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HEART FAILURE

Clonal haematopoiesis, IL-1β, and the NLRP3 inflammasome in HF

The highly proliferative haematopoietic system accumulates somatic mutations over time; particular mutations can give haematopoietic stem or progenitor cells a proliferative advantage, leading to the clonal expansion of cells with specific mutations. This process, termed clonal haematopoiesis, occurs with ageing in healthy individuals, but has also been associated with increased mortality from cancer, coronary heart disease, and stroke. New research now indicates that clonal haematopoiesis might also have a role in heart failure (HF).

Investigators used two mouse models of HF induced by pressure overload. The *TET2* gene, encoding an epigenetic regulatory protein involved in DNA methylation, is commonly mutated in clonal haematopoiesis. Researchers mimicked this state by competitive bone marrow transplantation with TET2-deficient cells or by specific *Tet2* ablation in myeloid cells.

In both models of HF, haematopoietic or myeloid TET2 deficiency worsened cardiac function and remodelling and increased IL-1β expression. IL-1β is processed to an active form and secreted by innate immune cells following cleavage by the NLRP3 inflammasome. Accordingly, treatment with the specific NLRP3 inflammasome inhibitor MCC950 protected against the development of HF and ameliorated differences in cardiac parameters between TET2-deficient and wild-type mice.

The CANTOS trial involving patients with stable coronary artery disease and elevated levels of C-reactive protein showed that the IL-1β-neutralizing antibody canakinumab can reduce the rate of major adverse cardiovascular events. "IL-1β blockade or NLRP3 inflammasome inhibition may be particularly effective for the treatment of cardiovascular disease in individuals who carry these [*TET2*] mutations," suggest the investigators.

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ORIGINAL ARTICLE Sano, S. *et al.* Tet2-mediated clonal hematopoiesis accelerates heart failure through a mechanism involving the IL-1β/NLRP3 inflammasome. *J. Am. Coll. Cardiol.* **71**, 875–886 (2018)

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