Single change in genetic code promotes development of inflammation, high blood pressure and resulting kidney damage

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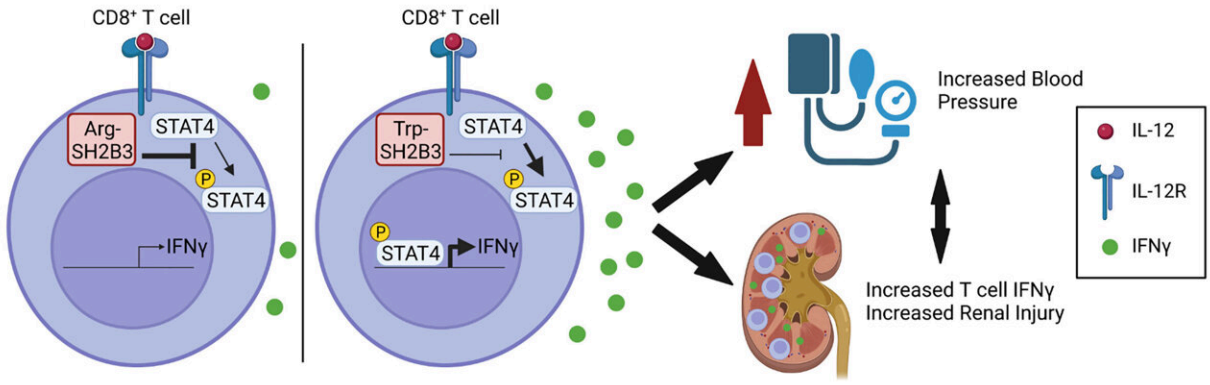

Credit: *Circulation Research* (2022). DOI: 10.1161/CIRCRESAHA.121.320625

Researchers at Vanderbilt University Medical Center have found that the change in a single letter of the genetic code promotes, in a mouse model, the development of inflammation, high blood pressure and resulting kidney damage.

Their findings, featured Oct. 14 on the cover of *Circulation Research*, suggest that targeting inflammatory cytokines, signaling proteins produced by immune cells, could have "a significant public health impact," particularly in people who carry this common genetic change.

"These findings have important implications for precision medicine based on a person's genetic code," said the paper's senior author, Meena Madhur, MD, Ph.D., associate professor of Medicine and of Molecular Physiology and Biophysics.

Hypertension is a complex disease, for which therapeutic options are limited. Current therapy fails to control high blood pressure in nearly half of patients.

Evidence from Madhur's group and others indicates that hypertension is an inflammatory process. A primary suspect is the SH2B3/LNK gene, which encodes a sequence of amino acids—a protein—that normally turns down inflammatory cytokine signaling.

In 46% to 50% of people of European ancestry, however, a single nucleotide polymorphism (SNP), or variation in one of the nucleotide "letters" in the gene's DNA sequence, exchanges the amino acid arginine at position 262 in the encoded protein for the amino acid tryptophan.

To determine whether the amino-acid swap contributes to hypertension, Madhur, Matthew Alexander, MD, Ph.D., and their colleagues used a gene-editing technique called CRISPR-Cas9 to modify the SH2B3/LNK gene in mice. Alexander, assistant professor of Medicine, is the paper's first and co-corresponding author.

The researchers found that mice which carried two copies of the amino acid tryptophan at the orthologous position 262 of the protein had higher blood pressure and greater kidney damage, compared to mice which carried two copies of arginine at the same position.

Replacing the amino acid arginine with tryptophan also increased signaling by an inflammatory cytokine, interleukin-12, and increased production of interferon-gamma, another cytokine. Interferon-gamma is

thought to recruit cytokine-secreting white blood cells called macrophages to the kidney, where they cause damage and scarring.

If further study confirms these findings, they raise "the potential for a precision medicine approach targeting inflammatory cytokines such as interferon-gamma to lower blood pressure and reduce (kidney) damage," particularly in individuals carrying the SNP, the researchers concluded.

More information: Matthew R. Alexander et al, A Single Nucleotide Polymorphism in SH2B3/LNK Promotes Hypertension Development and Renal Damage, *Circulation Research* (2022). DOI: 10.1161/CIRCRESAHA.121.320625

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