DNMT3A clonal hematopoiesis-driver mutations are associated with profound changes in monocyte and T cell signatures in humans with heart failure

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Background: Clonal hematopoiesis (CH) driven by mutations of DNA methyltransferase 3a (DNMT3A) is associated with increased incidence of cardiovascular disease and poor prognosis of patients with chronic heart failure (HF) and aortic stenosis. Although experimental studies suggest that DNMT3A CH-driver mutations may enhance inflammation, specific signatures of inflammatory cells in humans are missing. Single-cell RNA-sequencing provides a novel opportunity to define subsets of immune cells mediating inflammation in humans.

Methods: Transcriptomic profiles of peripheral blood mononuclear cells were analysed in N=6 HF patients harboring DNMT3A CH-drived mutations and with HF and N=5 patients with HF and DNMT3A mutations by single-cell RNA-sequencing.

Results: Monocytes of HF patients carrying DNMT3A mutations demonstrated a significantly increased expression of inflammatory genes compared to monocytes derived from patients with HF without DNMT3A mutations. Among the specific up-regulated genes were the prototypic inflammatory interleukins (IL) IL1B, IL6, and IL8, the macrophage inflammatory proteins CCL3 and CCL4 as well as restin, which augments monocyte-endothelial adhesion. The classical monocyte subset of DNMT3A mutation carriers showed increased expression of immunoglobulin superfamily members CD80, CD300LB, and SIGLEC12, as well as the cell adhesion molecule CD58, all of which may be involved in monocyte-T cell interactions. DNMT3A mutation carriers were further characterized by increased expression of T cell receptor chains and Th1, Th17, CD8+ and Treg specific signatures.

Conclusions: This study demonstrates that circulating monocytes and T cells of HF patients harboring CHIP-driver mutations in DNMT3A exhibit a highly inflamed transcriptome, which may contribute to the aggravation of chronic heart failure.