Modeling cardiopathologic TET2 CHIP in engineered cardiac ventricular tissue reveals therapeutics for disease resolution.

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Generation of synthetic human tissue necessitates mimicry of native tissue cell composition, architecture and molecular fidelity. Here, we detail the establishment of developmentally-staged engineered iPSC-derived human ventricular cardiac tissue (iHCT) comprising of all cell-types of native human cardiac ventricles with its concordant molecular, metabolic, structural and physiologic characteristics. iHCTs exhibit the necessary vascularization and innervation to interrogate, at high resolution, the contribution of loss-of-function (LOF) TET2-mutant myeloid clonal hematopoiesis of indeterminate potential (CHIP) on cardiac inflammation and consequent heart failure. In challenging iHCTs with TET2-depleted myeloid cells, we demonstrate the causal role and sufficiency of myeloid TET2-depletion in driving cardiopathology. Combining this model with synthetic lethality screening, we identify the FDA/EMA-approved compounds for potential resolution of myeloid TET2-LOF driven cardiac inflammation and cardiopathology. Given the high unmet therapeutic need, our data suggests potential benefit in repurposing these identified compounds for treatment of cardiopathologic TET2 CHIP in patients.