Thus, hypoxic preconditioning may be used in diabetic heart to improve myocardial metabolism and heart protection.

P1594 | BENCH
Role of CTCF in maintenance of global chromatin architecture in the heart
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Chromatin organization is crucial for the regulation of the genes in the nucleus. Many chromatin proteins work in concert to provide chromatin structural environments that are permissive for gene activation or repression. The multifunctional chromatin protein CTCF plays a role in chromatin looping, gene activation, and gene repression, however, there is a gap in our understanding of CTCF-mediated organization of the cardiomyocyte genome.

We recently observed that CTCF abundance is negatively correlated with heart weight and ejection fraction across a panel of genetically diverse mouse strains subjected to different heart failure phenotypes. To determine whether CTCF levels directly affect cardiac function, we generated an inducible, cardiac-specific CTCF knockout mouse. Loss of CTCF induced a decrease in ejection fraction (from 40% to 10%, n=50) and an increase in heart weight to body weight ratio (from 0.10 to 0.13, p<0.05) to that seen in wild type to that seen in wild type subjected to transverse aortic constriction (TAC), a pressure overload model of heart failure. In addition, CTCF knockout mice had increased cardiomyocyte size as well as fibrotic area. To investigate transcriptome remodeling in these pathological conditions, we performed RNA-seq in control, CTCF knockout and TAC mice. These experiments showed that 40% of differentially expressed genes are shared between CTCF knockout and TAC conditions, including those in the canonical fetal gene program (i.e., Nppa, Myh6, or Alp2a2). To determine the molecular mechanisms underlying the transcriptome regulation, we performed high-throughput chromosome conformation capture (Hi-C) in control, CTCF depleted, and TAC mice. In both types of pathological samples, locations of topologically associating domains were not dramatically affected; however, 45% of the boundary regions located between these domains show changes in strength. In addition, 4% of genes undergo a change in active versus inactive compartmentalization, including genes involved in heart disease. Furthermore, 20% of chromatin loops were lost in both pathological conditions, and the number of interactions from previously identified cardiac enhancer CTCF binding sites reduced in both pathological samples. Finally, our work using human heart samples before and after implantation of left ventricular assist devices showed a mean 1.7-fold recovery of CTCF levels at the time of explant, suggesting CTCF plays a role in the disease process in humans.

Taken together, our results show that global reorganization of long range regulatory domains during heart failure is a shared feature independent of etiology, suggesting that modulating chromatin accessibility is a novel target for therapeutic intervention.

P1595 | BENCH
Cardioprotective effects of statin in doxorubicin-induced cardiotoxicity by modulating survivin expression through inhibition of FoxO1 activity
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Background: Survivin is an inhibitor of apoptosis protein (IAP). Our previous study reported that survivin has an anti-apoptotic effect against doxorubicin (DOX)-induced cardiotoxicity. Statin use was associated with a lower risk for in- cident heart failure in breast cancer patients with DOX chemotherapy. So, we investigated whether survivin mediates the protective effect of statin against DOX- induced cardiotoxicity.

Methods and results: DOX (1 μM) suppressed survivin expression via activation of FoxO1 in H9C2 cardiomyocytes. Interestingly, statin (10 mg/kg) inhibited FoxO1 by not only increasing phosphorylation, but also inhibiting nuclear localization, which relieved survivin expression in DOX-induced cardiomyocytes. These effects were reversed by FoxO1 small interfering RNA. We found that DOX induced FoxO1 bound to STAT3 and prevented STAT3 from interacting with Sp1. However, statin significantly inhibited FoxO1 binding to STAT3 and restored STAT3 binding to Sp1 and stabilized transcription complex of FoxO1/Sp1. Chromatin immunoprecipitation analysis demonstrated that DOX decreased Sp1-STAT3 complex, whereas statin increased this complex binding to the promoter region of the survivin gene. In chronic DOX-induced cardiomyopathy mouse model, oral administration of statin rescued decrease of survivin expression in myocardium and left ventricular ejection fraction measured by cardiac MRI.

