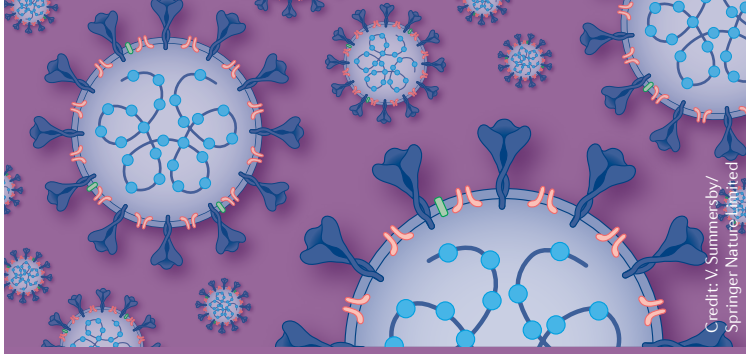


COVID-19

# ACEi reduces hypertension-induced hyperinflammation in COVID-19

Hypertension is associated with a pro-inflammatory state that worsens the prognosis of patients with coronavirus disease 2019 (COVID-19). According to a new study, antihypertensive blockade of the renin–angiotensin–aldosterone system (RAAS), particularly with the use of an angiotensin-converting enzyme inhibitor (ACEi), might improve outcomes in patients with hypertension and COVID-19.

Irina Lehmann, Ulf Landmesser, Roland Eils and colleagues combined clinical data from 144 patients with COVID-19, single-cell sequencing data from 48 airway tissue samples and data from in vitro experiments. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds to ACE2 to gain entry into cells. Uncertainty had been raised whether RAAS blockade upregulates the expression of *ACE2*, causing ACEi-treated or angiotensin-receptor blocker (ARB)-treated patients to be more susceptible to SARS-CoV-2 infection. However, the researchers found no evidence that treatment with either an ACEi or an ARB increased the expression of *ACE2* in patients with or without SARS-CoV-2 infection. "This result is in line with findings from observational studies that patients receiving antihypertensive treatment with an ACEi or ARB are not more susceptible to SARS-CoV-2 infection," comments Lehmann. Moreover, the induction of *ACE2* expression that occurs after SARS-CoV-2 infection was unaltered by either ACEi or ARB therapy.

The investigators identified a hypertension-associated increase in immunological activity as being the prominent factor contributing to the worse prognosis of patients with high blood pressure and COVID-19. In response to SARS-CoV-2 infection, patients treated with an ARB had an exaggerated hyperinflammatory response, which was alleviated in patients treated with an ACEi, thereby reducing the risk of severe outcomes of COVID-19.

Whereas SARS-CoV-2 clearance in patients with hypertension who were treated with an ACEi was similar to that in patients without hypertension, viral clearance was delayed in patients with hypertension who were treated with an ARB. In particular, cell-intrinsic antiviral signalling via interferon regulatory factor 3 was weaker in patients with SARS-CoV-2 infection who were treated with an ARB than in those treated with an ACEi.

"Our data are in line with the general guideline recommendations discouraging discontinuation of ACEi or ARB treatment," conclude the researchers. "In fact, our results might suggest that ACEi could be the more beneficial antihypertensive treatment during COVID-19." Several randomized, controlled trials are ongoing to compare the use of an ACEi versus an ARB in patients with hypertension and COVID-19.

*Gregory B. Lim*

**ORIGINAL ARTICLE** Trump, S. et al. Hypertension delays viral clearance and exacerbates airway hyperinflammation in patients with COVID-19. *Nat. Biotechnol.* https://doi.org/10.1038/s41587-020-00796-1 (2020)

**RELATED ARTICLE** Gu, S. X. et al. Thrombocytopathy and endotheliopathy: crucial contributors to COVID-19 thromboinflammation. *Nat. Rev. Cardiol.* https://doi.org/10.1038/s41569-020-00469-1 (2020)

# IN BRIEF

## ADIPOSE TISSUE

### Brown fat promotes cardiometabolic health

Thermogenic brown adipose tissue (BAT) is associated with a lower prevalence of cardiometabolic disease in humans, particularly in individuals who are overweight or obese, according to a retrospective cohort study. Cold-activated BAT is associated with increased energy expenditure and improved disposal of glucose and free fatty acids. Researchers analysed 134,529 PET–CT scans from 52,487 patients that were performed for indications relating to cancer diagnosis, treatment or surveillance. The individuals were categorized according to the presence or absence of BAT. The presence of BAT independently correlated with a lower likelihood of type 2 diabetes mellitus, dyslipidaemia, coronary artery disease, heart failure and hypertension. Of note, a lower prevalence of cardiometabolic disease was observed in individuals with obesity and BAT than in individuals with obesity without BAT. Given the global obesity crisis, potentially targeting BAT to promote cardiometabolic health is intriguing.

**ORIGINAL ARTICLE** Becher, T. et al. Brown adipose tissue is associated with cardiometabolic health. *Nat. Med.* https://doi.org/10.1038/s41591-020-1126-7 (2021)

## CARDIAC REGENERATION

### Transcriptional atlas of mouse heart regeneration

Using single-cell RNA and ATAC sequencing of neonatal mouse hearts, which can regenerate for a short time after birth, researchers have produced an atlas of the transcriptional basis for cardiac regeneration. To investigate the multifaceted contributions of resident cardiac cell types as well as infiltrative immune cells, investigators subjected neonatal mouse hearts to myocardial infarction. At subsequent time points, they performed single-cell and bulk-tissue RNA sequencing as well as single-cell ATAC sequencing to reveal the dynamics of the gene-regulatory networks and open chromatin landscapes underlying cardiomyocyte proliferation, angiogenesis and fibroblast activation. The data provide insights into the cellular heterogeneity and crosstalk involved in cardiac regeneration.

**ORIGINAL ARTICLE** Wang, Z. et al. Cell-type-specific gene regulatory networks underlying murine neonatal heart regeneration at single-cell resolution. *Cell Rep.* **33**, 108472 (2020)

## ATHEROSCLEROSIS

### SIRT6 slows VSMC senescence and atherogenesis

NAD-dependent protein deacetylase sirtuin 6 (SIRT6) protects vascular smooth muscle cells (VSMCs) against senescence and thereby inhibits the development of atherosclerosis. In mouse and human VSMCs from atherosclerotic plaques, levels of SIRT6 protein expression were markedly reduced compared with healthy aortic VSMCs. SIRT6 is involved in telomere maintenance. Inhibition of SIRT6 shortened human VSMC lifespan and induced senescence, with markers of telomere damage. By contrast, SIRT6 overexpression preserved telomere integrity, delayed senescence and promoted proliferation. Atheroprone *Apoe*$^{-/-}$ mice with VSMC-specific SIRT6 overexpression had reduced atherosclerosis and markers of senescence compared with littermate controls. However, *Apoe*$^{-/-}$ mice overexpressing an inactive form of SIRT6 in VSMCs had more unstable atherosclerotic plaques. "Our data show that endogenous SIRT6 deacetylase is an important and unrecognized inhibitor of VSMC senescence and atherosclerosis," summarize the researchers.

**ORIGINAL ARTICLE** Grootaert, M. et al. SIRT6 protects smooth muscle cells from senescence and reduces atherosclerosis. *Circ. Res.* https://doi.org/10.1161/CIRCRESAHA.120.318353 (2020)