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HEART FAILURE

BRD4 inhibition slows HF progression

Inhibition of the epigenetic regulator bromodomain-containing protein 4 (BRD4) using the small molecule JQ1 attenuates the progression of heart failure (HF) in mice, according to a new study published in *Science Translational Medicine*. "A dominant mechanism of action of JQ1 is that it is suppressing innate inflammatory and pro-fibrotic pathways in the heart," says Saptarsi Haldar, a physician-scientist at Gladstone Institutes and University of California, San Francisco, and corresponding author on the paper.

BRD4 belongs to the bromodomain and extraterminal (BET) proteins, which act as 'readers' of acetylated lysines on chromatin to regulate gene transcription. Inhibition of this protein is currently being explored for the treatment of several types of cancer. "We recognized that there may be some shared features of cancer pathogenesis and HF pathobiology — namely the 'dependence' on transcriptional signalling to sustain a pathological state," explains Haldar.

> "… treatment with JQ1 alleviated features of [heart failure] in a mouse model of myocardial infarction"

The researchers showed that in mice subjected to transverse aortic constriction (TAC), treatment with JQ1 attenuated the progression of HF symptoms when compared with vehicle-treated mice, even when robust disease was already present. Consistent with this finding, treatment with JQ1 alleviated features of HF in a mouse model of myocardial infarction (MI). RNA sequencing analyses revealed that genes involved in HF-specific pathological processes such as extracellular matrix deposition, inflammatory and immune responses, and cell growth were specifically suppressed by JQ1 treatment in both TAC and MI mouse models.

To investigate the inhibition of BRD4 in human cells, Haldar and colleagues tested the effect of JQ1 in human induced pluripotent stem cell-derived cardiomyocytes (IPSC-CMs). Treatment of IPSC-CMs with JQ1 blocked cell hypertrophy induced by endothelin 1. Furthermore, RNAseq analysis showed that transcriptional signatures affected by JQ1 in IPSC-CMs were similar to those affected by the drug in the two mouse models.

These findings indicate that inhibition of BRD4 with a small molecule alleviates HF through the modulation of specific transcriptional programmes. "Our next step is to test BET inhibitor drugs in other preclinical models; [these] studies could lay the groundwork for human trials," remarks Haldar. "We are also actively working on discovering even more precise mechanisms of exactly how BET inhibitors work in the heart," he concludes.

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