Conclusion: Our results suggest that survivin mediates protective effect of statin against DOX-induced cardiotoxicity via FoxO1/STAT3/Sp1 transcriptional network.

Table 1

<table>
<thead>
<tr>
<th>Table 1</th>
<th>DES+ mutation (n=17)</th>
<th>DES− mutation (n=13)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean, female, n (%)</td>
<td>37, 4±18, 11 (64%)</td>
<td>46, 9±17, 14, 6 (46.2%)</td>
<td>p=0.159, 0.356</td>
</tr>
<tr>
<td>LV end diastolic volume (mL)</td>
<td>46, 2±17, 6 (64.2%)</td>
<td>37, 3±17, 6 (46.2%)</td>
<td>p=0.354</td>
</tr>
<tr>
<td>LVEDVI (mL/m²)</td>
<td>98±23, 6</td>
<td>83, 10±4, 4</td>
<td>p=0.072</td>
</tr>
<tr>
<td>LGE pattern, n (%)</td>
<td>Circumferential (64.7%)</td>
<td>Circumferential (1, 7%)</td>
<td>p=0.00</td>
</tr>
</tbody>
</table>

LVEF, left ventricle ejection fraction; LVEDVI, indexed left ventricle end-diastolic volume; LGE, late gadolinium enhancement.

P1596 | BEDSIDE
Tissue characterization in Arrhythmogenic Cardiomyopathy: diagnostic impact of combined endomyocardial biopsy and cardiac magnetic resonance approach
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Background: Arrhythmogenic cardiomyopathy (AC) is a primary heart muscle (both left and right ventricle) disease characterized by myocardial atrophy and fibro-fatty replacement. The diagnosis of AC is typically multiparametric, and currently is based on the Revised Task Force Criteria 2010 (TFC), including endomyocardial biopsy (EMB). However, current TFC criteria do not consider tissue characterization by contrast-enhanced cardiac magnetic resonance (CE-CMR).

Purpose: To compare EMB and CE-CMR findings in patients with a clinical suspicion of AC, in particular to investigate the role of tissue characterization through CE-CMR, which is still not included among the AC criteria, and to verify the contribution of both tools to the final diagnosis.

Methods: Patients with definite, borderline or possible AC diagnosis according to 2010 TFC, in which both CMR and EMB histologic data were available but not included in the scoring system, were enrolled. EMB samples were obtained from a region of interest at the end-diastolic phase between the ventricular septum and the anterior right ventricle (RV) free wall, and then processed for histological examination. Histomorphometric analysis was performed on digitally acquired trichrome-stained slides in order to calculate the area of myocardium, fibrous tissue and fatty tissue. CMR was performed on 1.5-T CMR scanners. CMR-derived information was compared to histologic and CE-CMR images and, tissue characterization sequences by using T1-weighted turbo spin-echo (TSE), for fatty infiltration detection, and contrast-injection inversion recovery (IP) sequences, for fibrosis detection in terms of Late Gadolinium Enhancement (LGE).

Results: 27 patients (mean age 34±15 years, male 74%) were enrolled, i.e. 10 (37%) with a certain, 3 (11%) borderline and 14 (52%) possible AC diagnosis according to 2010 TFC with exclusion of the tissue characterization category. Out of 27 patients, 19 (70%) showed left ventricular (LV) LGE. By adding tissue characterization (either RV or LV) by CE-CMR to the TFC for AC, 22 (81%) patients reached a certain diagnosis, 4 (15%) borderline and 1 (4%) possible. Finally, by adding EMB, 28 (96%) reached a certain diagnosis and only one 4% had a borderline diagnosis, showing that EMB would still be determinant in selected cases when CMR findings are not conclusive.

Conclusions: Our data shows as CMR and EMB can identify different patterns of tissue abnormalities in AC. A combined approach for tissue characterization in the diagnostic work up of AC is able to upgrade the diagnostic score and to increase both EMB sensitivity and CE-CMR specificity.