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Diastolic blood pressure and cardiovascular outcomes had a J-curve relationship that was explained, at least in part, by age and other covariates. Furthermore, systolic hypertension had a greater effect on cardiovascular outcomes among participants with the lowest diastolic blood-pressure levels.

Similar results were observed with the lower threshold of hypertension ($\geq 130/80$ mmHg) — a finding that according to the investigators supports the guideline changes tightening blood-pressure targets for patients at high-risk of CVD — and in models in which systolic and diastolic blood pressure were used without hypertension thresholds.

Irene Fernández-Ruiz

ORIGINAL ARTICLE Flint, A. C. et al. Effect of systolic and diastolic blood pressure on cardiovascular outcomes. *N. Engl. J. Med.* **381**, 243–251 (2019)

“this relationship is not altered by the threshold used for the definition of hypertension”

components, such as NLRP3, caspase 1 and IL-1 β .

Expression of Krüppel-like factor 2 (KLF2) is reduced by oscillatory shear stress, as occurs at atheroprone regions, and this decrease in KLF2 level directly reduces the expression of FOXP1. Of note, simvastatin induces the expression of KLF2–FOXP1 in atheroprone endothelium and thereby inhibits endothelial inflammasome activation and alleviates vascular inflammation, revealing a novel atheroprotective mechanism for this drug.

“We will evaluate the effects of target inhibition of NLRP3 inflammasome components specifically in the vascular endothelium on the prevention of atherosclerosis progression,” say the researchers. “Our future studies will [also] evaluate the effects of simvastatin on improvement of endothelial dysfunction and alleviation of vascular inflammation.”

Gregory B. Lim

ORIGINAL ARTICLE Zhuang, T. et al. Endothelial Foxp1 suppresses atherosclerosis via modulation of Nlrp3 inflammasome activation. *Circ. Res.* <https://doi.org/10.1161/CIRCRESAHA.118.314402> (2019)

“Simvastatin can upregulate FOXP1 expression, thus revealing a novel anti-atherogenic effect of this drug”

CARDIOMYOPATHIES

PDGF pathway in LMNA-related dilated cardiomyopathy

Activation of the platelet-derived growth factor (PDGF) pathway is involved in the pathogenesis of dilated cardiomyopathy (DCM) caused by mutations in *LMNA*. This new finding suggests that inhibition of PDGF receptor- β (PDGFR β) is a novel therapeutic target for patients with *LMNA*-related DCM.

Many mutations that cause DCM are in genes that encode sarcomeric proteins; however, 5–10% of DCM-causing mutations occur in *LMNA*, which encodes lamin A/C, major structural proteins of the nuclear envelope. The mechanisms by which these mutations cause DCM are uncertain, leading Joseph Wu and colleagues to model this aetiology of DCM in induced pluripotent stem cells (iPSCs), with the aim also to identify potential therapeutic targets.

Wu and colleagues recruited a large family cohort, members of which had a frameshift mutation in *LMNA* that led to early termination of translation. The researchers generated multiple patient-specific iPSC lines and derived cardiomyocytes (iPSC-CMs) to study electrophysiological properties at the single-cell level. *LMNA*-mutant iPSC-CMs had proarrhythmic activity, abnormal Ca²⁺ transients and increased phosphorylation of ryanodine receptor 2 mediated by Ca²⁺/calmodulin-dependent protein kinase type II.

Moreover, the *LMNA*-mutant iPSC-CMs had abnormal nuclear structures, with reduced expression of lamin A/C. The researchers established that nonsense-mediated mRNA decay led to degradation of the mutant *LMNA* mRNA, inducing lamin A/C haploinsufficiency. Lamin A/C interacts with heterochromatin-rich genomic regions at the nuclear envelope called lamin-associated domains (LADs). Lamin A/C haploinsufficiency caused local changes at LADs, leading to transcriptional activation.

Among the genes that were upregulated in the *LMNA*-mutant iPSC-CMs were those associated with the PDGF signalling pathway. In particular, *PDGFRB* mRNA and protein levels were significantly increased. Consistent with these findings, reduced expression of *LMNA* and increased expression of *PDGFRB* were found in heart tissue samples from patients with *LMNA*-related DCM.

Knockdown of *PDGFRB* expression with small interfering RNA or inhibition of PDGFR β using two specific inhibitors (crenolanib and sunitinib) ameliorated the arrhythmogenic phenotype of *LMNA*-mutant iPSC-CMs. “Our study suggests that several FDA-approved PDGFR β inhibitors ... may be repurposed [for the treatment of DCM],” say the researchers. However, these tyrosine kinase inhibitors might be associated with dose-dependent cardiotoxicity. “We hope that further studies will identify proper concentrations of small molecules that can be safely used in vivo to optimally alter the activity of PDGFR β ,” continue the researchers. “We could also target the upstream PDGF signalling pathway, such as transcription factors of *PDGFRB*.”

Gregory B. Lim

ORIGINAL ARTICLE Lee, J. et al. Activation of PDGF pathway links *LMNA* mutation to dilated cardiomyopathy. *Nature* <https://doi.org/10.1038/s41586-019-1406-x> (2019)