart, the concept that the regulation of TGF-β signaling, even if directed solely to activated fibroblasts to control collagen production, might also be problematic. As with many tissues, having optimal levels of cardiac collagen is critical for function. Illustrated by fibroblast deletion of SMAD3, loss of SMAD3 in activated fibroblasts gives rise to increased rupture and accentuates adverse remodeling following infarction, whereas, in response to pressure overload, less pathological fibrosis is observed with deletion of SMAD3 in activated fibroblasts (4,6). Simplistically, overdeposition of collagen can lead to increases in stiffness associated with diastolic dysfunction, whereas decreases in collagen content can lead to cardiac rupture after infarction (9). However, a growing appreciation that alterations in collagen assembly and cross-linking, fiber alignment, and ECM composition each influence progression of cardiac remodeling in disease is emerging. Each of these processes is likely to be influenced by TGF-β signaling in fibroblasts and in inflammatory cells. Likewise, insight into the role of TGF-β in controlling myocyte activity also deserves further analysis, as these pathways might also be exploited to improve cardiac function in disease. Fine-tuning distinct pathways and outcomes in cardiac cell types to TGF-β (and other TGF-β family members) is necessary to design innovative approaches for treating cardiac dysfunction in adult heart failure.

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REFERENCES

1. Umbarkar P, Singh AP, Gupte M, et al. Cardiomyocyte SMAD4-dependent TGF-β signaling is essential to maintain adult heart homeostasis. J Am Coll Cardiol Basic Trans Sci 2019;4:41–53.

2. Nie X, Deng CX, Wang Q, Jiao K. Disruption of Smad4 in neural crest cells leads to mid-gestation death with pharyngeal arch, craniofacial and cardiac defects. Dev Biol 2008;316:417–30.

3. Kuwahara F, Kai H, Tokuda K, et al. Transforming growth factor-beta function blocking prevents myocardial fibrosis and diastolic dysfunction in pressure-overloaded rats. Circulation 2002;106:130–5.

4. Khalil H, Kanisicak O, Prasad V, et al. Fibroblast-specific TGF-beta-Smad2/3 signaling underlies cardiac fibrosis. J Clin Invest 2017;127:3770–83.

5. Meng Q, Bhandary B, Bhuiyan MS, et al. Myofibroblast-specific TGFbeta receptor II signaling in the fibrotic response to cardiac myosin binding protein C-induced cardiomyopathy. Circ Res 2018;123:1285–97.

6. Kong P, Shinde AV, Su Y, et al. Opposing actions of fibroblast and cardiomyocyte Smad3 signaling in the infarcted myocardium. Circulation 2018;137:707–24.

7. Lin AE, Michot C, Cormier-Daire V, et al. Gain-of-function mutations in SMAD4 cause a distinctive repertoire of cardiovascular phenotypes in patients with Myhre syndrome. Am J Med Genet A 2016;170:2617–31.

8. Gallione C, Aylsworth AS, Beis J, et al. Overlapping spectra of SMAD4 mutations in juvenile polyposis (JP) and JP-HHT syndrome. Am J Med Genet A 2010;152a:333–9.

9. Frangogiannis NG. Cardiac fibrosis: cell biological mechanisms, molecular pathways and therapeutic opportunities. Mol Aspects Med 2018 Aug 2 [E-pub ahead of print].

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