Matrix Biology Highlights
Edited by Tom Neill and Jason Zoeller

1). Tuggin' on the heartstrings: aberrant fibrillin 1 mechanosignaling triggers cardiomyopathies in Marfan Syndrome

Reference | Cook, J.R., Carta, L., Benard, L., Chemaly, E.R., Chiu, E., Rao, S.K., Hampton, T.G., Yurchenco, P., GenTAC Registry Consortium, Costa, K.D., Hajjar, R.J., Ramirez, F., 2014. Abnormal muscle mechanosignaling triggers cardiomyopathy in mice with Marfan Syndrome. *J. Clin. Invest.* 124:1329-1339. http://www.ncbi.nlm.nih.gov/pubmed/24867163

In a recently published article in the *Journal of Clinical Investigation,* J.R. Cook and colleagues revealed that severe Marfan syndrome (MFS) cases with related dilated cardiomyopathy (DCM) occurs primarily as a result of aberrant mechanosignaling orchestrated by the cardiomyocytes. Genetic lesions throughout *FBN1* (fibrillin 1) manifest as MFS where patients are especially susceptible to stress-induced cardiac dysfunction. Utilizing several genetic models, the authors discovered that reduced fibrillin 1 synthesis by cardiomyocytes spontaneously triggers DCM. Moreover, the authors mechanistically and causally linked an ECM constituent whose absence subsequently results in a structurally deficient cardiac matrix environment subject to increased mechanical stress. Myocardial ECM devoid of fibrillin 1 is mechanically impaired as denoted by a reduced elastic modulus and passive mechanical tension. The compromised myocardial architecture abnormally activated ERK1/2, via the AT1R/β-arrestin 2 mechanosensing pathway, and attenuated FAK function, independent of AngII (Fig. 1). Administration of an AT1R antagonist or mice lacking AT1R or β-arrestin ameliorated the DCM phenotype and restored physiologically relevant cardiac parameters. Mice under-expressing cardiac *FBN1* was sufficient in recapitulating the DCM pathology. These findings place emphasis on the critical role fibrillin 1-microfibrils play in relaying physical extracellular derived signals for appropriate intracellular responses while uncovering the fundamental and primary origin of DCM in MFS.

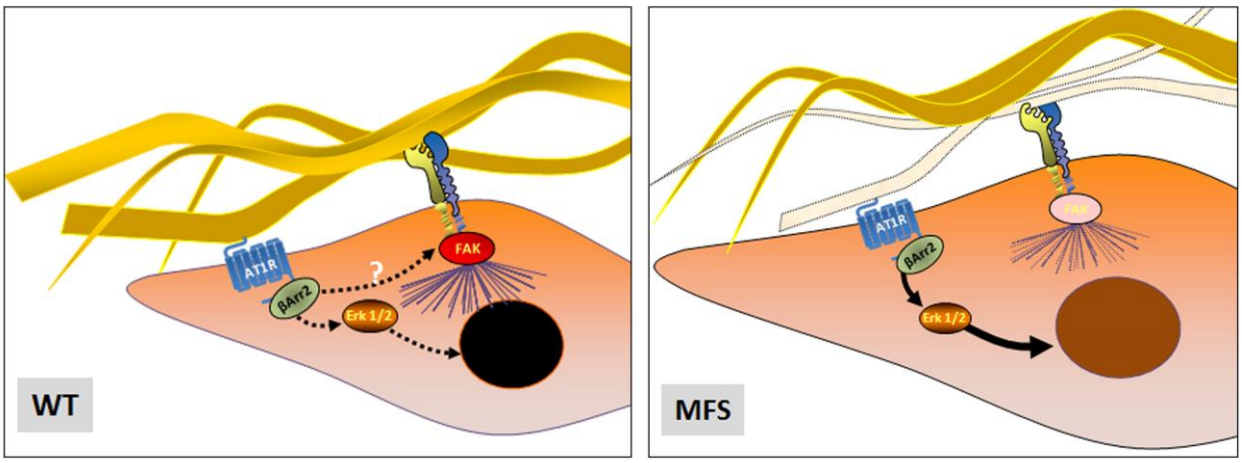

Fig. 1. Schematic representation of ECM interactions with cardiomyocytes mediated by AT1 and β1-integrin receptors in the tissue of healthy and MFS mice. The dotted line with the question mark above signifies the postulated hierarchical interaction between AT1R and integrins in their response to mechanical stress. We thank Cook, J.R. for kindly providing the above figure.

2). Taking down the DECORINations: FOXD1 represses decorin for nephron progenitor differentiation

Reference | Fetting, J.L., Guay, J.A., Karolak, M.J., Iozzo, R.V., Adams, D.C., Maridas, D.E., Brown, A.C., Oxburgh, L., 2014. FOXD1 promotes nephron progenitor differentiation by repressing decorin in the embryonic kidney. *Development* 141, 17-27. http://www.ncbi.nlm.nih.gov/pubmed/24284212.

As published by Fetting *et al* in *Development,* a novel role for Foxd1, a forkhead transcription factor that controls various developmental programs, in suppressing decorin for proper differentiation of nephron progenitors. Transcriptome profiling of Foxd1-regulated targets in embryonic kidneys identified several candidate genes expressed within the cortical interstitium. It was determined that *Dcn* harbors multiple Foxd1 binding sites and ChIP analysis revealed a physical interaction of Foxd1 with the *Dcn* locus. Further, *Dcn* expression significantly increased upon *Foxd1* ablation; in contrast, Foxd1 over-expression suppressed *Dcn* transcription. Therefore, these data established *Dcn* as a novel and *bona fide* Foxd1 target in the developing kidney. Decorin chiefly localizes to the medullary interstitium in the wildtype (WT) kidney with a small CITED1+ population in the cortex (Fig. 2A); however, in the context of Foxd1 loss, aberrant decorin synthesis promotes widespread localization and an expanded CITED1+ population (Fig. 2B). Functionally, abnormal *Dcn* expression inhibits BMP signaling within the cap mesenchyme cells and functionally blocks the adjacent nephron progenitor cells from transitioning to a state conducive for epithelial induction. This immediately suggests that decorin maintains the progenitor cells as undifferentiated (CITED1+) entities by attenuating the SMAD1/5/8-BMP7 pathway and prevents epithielization of critical structures (Fig 2C,D). Importantly, genetically inactivating *Dcn* in the *Foxd1* null background partially rescues the progenitor cell population as denoted by diminished CITED1+ progenitors in nephrogenic structures and a corresponding increase in differentiated nephron components and patterning.

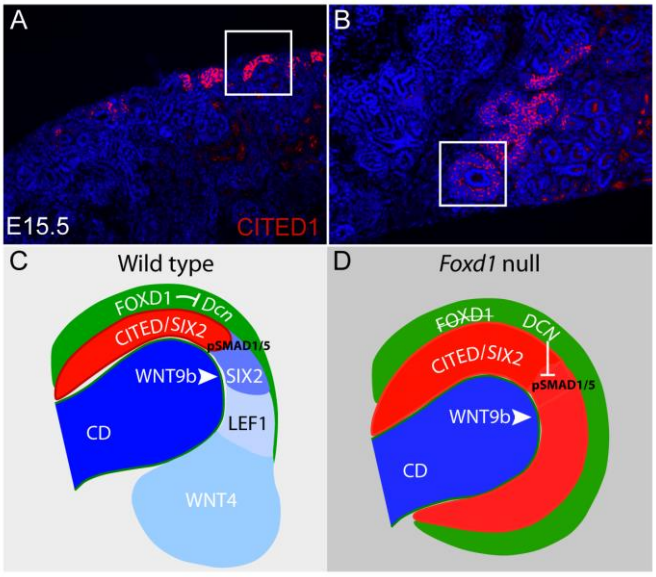

Fig. 2. (A) Small CITED1+ (red) cap mesenchymes localize to the cortex of E15.5 WT kidneys. (B) *Foxd1*$^{-/-}$ kidneys contain mislocalized, expanded regions of CITED1+ cap mesenchyme. (C) In the WT kidney, Foxd1 represses expression of Dcn in cortical interstitial cells, allowing the CITED1+ SIX2+ nephron progenitors to respond to BMP7 signaling via the SMAD1/5 pathway and transition into the SIX2 only compartment. Here, the cells become competent to respond to the WNT9b inductive signal and differentiate into LEF1+ WNT4+ renal vesicles. (D) In the Foxd1-/- kidney, Dcn is ectopically expressed in cortical interstitial cells and completely surrounds the nephron progenitor cells. Dcn inhibits BMP7 signaling in the CITED1+ SIX2+ compartment, preventing SMAD1/5/8 phosphorylation and transition into the SIX2 only compartment, preventing differentiation. We thank Fetting, J.L. for kindly providing the figure.